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ESC GUIDELINES

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

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The disclosure forms of all experts involved in the development of these guidelines are available on the ESC website www.escardio.org/guidelines

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the Guidelines see *European Heart Journal* online.

Click here to access the corresponding chapter in section 41 - Atrial fibrillation

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Abbreviations and acronyms

Abbreviations and acronyms

4S-AF	Stroke risk, Symptom severity, Severity of AF burden, Substrate severity
AAD	Antiarrhythmic drug
ABC	Atrial fibrillation Better Care [includes A (avoid stroke), B (better symptom control), and C (cardiovascular risk factors and comorbid conditions management)]
ABC-bleeding	Age, Biomarkers (haemoglobin, cTnT hs T, GDF-15), and Clinical history (prior bleeding)
ABC-stroke	Age, Biomarkers, Clinical history (stroke risk score)
ACS	Acute coronary syndromes
ACTIVE W	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events trial
AF	Atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFL	Atrial flutter
AHRE	Atrial high-rate episode
AMICA	Atrial Fibrillation Management in Congestive Heart Failure With Ablation
ARCADIA	AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ARREST-AF	Aggressive Risk Factor Reduction Study – Implication for AF
AST	Aspartate aminotransferase
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation (score)
ATTICUS	Apixaban for treatment of embolic stroke of undetermined source
AVERROES	Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment
b.i.d.	bis in die (twice a day)
BP	Blood pressure
bpm	Beats per minute
C_2HEST	CAD/COPD (1 point each), Hypertension (1 point), Elderly (≥75 years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score)
CABANA	Catheter ABlation vs. ANtiarrhythmic Drug Therapy for Atrial Fibrillation
CAD	Coronary artery disease
CAPTAF	Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation
CASTLE-AF	Catheter Ablation vs. Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation
CATCH-ME	Characterizing AF by Translating its Causes into Health Modifiers in the Elderly
CCB	Calcium channel blocker
CCS	Chronic coronary syndrome
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)
$CHADS_2$	CHF history, Hypertension history, Age ≥75 y, Diabetes mellitus history, Stroke or TIA symptoms previously
CHF	Congestive heart failure
CI	Confidence interval
CIED	Cardiac implantable electronic device
CKD	Chronic kidney disease
COP-AF	Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery

COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CrCl	Creatinine clearance
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTI	Cavotricuspid isthmus
cTnT-hs	High-sensitivity troponin T
DAPT	Dual antiplatelet therapy
EAST	Early treatment of Atrial fibrillation for Stoke prevention Trial
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association
ELAN	Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN
ENGAGE AF-TIMI 48	Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48
ENTRUST-AF PCI	Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
ESC	European Society of Cardiology
GARFIELD-AF	Global Anticoagulant Registry in the FIELD - Atrial Fibrillation
GDF-15	Growth differentiation factor-15
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
i.v.	intravenous
ICH	Intracranial haemorrhage
IMPACT-AF	Integrated Management Program Advancing Community Treatment of Atrial Fibrillation
INR	International normalized ratio
LA	Left atrium/atrial
LAA	Left atrial appendage
LEGACY	Long-term Effect of Goal-directed weight management on an Atrial fibrillation Cohort: a 5-Year follow-up study
LGE-CMR	Late gadolinium contrast-enhanced cardiac magnetic resonance
LMWH	Low-molecular-weight heparin
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
mAFA	Mobile AF App
MANTRA-PAF	Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
MRI	Magnetic resonance imaging
NDCC	Non-dihydropyridine calcium channel blocker
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
o.d.	omni die (once daily)
OAC	Oral anticoagulant
OPTIMAS	OPtimal TIMing of Anticoagulation after Stroke
OSA	Obstructive sleep apnoea
PACES	Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PCORI	Patient-Centred Outcomes Research Institute
PIONEER AF-PCI	OPen-Label, Randomized, Controlled, Multicenter Study ExplorIng TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention
PREVAIL	Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
PRO	Patient-reported outcome
PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation
PVI	Pulmonary vein isolation
QoL	Quality of life
QRS	QRS interval
QTc	Corrected QT interval
RACE	Race Control Efficacy in Permanent Atrial Fibrillation
RCT	Randomized controlled trial
RE-DUAL	Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention
RE-CIRCUIT	Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of different peri-proCedUral antIcoagulation sTrategies
REHEARSE-AF	REmote HEArt Rhythm Sampling using the AliveCor hear monitor to scrEen for Atrial Fibrillation
RE-LY	Randomized Evaluation of Long Term Anticoagulant Therapy
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SAMe-TT_2R_2	Sex (female), Age (<60 years), Medial history, Treatment, Tobacco use, Race (non-Caucasian) (score)
SBP	Systolic blood pressure
START	Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in AF

STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiography
TTR	Time in therapeutic range
UFH	Unfractionated heparin
US	United States of America
VHD	Valvular heart disease
VKA	Vitamin K antagonist
WOEST	What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EurObservational Research Programme of international registries of cardiovascular diseases and interventions which are essential to assess, diagnostic/therapeutic processes, use of resources and adherence to Guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded, in some of its guidelines, a set of quality indicators (QIs) which are tools to evaluate the level of implementation of the Guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice as well as used in educational programmes, alongside the key messages from the Guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines). This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

Table 1 Classes of recommendations

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

The ESC CPG supervises and coordinates the preparation of new Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists, and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access the full text version of the Guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate, and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

2 Introduction

Atrial fibrillation (AF) poses significant burden to patients, physicians, and healthcare systems globally. Substantial research efforts and resources are being directed towards gaining detailed information about the mechanisms underlying AF, its natural course and effective treatments (see also the *ESC Textbook of Cardiovascular Medicine: CardioMed*) and new evidence is continuously generated and published.

The complexity of AF requires a multifaceted, holistic, and multidisciplinary approach to the management of AF patients, with their active involvement in partnership with clinicians. Streamlining the care of patients with AF in daily clinical practice is a challenging but essential requirement for effective management of AF. In recent years, substantial progress has been made in the detection of AF and its management, and new evidence is timely integrated in this third edition of the ESC guidelines on AF. The 2016 ESC AF Guidelines introduced the concept of the five domains to facilitate an integrated structured approach to AF care and promote consistent, guideline-adherent management for all patients. The Atrial Fibrillation Better Care (ABC) approach in the 2020 ESC AF Guidelines is a continuum of this approach, with the goal to further improve the structured management of AF patients, promote patient values, and finally improve patient outcomes.

Reflecting the multidisciplinary input into the management of patients with AF and interpretation of new evidence, the Task Force includes cardiologists with varying subspecialty expertise, cardiac surgeons, methodologists, and specialist nurses amongst its members.

Further to adhering to the standards for generating recommendations that are common to all ESC guidelines (see *preamble*), this Task Force discussed each draft recommendation during web-based conference calls dedicated to specific chapters, followed by consensus modifications and an online vote on each recommendation. Only recommendations that were supported by at least 75% of the Task Force members were included in the Guidelines.

2.1 What is new in the 2020 Guidelines?

New recommendations

Recommendations	Class[a]
Recommendations for diagnosis of AF	
ECG documentation is required to establish the diagnosis of AF. A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.	I
Recommendations for structured characterization of AF	
Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different healthcare levels, inform treatment decision making, and facilitate optimal management of AF patients.	IIa
Recommendations for screening to detect AF	
When screening for AF it is recommended that: • The individuals undergoing screening are informed about the significance and treatment implications of detecting AF. • A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF. • Definite diagnosis of AF in screen-positive cases is established only after the physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.	I
Recommendations about integrated AF management	
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I
Recommendations for the prevention of thrombo-embolic events in AF	
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up.	IIa
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors	I
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made 4 - 6 months after the index evaluation.	IIa
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.	III
Recommendations for cardioversion	
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thrombo-embolic risk.	I
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (>500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III
Recommendations for rhythm control/catheter ablation of AF	
General recommendations	
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.	I
Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI.	IIa
AF catheter ablation after antiarrhythmic drug therapy failure	
AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.	IIa
First-line therapy	
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic: • Paroxysmal AF episodes, or	IIa
• Persistent AF without major risk factors for AF recurrence as an alternative to AAD class I or III, considering patient choice, benefit, and risk.	IIb

Continued

Techniques and technologies	
Use of additional ablation lesions beyond PVI (low voltage areas, lines, fragmented activity, ectopic foci, rotors, and others) may be considered but is not well established.	**IIb**
Lifestyle modification and other strategies to improve outcomes of ablation	
Strict control of risk factors and avoidance of triggers are recommended as part of rhythm control strategy.	**I**
Recommendations for stroke risk management peri-cardioversion	
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	**I**
In patients with AF duration of >24 h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors).	**IIa**
In patients with a definite duration of AF ≤24 h and a very low stroke risk (CHA_2DS_2-VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted.	**IIb**
Recommendations for stroke risk management peri-catheter ablation	
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and: • Preferably, therapeutic OAC for at least 3 weeks before ablation, or • Alternatively, the use of TOE to exclude LA thrombus before ablation.	**I** **IIa**
For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended.	**I**
Recommendations for long-term AADs	
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.	**I**
In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.	**IIa**
Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided.	**IIb**
Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in AF	
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.	**I**
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.	**I**
Opportunistic screening for AF is recommended in hypertensive patients.	**I**
Opportunistic screening for AF should be considered in patients with OSA.	**IIa**
Recommendations for patients with AF and an ACS, PCI, or CCS	
Recommendations for AF patients with ACS	
In AF patients with ACS undergoing an uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	**I**
Recommendations in AF patients with a CCS undergoing PCI	
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	**I**
Recommendations for the management of active bleeding on OAC	
Four-factor prothrombin complex concentrates should be considered in AF patients on VKA who develop a severe bleeding complication.	**IIa**
Recommendations for the management of AF during pregnancy	
Acute management	
In pregnant women with HCM, cardioversion should be considered for persistent AF.	**IIa**
Ibutilide or flecainide i.v. may be considered for termination of AF in stable patients with structurally normal hearts.	**IIb**
Long-term management (oral administration of drugs)	
Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail.	**IIa**
Digoxin or verapamil should be considered for rate control if beta-blockers fail.	**IIa**

Continued

Recommendations for postoperative AF	
Long-term OAC therapy to prevent thrombo-embolic events should be considered in patients at risk for stroke with postoperative AF after non-cardiac surgery, considering the anticipated net clinical benefit of OAC and informed patient preferences.	IIa
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery.	III
Recommendations pertaining to sex-related differences in AF	
Women with symptomatic paroxysmal or persistent AF should be offered timely access to rhythm control therapies, including AF catheter ablation, when appropriate for medical reasons.	IIa
Recommendations for quality measures in AF	
The introduction of tools to measure quality of care and identify opportunities for improved treatment quality and AF patient outcome should be considered by practitioners and institutions.	IIa

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; CCS = chronic coronary syndrome; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CrCl = creatinine clearance; ECG = electrocardiogram; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; HCM = hypertrophic cardiomyopathy; i.v. = intravenous; LA = left atrium/atrial; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; OSA = obstructive sleep apnoea; PCI = percutaneous coronary intervention; PRO = patient-reported outcome; PVI = pulmonary vein isolation; QTc = corrected QT interval; TOE = transoesophageal echocardiography; VKA = vitamin K antagonist therapy.
[a]Class of recommendation.

Changes in the recommendations

Recommendations about integrated AF management			
2020	**Class[a]**	**2016**	**Class[a]**
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that: • Physicians inform the patient about advantages/limitations and benefit/risks associated with considered treatment option(s); and • Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.	I	Placing patients in a central role in decision making should be considered in order to tailor management to patient preferences and improve adherence to long-term therapy	IIa
Recommendations for the prevention of thrombo-embolic events in AF			
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.	I	Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	IIa
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: • Switching to a NOAC but ensuring good adherence and persistence with therapy; or • Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).	I IIa	AF patients already on treatment with a VKAs may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contraindications to NOAC (e.g. prosthetic valve).	IIb
Recommendations for rhythm control/catheter ablation of AF			
AF catheter ablation after drug therapy failure			
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with: • Paroxysmal AF, or • Persistent AF without major risk factors for AF recurrence, or • Persistent AF with major risk factors for AF recurrence.	I	Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIa

Continued

First-line therapy			
AF catheter ablation: • Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.	I	AF ablation should be considered in symptomatic patients with AF and HFrEF to improve symptoms and cardiac function when tachycardiomyopathy is suspected.	IIa
• Should be considered in selected AF patients with HFrEF to improve survival and reduce HF hospitalization.	IIa		
Techniques and technologies			
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.	I	Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa
If patient has a history of CTI-dependent atrial flutter or if typical atrial flutter is induced at the time of AF ablation, delivery of a CTI lesion may be considered.	IIb	Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation	IIa
Lifestyle modification and other strategies to improve outcomes of ablation			
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.	I	In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF burden and symptoms.	IIa
Recommendations for stroke risk management peri-cardioversion			
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety as warfarin.	I	Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter.	IIa
Recommendations for stroke risk management peri-catheter ablation			
After AF catheter ablation, it is recommended that: • Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and • Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.	I	All patients should receive oral anticoagulation for at least 8 weeks after catheter ablation.	IIa
Recommendations for long-term antiarrhythmic drugs			
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	Amiodarone is more effective in preventing AF recurrences than other AAD, but extracardiac toxic effects are common and increase with time. For this reason, other AAD should be considered first.	IIa
Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF			
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	BP control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding	IIa
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.	IIa	Moderate regular physical activity is recommended to prevent AF, while athletes should be counselled that long-lasting intense sports participation can promote AF	I
Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms.	IIb	OSA treatment should be optimized to reduce AF recurrences and improve AF treatment results.	IIa
Recommendations for stroke prevention in AF patients after ICH			
In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: • A trauma-related ICH • Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits	IIa	After ICH oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb

Continued

Recommendations for postoperative AF				
Long-term OAC therapy to prevent thrombo-embolic events may be considered in patients at risk for stroke with postoperative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.	IIb	Long-term anticoagulation should be considered in patients with AF after cardiac surgery at risk for stroke, considering individual stroke and bleeding risk.	IIa	© ESC 2020

AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; CTI = cavotricuspid isthmus; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial haemorrhage; INR = international normalized ratio; LV = left ventricular; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant or oral anticoagulation; PVI = pulmonary vein isolation; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Class of recommendation.

3 Definition and diagnosis of atrial fibrillation

3.1 Definition

Table 3 Definition of atrial fibrillation

	Definition
AF	A supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. *Electrocardiographic characteristics of AF include:* • Irregularly irregular R-R intervals (when atrioventricular conduction is not impaired), • Absence of distinct repeating P waves, and • Irregular atrial activations.
	Currently used terms
Clinical AF	*Symptomatic* or *asymptomatic* AF that is documented by surface ECG. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or entire 12-lead ECG.[1,2]
AHRE, subclinical AF	Refers to individuals *without symptoms attributable to AF,* in whom *clinical AF is NOT previously detected (that is, there is no surface ECG tracing of AF),* see also *section 3.3*. **AHRE** - events fulfilling programmed or specified criteria for AHRE that are detected by CIEDs with an atrial lead allowing automated continuous monitoring of atrial rhythm and tracings storage. CIED-recorded AHRE need to be visually inspected because some AHRE may be electrical artefacts/false positives. **Subclinical AF** includes AHRE confirmed to be AF, AFL, or an AT, or AF episodes detected by insertable cardiac monitor or wearable monitor and confirmed by visually reviewed intracardiac electrograms or ECG-recorded rhythm.
Device-programmed rate criterion for AHRE is ≥175 bpm, whereas there is no specific rate limit for subclinical AF. The criterion for AHRE duration is usually set at ≥5 min (mainly to reduce the inclusion of artefacts), whereas a wide range of subclinical AF duration cut-offs (from 10 - 20 seconds to >24 hours) is reported in studies of the association of subclinical AF with thromboembolism. The reported duration refers to either the longest single episode or, more commonly, total duration of AHRE/subclinical AF during the specified monitoring period. Although not completely identical, the terms AHRE and subclinical AF are often used interchangeably (in this document the amalgamated term AHRE/subclinical AF will be used for practicality).[3–5] Whereas a large body of high-quality evidence from RCTs informing the management of AF patients pertains exclusively to 'clinical' AF (that is, the ECG documentation of AF was a mandatory inclusion criterion in those RCTs), data on optimal management of AHRE and subclinical AF are lacking. For this reason, AF is currently described as either 'clinical' or 'AHRE/subclinical', until the results of several ongoing RCTs expected to inform the management of AHRE and 'subclinical' AF are available.	

AHRE = atrial high-rate episode; AF = atrial fibrillation; ECG = electrocardiogram; AFL = atrial flutter; AT = atrial tachycardia; bpm = beats per minute; CIED = cardiac implantable electronic device; ECG = electrocardiogram; RCT = randomized controlled trial.

3.2 Diagnostic criteria for atrial fibrillation

The diagnosis of AF requires rhythm documentation with an electrocardiogram (ECG) tracing showing AF. By convention, an episode lasting at least 30 s is diagnostic for clinical AF.[6]

Recommendations for diagnosis of AF

Recommendations	Class[a]	Level[b]
ECG documentation is required to establish the diagnosis of AF. • A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.[6]	I	B

AF = atrial fibrillation; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

3.3 Diagnosis of atrial high-rate episodes/subclinical atrial fibrillation

Various implanted devices and wearable monitors allow detection of atrial high-rate episodes (AHRE) /subclinical AF (*Figure 1*).[3] Owing to a short monitoring, detection of AHRE/subclinical AF via external ECG is less likely.[7]

When AHRE/subclinical AF is detected by a device/wearable, inspection of the stored electrograms/ECG rhythm strips is recommended to exclude artefacts or other causes of inappropriate detection.[8,9]

4 Epidemiology

Worldwide, AF is the most common sustained cardiac arrhythmia in adults[10] (*Figure 2*, upper panel). AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy (*Figure 2*, lower panel) (*Supplementary section 1*).

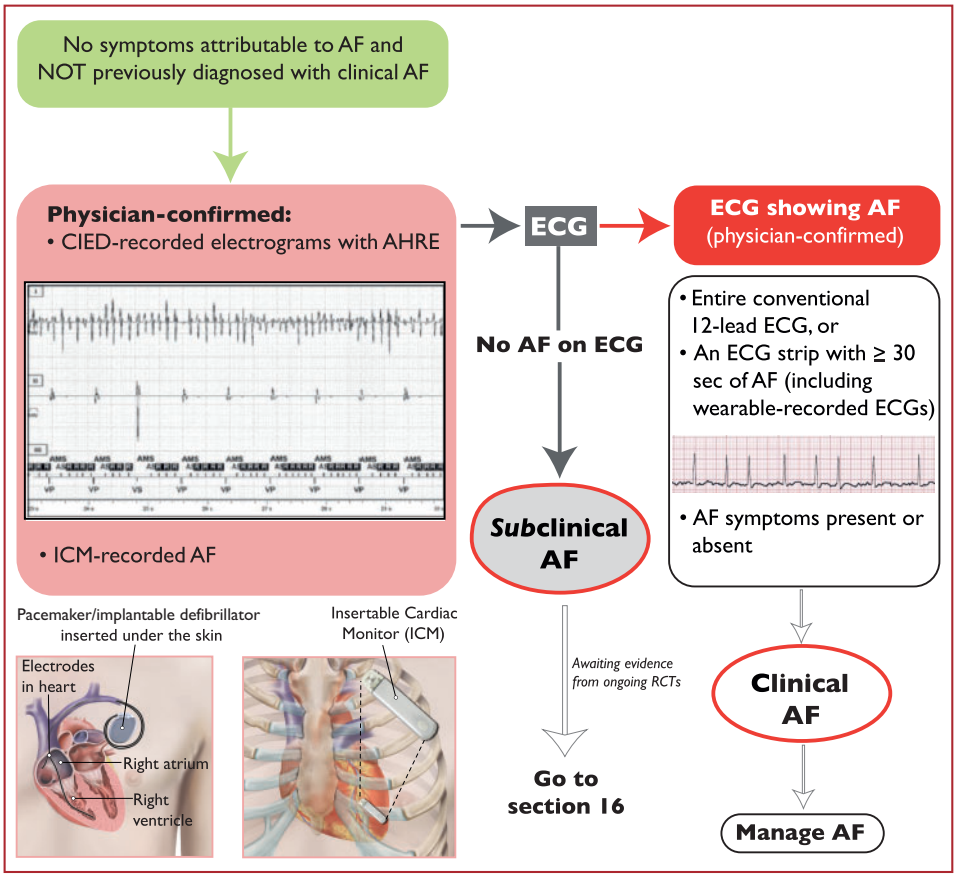


Figure 1 Diagnosis of AHRE/subclinical AF. CIEDs with an atrial lead can monitor atrial rhythm and store the tracings. ICMs have no intracardiac leads but continuously monitor cardiac electrical activity by recording and analysing a single-lead bipolar surface ECG based on a specific algorithm. Left-bottom image: pacemaker with a right atrial lead, and a ventricular lead in the right ventricular apex. In addition to pacing at either site, these leads can sense activity in the respective cardiac chamber. The device can also detect pre-programmed events, such as AHRE. Right-bottom image: subcutaneous ICM: these devices have no intra-cardiac leads and essentially record a single, bipolar, surface ECG, with inbuilt algorithms for detection of AHRE or AF. AF = atrial fibrillation; AHRE = atrial high rate episode; CIED = cardiac implantable electronic device; ECG = electrocardiogram; ICM = insertable cardiac monitor; RCT = randomized clinical trial.

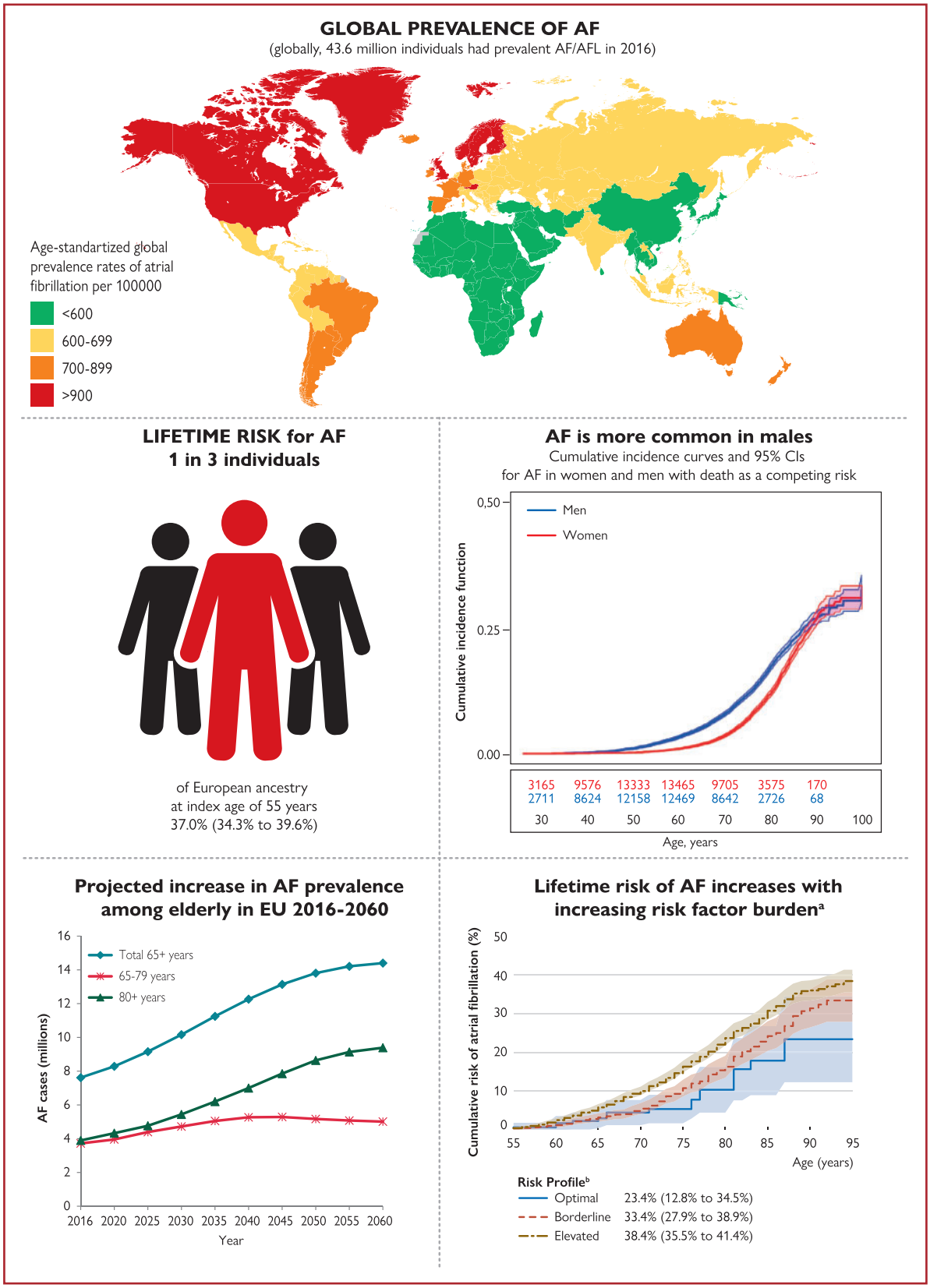


Figure 2 Epidemiology of AF: prevalence (upper panel)[10–20]; and lifetime risk and projected rise in the incidence and prevalence (lower panel).[19,21–34] AF = atrial fibrillation; AFL = atrial flutter; BP = blood pressure; CI = confidence interval; EU = European Union. [a]Smoking, alcohol consumption, body mass index, BP, diabetes mellitus (type 1 or 2), and history of myocardial infarction or heart failure. [b]Risk profile: *optimal* - all risk factors are negative or within the normal range; *borderline* - no elevated risk factors but >1 borderline risk factor; *elevated* - >1 elevated risk factor.

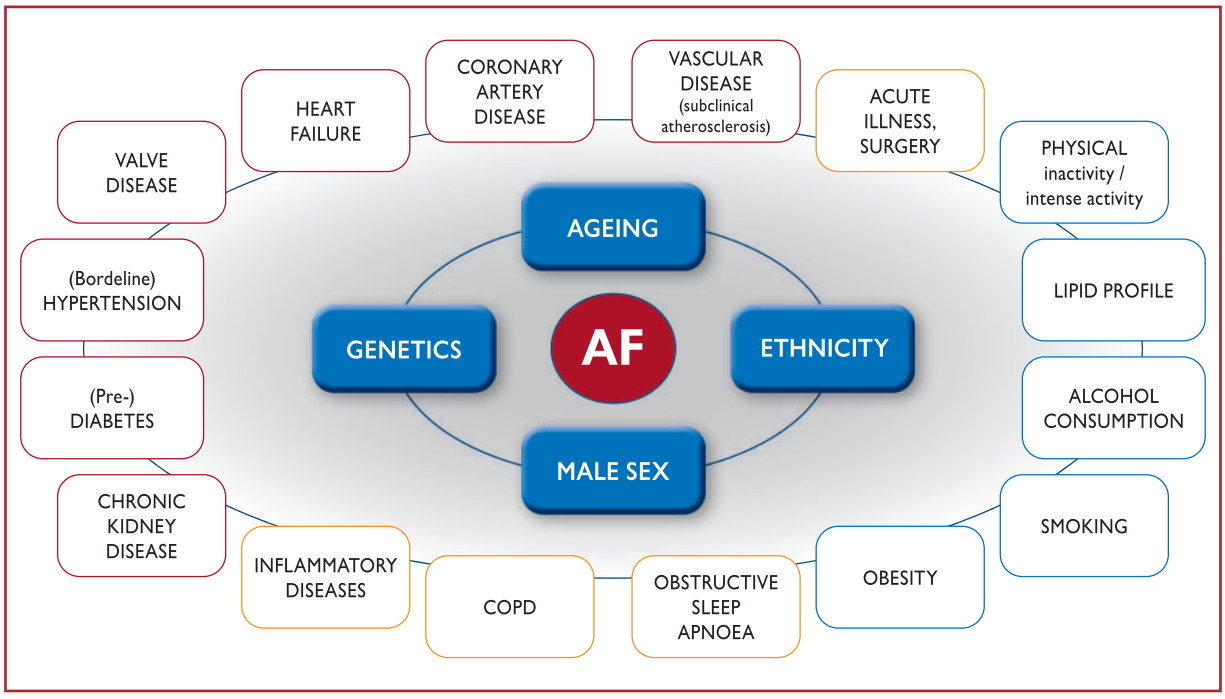


Figure 3 Summary of risk factors for incident AF[10,22,33,35–72] (*Supplementary Table 1* for full list). AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease.

The currently estimated prevalence of AF in adults is between 2% and 4%,[10] and a 2.3-fold rise[11] is expected,[12,13] owing to extended longevity in the general population and intensifying search for undiagnosed AF.[15] Increasing age is a prominent AF risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD),[21] obesity, and obstructive sleep apnoea (OSA) is also important;[22–26] modifiable risk factors are potent contributors to AF development and progression[27,28] (*Figure 3*). The age-adjusted incidence, prevalence, and lifetime risk of AF are lower in women vs. men and in non-Caucasian vs. Caucasian cohorts.[10,14–20] A previous lifetime AF risk estimate of 1 in 4 individuals[29,30] was recently revised to 1 in 3 individuals of European ancestry at index age of 55 years.[31,32] The AF lifetime risk depends on age, genetic, and (sub)clinical factors.[10,33,34] The observed impact of clinical risk factor burden/multiple comorbidity on AF risk (*Figure 3*, lower panel[31]) suggests that an early intervention and modifiable risk factor control could reduce incident AF.

4.1 Prediction of incident atrial fibrillation

Identifying individuals at higher risk of developing AF in the community could facilitate targeting of preventive interventions and screening programmes for early AF detection, for example in high-risk subgroups such as post-stroke patients.[73] Various predictive scores for new-onset AF have been proposed (*Supplementary Table 2*), but none has been widely used in clinical practice.

4.2 Pathophysiology of atrial fibrillation

A complex interplay of triggers, perpetuators, and substrate development eventually resulting in AF occurrence is shown in *Supplementary Figure 1*.

5 Clinical features of atrial fibrillation

Clinical presentation of AF and AF-related outcomes are shown in *Figure 4* (see also *Supplementary section 2* and *Supplementary Box 1*).

6 Atrial fibrillation subtypes, burden, and progression

6.1 Classification of atrial fibrillation

Different AF classifications have been proposed but, traditionally, five patterns of AF are distinguished, based on presentation, duration, and spontaneous termination of AF episodes (*Table 4*).[143]

In patients experiencing both paroxysmal and persistent AF episodes, the more common type should be used for classification. However, clinically determined AF patterns do not correspond well to the AF burden measured by long-term ECG monitoring.[144–146]

Other classifications of AF reflect the presence of symptoms (asymptomatic AF is diagnosed with an opportune 12-lead ECG or rhythm strip in asymptomatic patients) or underlying cause of AF

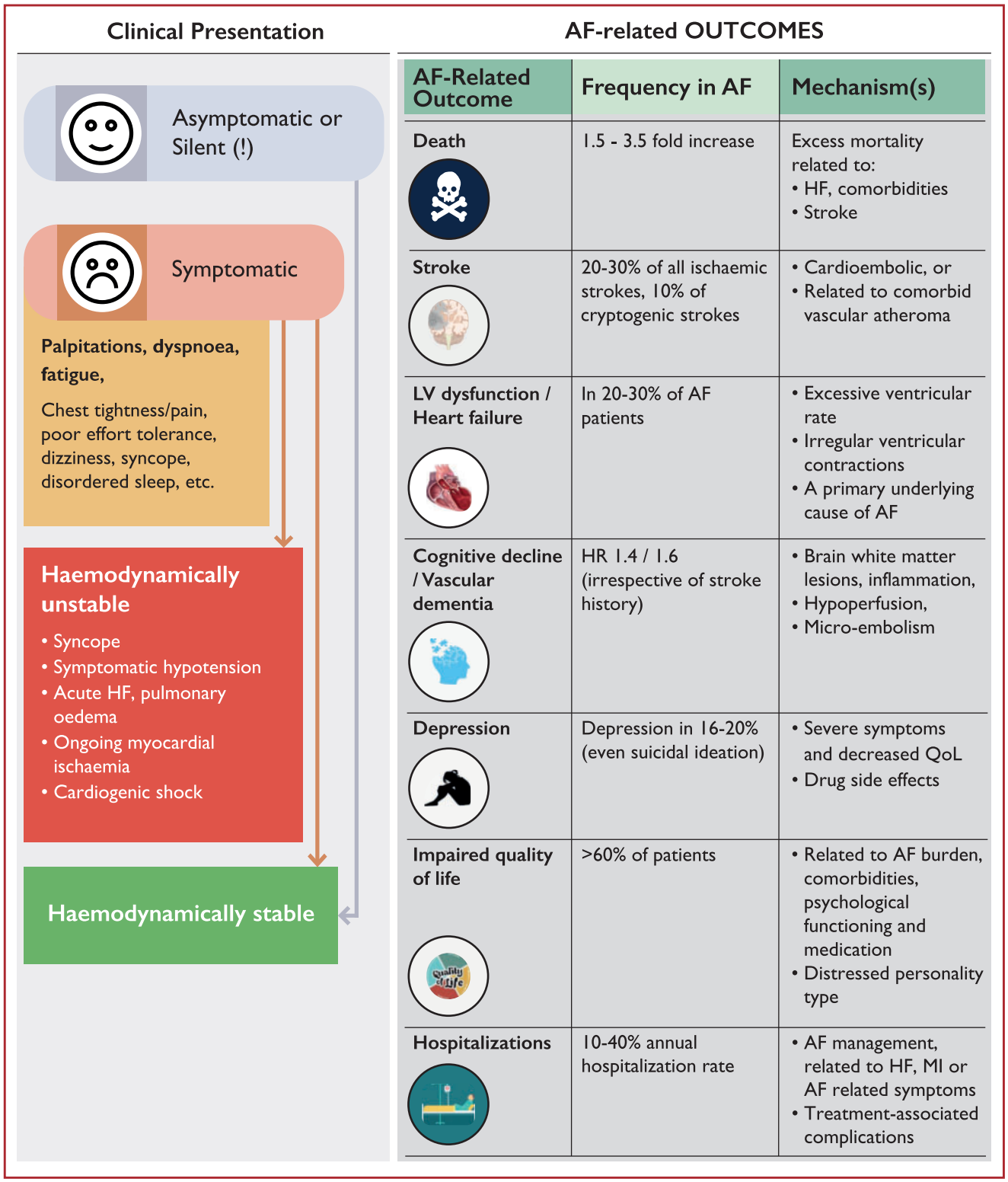


Figure 4 Clinical presentation of AF and AF-related outcomes.[10,31,74–140] AF = atrial fibrillation; HF = heart failure; HR = Hazard Ratio; LV = left ventricle; MI = myocardial infarction; QoL = quality of life.

Patients with AF may have various symptoms[92,108,109,128,131] but 50-87% are initially asymptomatic,[75,82,88,111,117,120,125,127] with possibly a less favourable prognosis.[79,82,87,88,117,119,127,134,139] First-onset AF symptoms are less well studied,[92,105,108,109,127] may change with treatment[119] and AF recurrences are commonly asymptomatic.[113]

Stroke/systolic embolism: annual AF-related stroke risk in AF patients depends on comorbidities.[78,84,85,91,106,112] Cardioembolic strokes associated with AF are usually severe, highly recurrent, often fatal, or with permanent disability.[10,83,115] In a population-based registry, patients with new-onset AF also had increased rates of systemic embolism.[89]

Figure 4 Continued

Left ventricular (LV) dysfunction and HF: multiple AF-associated mechanisms/myocardial alterations may lead to LV dysfunction and HF,[102,138] resulting in a high prevalence and incidence of HF among AF patients. Sharing common risk factors, AF and HF often coexist, or may precipitate/exacerbate each other, resulting in significantly greater mortality than either condition alone.[140]

Hospitalization: approximately 30% of AF patients have at least one, and 10% have ≥2, hospital admissions annually,[99,110,129] being twice as likely to be hospitalized as age- and sex-matched non-AF individuals (37.5% vs. 17.5%, respectively).[98] In a nationwide cohort, AF was the main cause for admission in 14% of hospitalized patients but their in-hospital mortality was <1%.[101] The most common reasons for hospitalization of AF patients were cardiovascular disorders (49%), non-cardiovascular causes (43%) and bleeding (8%).[129]

Quality of life (QoL) and functional status: >60% of AF patients have significantly impaired QoL/exercise tolerance,[81,88,136] but only 17% have disabling symptoms.[88] QoL is significantly lower in women,[81,107,114,124] young individuals, and those with comorbidities.[118] AF burden[100] may also affect QoL, but only psychological functioning consistently predicted symptoms and QoL.[136] Patients with AF more often developed anxiety disorders,[126] had a higher burden of depressive symptoms,[123] and poorer QoL with a Distressed personality type (Type D).[103] Key symptom and QoL drivers are important to identify optimal AF treatment. It is also important to confirm that symptoms are related to AF or, if absent, to exclude a subconscious adaptation to living with suboptimal physical capacity by asking for breathlessness or fatigue on exertion and recording possible improvements after cardioversion.

Cognitive impairment/dementia: AF may lead to cognitive impairment ranging from mild dysfunction to dementia[97,104,141] via clinically apparent or silent stroke or insufficiently understood stroke-independent pathways.[94,96,97,122] Magnetic resonance imaging (MRI) studies have shown that AF is associated with a greater than twofold increase in the odds of having silent cerebral ischaemia.[90,121,142] A recent expert consensus paper summarized the available data.[86]

Mortality: AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increase in men,[77,80,130,137] with an overall 3.5-fold mortality risk increase.[31] Whereas the mechanistic explanation for this association is multifaceted, associated comorbidities play an important role.[95] In a recent study, the most common causes of death among AF patients were HF (14.5%), malignancy (23.1%), and infection/sepsis (17.3%), whereas stroke-related mortality was only 6.5%.[76] These and other recent data indicate that, in addition to anticoagulation and HF treatment, comorbid conditions need to be actively treated in the endeavour to reduce AF-related mortality.[77,93,116,133]

Table 4 Classification of AF

AF pattern	Definition
First diagnosed	AF not diagnosed before, irrespective of its duration or the presence/severity of AF-related symptoms.
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset.
Persistent	AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥7 days
Long-standing persistent	Continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.
Permanent	AF that is accepted by the patient and physician, and no further attempts to restore/maintain sinus rhythm will be undertaken. Permanent AF represents a therapeutic attitude of the patient and physician rather than an inherent pathophysiological attribute of AF, and the term should not be used in the context of a rhythm control strategy with antiarrhythmic drug therapy or AF ablation. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.
Terminology that should be abandoned	
Lone AF	A historical descriptor. Increasing knowledge about the pathophysiology of AF shows that in every patient a cause is present. Hence, this term is potentially confusing and should be abandoned.[147]
Valvular/non-valvular AF	Differentiates patients with moderate/severe mitral stenosis and those with mechanical prosthetic heart valve(s) from other patients with AF, but may be confusing[148] and should not be used.
Chronic AF	Has variable definitions and should not be used to describe populations of AF patients.

AF = atrial fibrillation.

(e.g. postoperative AF, see *section 11.19*). Classifying AF by underlying drivers could inform management, but the evidence in support of the clinical use of such classification is lacking (*Supplementary Table 3*). Terms that should no longer be used to describe AF are listed in *Table 4*.

Recommendations for AF management are not based on the temporal AF patterns, except for the restoration of sinus rhythm.[143,149,150] It is very unlikely that a simple but comprehensive AF classification will be proposed, given the multiplicity of factors relevant for its management, advances in AF monitoring, multiplicity of risk assessment tools, evolving treatments, and complexity of AF itself. Indeed, a paradigm shift from classification towards a *structured characterization* of AF, addressing specific domains with treatment and prognostic implications has been recently proposed.[151] Such a scheme would streamline the assessment of AF patients at any healthcare level, thus facilitating communication among physicians,

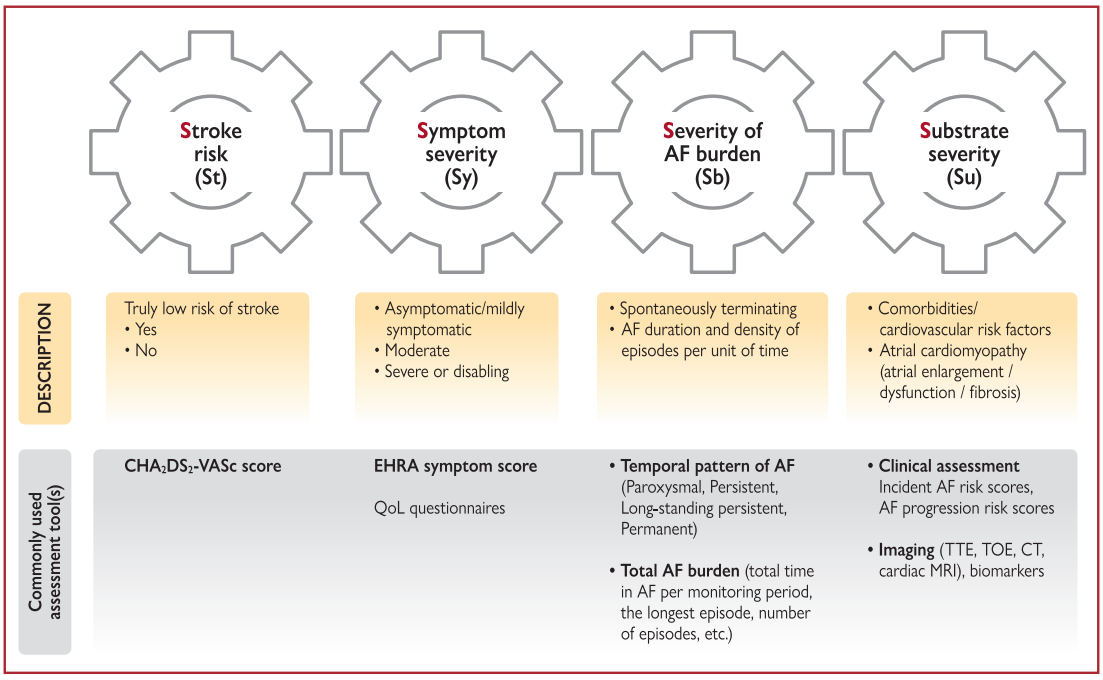


Figure 5 4S-AF scheme as an example of structured characterization of AF.[151] AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CT = computed tomography; EHRA = European Heart Rhythm Association; LA = left atrium; MRI = magnetic resonance imaging; QoL = quality of life; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

treatment decision making, and optimal management of AF patients, and should become a standard in clinical practice when reporting an AF case.

The proposed 4S-AF scheme (Stroke risk, Symptom severity, Severity of AF burden, Substrate severity) includes four AF-related domains (*Figure 5*).[151] The currently used assessment tools/classifications pertinent to specific domains (e.g. stroke risk scores, symptom scores, clinical factors, imaging modalities, etc.) can be easily fitted in, but the 4S-AF has great potential for future refinements guided by advances in technology, and the most appropriate descriptors of AF domains are yet to be defined. Given the descriptors of AF included in the 4S-AF scheme, the structured characterization of AF patients using 4S-AF could also provide prognostic information, but the clinical utility and prognostic value of the 4S-AF scheme needs extensive validation in different AF cohorts and clinical settings.

Recommendations for structured characterization of AF

Recommendations	Class[a]	Level[b]
Structured characterization of AF, which includes clinical assessment of stroke risk, symptom status, burden of AF, and evaluation of substrate, should be considered in all AF patients, to streamline the assessment of AF patients at different healthcare levels, inform treatment decision-making, and facilitate optimal management of AF patients.[151]	IIa	C

AF = atrial fibrillation
[a]Class of recommendation.
[b]Level of evidence.

6.2 Definition and assessment of atrial fibrillation burden

The term 'burden' refers to various AF aspects (e.g. epidemiological, economic).[144] Regarding continuous device-based monitoring, 'AF burden' is currently defined as the overall time spent in AHRE/subclinical AF during a specified monitoring period (e.g. 1 day). Both the time in AF and the monitoring period should be acknowledged when reporting AF burden (most studies reported the maximum time spent in AF over a 24-h period), but optimal measures are yet to be determined.[152] The term 'AF burden' is different from 'burden of AF', the latter referring to AF consequences.

Clinical AF burden is routinely determined by AF temporal pattern[146] (*Table 4*) and intermittent ECG monitoring,[153] neither corresponding well to the long-term ECG monitoring. The relationship of clinical AF burden with specific outcomes is not well characterized,[154] but may be associated with higher risk of incident HF[155] and all-cause mortality,[156] while the association with quality of life (QoL) is complex and data about cognitive impairment/dementia are lacking.[86] Recent randomized controlled trial (RCT) data consistently showed significantly lower residual thrombo-embolic risk among anticoagulated patients with paroxysmal vs. persistent AF,[156–159] whereas earlier trial-based[160] and observational data[161,162] are contradictory. Among non-anticoagulated patients, stroke risk was lower with paroxysmal than non-paroxysmal AF,[156] and a greater total AF burden (but not the longest AF episode) was independently associated with higher thrombo-embolic event rates.[163] Clinical AF burden may influence the response to rhythm control therapy.[164,165] The presence of >6 h of AF per week (especially when progressing to >24 h weekly) was associated with increased mortality, especially in women.[166]

Available evidence on the association of AF burden with AF-related outcomes is insufficient to guide treatment and should not be a major factor in treatment decisions. Comprehensive management of modifiable cardiovascular risk factors/comorbidity reduces AF burden (*section 10.3*).

6.3 Atrial fibrillation progression

Transition from paroxysmal to non-paroxysmal AF (or from subclinical to clinical AF)[154,167–169] is often characterized by advancing atrial structural remodelling or worsening of atrial cardiomyopathy.[170,171]

Assessment of AF progression depends on duration of rhythm monitoring and underlying substrate.[172,173] Reported annual rates of paroxysmal AF progression range from <1% to 15% (up to 27 - 36% in studies with ≥10-year follow-up).[169,174] Risk factors for AF progression include age, HF, hypertension, CKD, chronic pulmonary diseases, diabetes mellitus, previous stroke, and left atrial (LA) size,[167] whereas the added predictive value of biomarkers is presently not well defined. Older age is associated with permanent AF,[82,117,154] and various triggers may also play a role, with different progression patterns resulting from their interaction with substrate remodelling.[171] Progression to persistent/permanent AF is associated with adverse cardiovascular events, hospitalizations, and death,[166] but it is unclear whether AF progression is a determinant of adverse prognosis or rather a marker of an underlying progressive disease/substrate.[175,176] The true impact of different therapeutic interventions at different disease stages on AF progression and associated outcomes is also less well defined.

6.4 Atrial cardiomyopathy: definition, classification, clinical implications, and diagnostic assessment

Important progress in understanding AF mechanisms and thrombogenicity reconsiders the role of atrial cardiomyopathy (i.e. atrial structural, architectural, contractile, or electrophysiological changes with potentially relevant clinical manifestations).[170]

Clinical classification of atrial cardiomyopathy should be based on the atrial structure, morphology, electrical and mechanical function, and the diagnosis could be based on easily accessible parameters (e.g. aetiology, the prothrombotic state,[177] and abnormal LA volume/function).[178] Major clinical issues in AF (i.e. prevention of thromboembolic complications and AF progression) are influenced by atrial remodelling; and, importantly, AF is not only a risk factor for but also a marker of atrial cardiomyopathy, which could explain the lack of temporal relationship between detected AF and stroke.[179]

The diagnostic algorithm for atrial cardiomyopathy should follow a stepwise approach, identifying risk factors for atrial cardiomyopathy,[170] atrial electrical and mechanical dysfunction,[180] and increased thrombotic risk.[181] More data are needed to define prognostic and treatment implications of different atrial cardiomyopathy morpho-functional forms.

7 Screening for atrial fibrillation

Multiple factors (i.e. increasing AF prevalence, previously unknown AF detection in about 10% of all ischaemic strokes,[4,182] high prevalence of asymptomatic AF,[117] potential to prevent AF-related strokes with appropriate treatment and increasing availability of AF detection tools) have fuelled international initiatives to implement screening for AF in clinical practice.[172]

Asymptomatic clinical AF has been independently associated with increased risk of stroke and mortality compared with symptomatic AF.[82,117,127,183] Data derived from studies of incidentally detected asymptomatic AF are the closest possible approximation of the risk of stroke and death in screen-detected AF subjects, because delaying treatment to discern a natural history would be unethical. Observational data suggest that screen-detected AF responds to treatment similarly to AF detected by routine care,[183] thus favouring AF screening.

Although AF fulfils many of the criteria for disease screening[184] (*Supplementary Figure 2*), RCT data to confirm the health benefits from screening for AF and inform the choice of optimal screening programmes and strategies for its implementation are scarce.[185,186] Advances in wearable technology will likely yield inexpensive and practical options for AF detection and AF burden assessment in the near future.

7.1 Screening tools

The systems used for AF screening are shown in *Table 5* and *Figure 6*.[173,187]

Mobile health technologies are rapidly developing for AF detection and other purposes (>100 000 mHealth apps and ≥400 wearable activity monitors are currently available).[197] Caution is needed in their clinical use, as many are not clinically validated. Several studies evaluated AF detection using smartwatches,[198,199] thus opening new perspectives for AF detection targeting specific populations at risk. Machine learning and artificial intelligence may be capable of identifying individuals with previous AF episodes from a sinus rhythm ECG recording,[200] which would be a major technological breakthrough in AF detection.[200]

The Apple Heart study[201] included 419 297 self-enrolled smartwatch app users (mean age 40 years) in the United States of America (USA), of whom 0.5% received an irregular pulse notification (0.15% of those aged <40 years, 3.2% among those aged >65 years). Subsequent (notification-triggered) 1-week ECG patch monitoring revealed AF in 34% of monitored participants. The Huawei Heart study[202] included 187 912 individuals (mean age 35 years, 86.7% male), of whom 0.23% received a 'suspected AF' notification. Of those effectively followed up, 87.0% were confirmed as having AF, with the positive predictive value of photoplethysmography signals being 91.6% [95% confidence interval (CI) 91.5 - 91.8]. Of those with identified AF, 95.1% entered an integrated AF management programme using a mobile AF App (mAFA).

When AF is detected by a screening tool, including mobile or wearable devices, a single-lead ECG tracing of ≥30 s or 12-lead ECG showing AF analysed by a physician with expertise in ECG rhythm interpretation is necessary to establish a definitive diagnosis of AF (devices capable of ECG recording enable direct analysis of the device-provided tracings). When AF detection is not based on an ECG recording (e.g. with devices using photoplethysmography) or in case of uncertainty in the interpretation of device-provided ECG tracing, a confirmatory ECG diagnosis has to be obtained using additional ECG recording (e.g. 12-lead ECG, Holter monitoring, etc.)

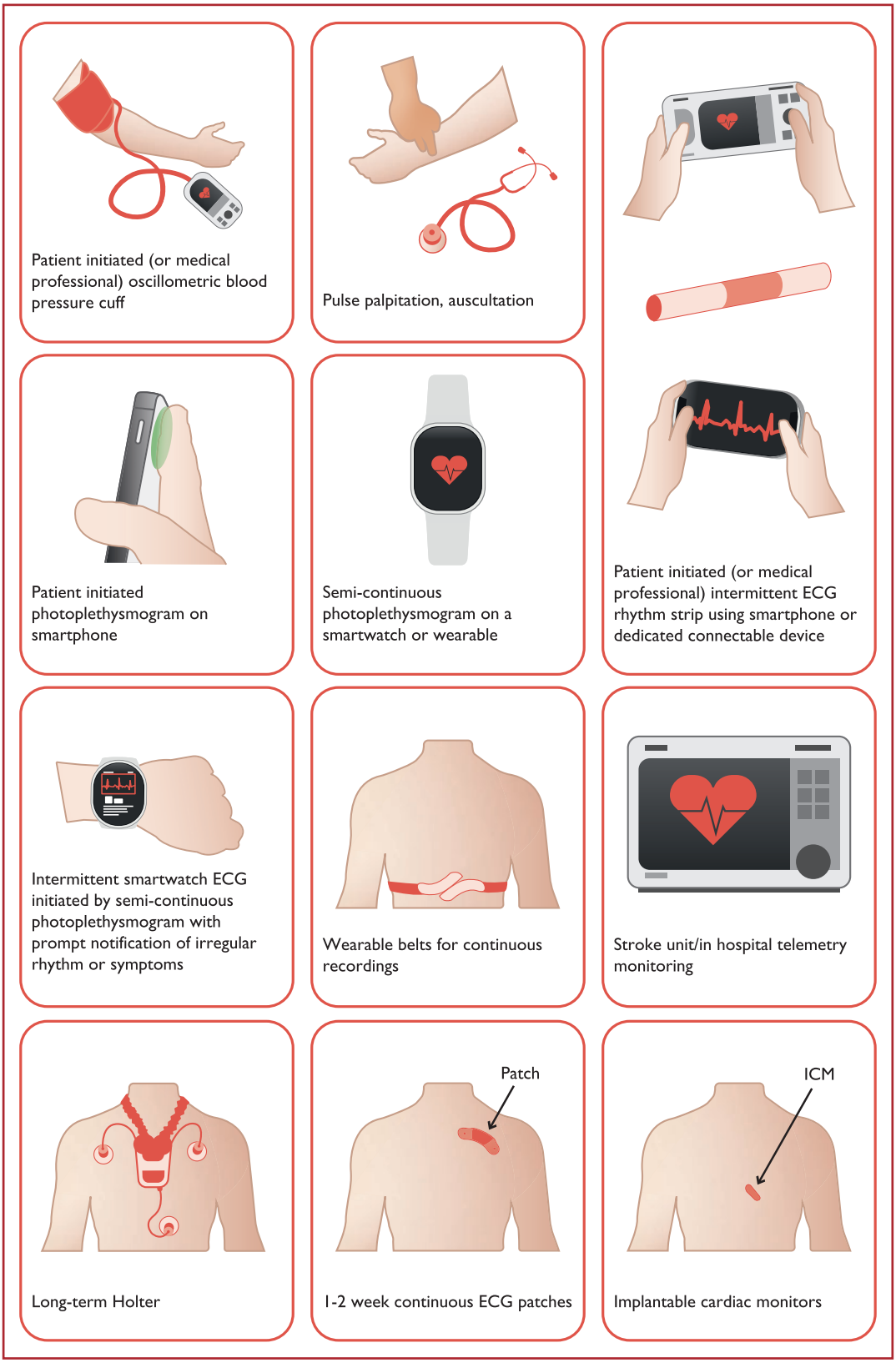


Figure 6 Systems used for AF screening. Pulse palpation, automated BP monitors, single-lead ECG devices, PPG devices, other sensors (using seismocardiography, accelerometers, and gyroscopes, etc.) used in applications for smartphones, wrist bands, and watches. Intermittent smartwatch detection of AF is possible through PPG or ECG recordings. Smartwatches and other 'wearables' can passively measure pulse rate from the wrist using an optical sensor for PPG and alerting the consumer of a pulse irregularity (based on a specific algorithm for AF detection analysing pulse irregularity and variability).[172,173,188–196] AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram; PPG = photoplethysmography.

Table 5 Sensitivity and specificity of various AF screening tools considering the 12-lead ECG as the gold standard[173]

	Sensitivity	Specificity
Pulse taking[203]	87 - 97%	70 - 81%
Automated BP monitors[204–207]	93 - 100%	86 - 92%
Single lead ECG[208–211]	94 - 98%	76 - 95%
Smartphone apps[188,189,191,195,212,213]	91.5 - 98.5%	91.4 - 100%
Watches[196,198,213,214]	97 - 99%	83 - 94%

AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram.

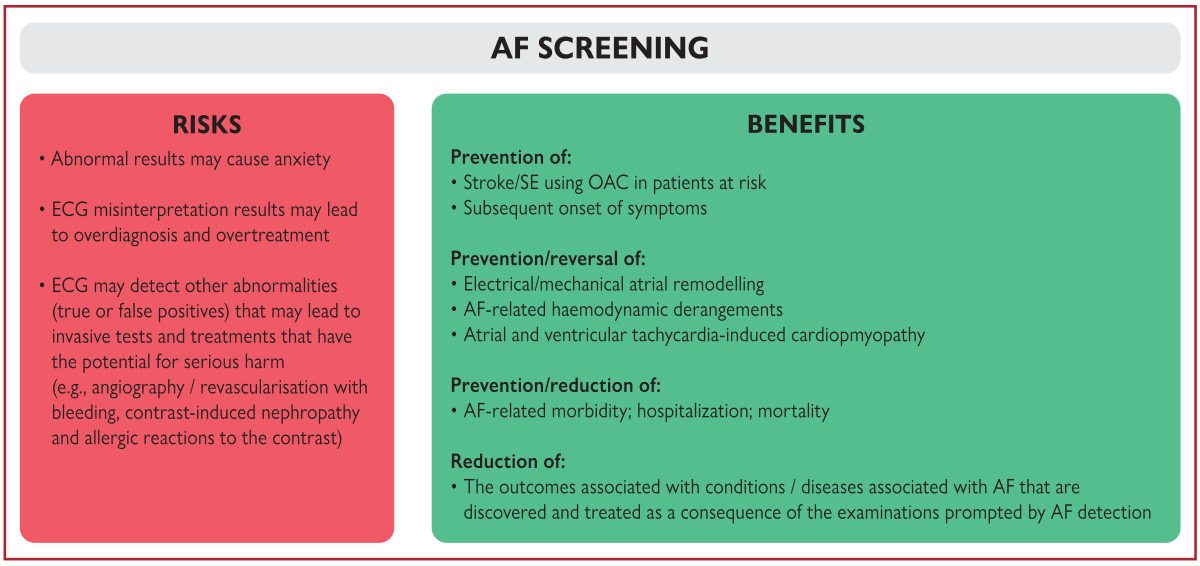


Figure 7 Potential benefits from and risks of screening for AF. AF = atrial fibrillation; ECG = electrocardiogram; OAC = oral anticoagulant; SE =systemic embolism.

The data reported in *Table 5* should be interpreted with caution, as assessment of sensitivity and specificity in many studies was based on small observational cohorts, with a substantial risk of bias due to signal selection. Moreover, there is a continuous evolution of algorithms and technologies available in commercial devices.

Two recent meta-analyses reported that screening for AF using an ECG would not detect more cases than would screening with pulse palpation.[215]

7.2 Screening types and strategies

Commonly used AF screening types and strategies[172,173,216] include opportunistic or systematic screening of individuals above a certain age (usually ≥65 years) or with other characteristics suggestive of increased stroke risk, using intermittent single-point or repeated 30-s ECG recording over 2 weeks. The appropriate frequency of monitoring using smartphones or watches is undefined. Primary care, pharmacies, or community screening during special events is a good setting for AF screening.[172,173] Overall, there was no significant difference between systematic vs. opportunistic or general practice vs. community screening in a meta-analysis, but repeated heart rhythm monitoring was associated with significantly better effectiveness compared with single assessment.[215] Importantly, a structured referral of screen-detected or suspected AF cases for further clinical evaluation should be organized, to provide an appropriate management.

7.3 Benefits from and risks of screening for atrial fibrillation

Potential advantages and disadvantages of detecting a previously undiagnosed AF through screening are shown in *Figure 7*.[173]

Screening can also highlight cases of known suboptimally managed AF.[217] Intermittent ECG recording increased new AF detection four-fold.[217] In the REHEARSE-AF (REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation) controlled study using a smartphone/tablet-based single-lead ECG system twice weekly over 12 months vs. routine care resulted in a 3.9-fold increase in AF detection in patients aged ≥65 years.[218] Appropriate patient information and screening programme organization with rapid ECG clarification may reduce anxiety induced by suspicion of abnormality.

7.4 Cost-effectiveness of screening for atrial fibrillation

Higher AF-related medical costs justify strategies to identify and treat undiagnosed AF.[219] Opportunistic AF screening is associated with lower costs than systematic screening.[173] Appropriate choice of the screening tool and setting is important,[220] and a favourable cost-effectiveness profile has been estimated for screening programmes based on pulse palpation, hand-held ECG devices, and

smartphones with pulse photoplethysmography algorithms.[172] Both systematic and opportunistic screening are more cost-effective than routine practice for patients ≥65 years, with opportunistic screening more likely to be cost-effective than systematic population screening.[1491]

7.5 Screening in high-risk populations

7.5.1 Elderly

The risk of AF (often asymptomatic) and stroke increase with age,[82,127,221] thus justifying AF screening in the elderly. Opportunistic AF screening seems to be cost-effective in elderly populations (≥65 years)[222] and among 75 - 76-year-old individuals undergoing a 2-week intermittent ECG screening.[223]

Pulse palpation and/or short-term ECG among the elderly (≥65 years) yielded an AF prevalence of 4.4%, with previously undiagnosed AF in 1.4%, suggesting a number needed to screen of 70.[224] Repeated hand-held ECG recordings over 2 weeks in an unselected population aged 75 - 76 years increased the detection of asymptomatic AF up to 7.4% in subjects with ≥2 stroke risk factors.[225]

Recommendations for screening to detect AF

Recommendation	Class[a]	Level[b]
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.[188,211,223,225]	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.[c224,226]	I	B
When screening for AF it is recommended that:[217,218] • The individuals undergoing screening are informed about the significance and treatment implications of detecting AF. • A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF. • Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.	I	B
Systematic ECG screening should be considered to detect AF in individuals aged ≥75 years, or those at high risk of stroke.[212,224,227]	IIa	B

AF = atrial fibrillation; AHRE = atrial high-rate episode; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *sections 3.2* and *3.3* for diagnostic criteria for AF and AHRE, and *section 16* for the management of patients with AHRE.

8 Diagnostic assessment in atrial fibrillation

Often occurring in patients with cardiovascular risk factors/comorbidities, AF may sometimes be a marker of undiagnosed conditions. Hence, all AF patients will benefit from a comprehensive cardiovascular assessment (*Figure 8*).

The 'standard package' for diagnostic evaluation of AF patients should include complete medical history and assessment of concomitant conditions, AF pattern, stroke risk, AF-related symptoms, thrombo-embolism, and LV dysfunction.[143] A 12-lead ECG is recommended in all AF patients, to establish the diagnosis of AF, assess ventricular rate during AF, and check for the presence of conduction defects, ischaemia, or signs of structural heart disease. Laboratory tests (thyroid and kidney function, serum electrolytes, full blood count) and transthoracic echocardiography (LV size and function, LA size, valvular disease, and right heart size and systolic function) are needed to guide treatment. Based on the patient's characteristics, specific additional information can be obtained. Most AF patients need regular follow-up (primary care) to ensure continued optimal management.

8.1 Symptoms and quality of life

As symptoms related to AF may range from none to disabling, and rhythm control treatment decisions (including catheter ablation) are influenced by symptom severity, symptom status should be characterized using the European Heart Rhythm Association (EHRA) symptom scale[228] (*Table 6*), and the relation of symptoms (especially if non-specific, such as shortness of breath, fatigue, chest discomfort, etc.) to AF should be elucidated because symptoms may also result from undiagnosed or suboptimally managed concomitant cardiovascular risk factors or pathological conditions.[229]

In selected AF patients, long-term ECG monitoring is recommended to assess the adequacy of rate control or to relate symptoms with AF episodes. Sometimes the association of symptoms with AF can be established only retrospectively, after successful rhythm control intervention. In selected patients, a trial of sinus rhythm using cardioversion and a quantified patient perception of symptoms using a validated assessment tool (*Supplementary Table 4*) may inform the decision about subsequent AF catheter ablation (*section 10.2*).

Symptomatic and functional improvement with rhythm control therapies (cardioversion,[232–234] antiarrhythmic medications, and AF catheter-ablation procedures[235–242]) largely depends on sinus rhythm maintenance[243]; however, QoL may improve despite AF recurrences, unless AF burden is high[244] (e.g. >2 h daily[100]) owing to optimized management of cardiovascular risk factors or comorbidities[245] or a treatment expectancy effect. The effect of AF treatment[246,247] is supported by reports of persistently improved QoL 10 years after paroxysmal AF catheter ablation in patients with a low AF progression rate.[248]

8.2 Substrate

The substrate for AF relates to LA dilation and fibrosis with subsequent LA dysfunction and delay in electromechanical conduction.

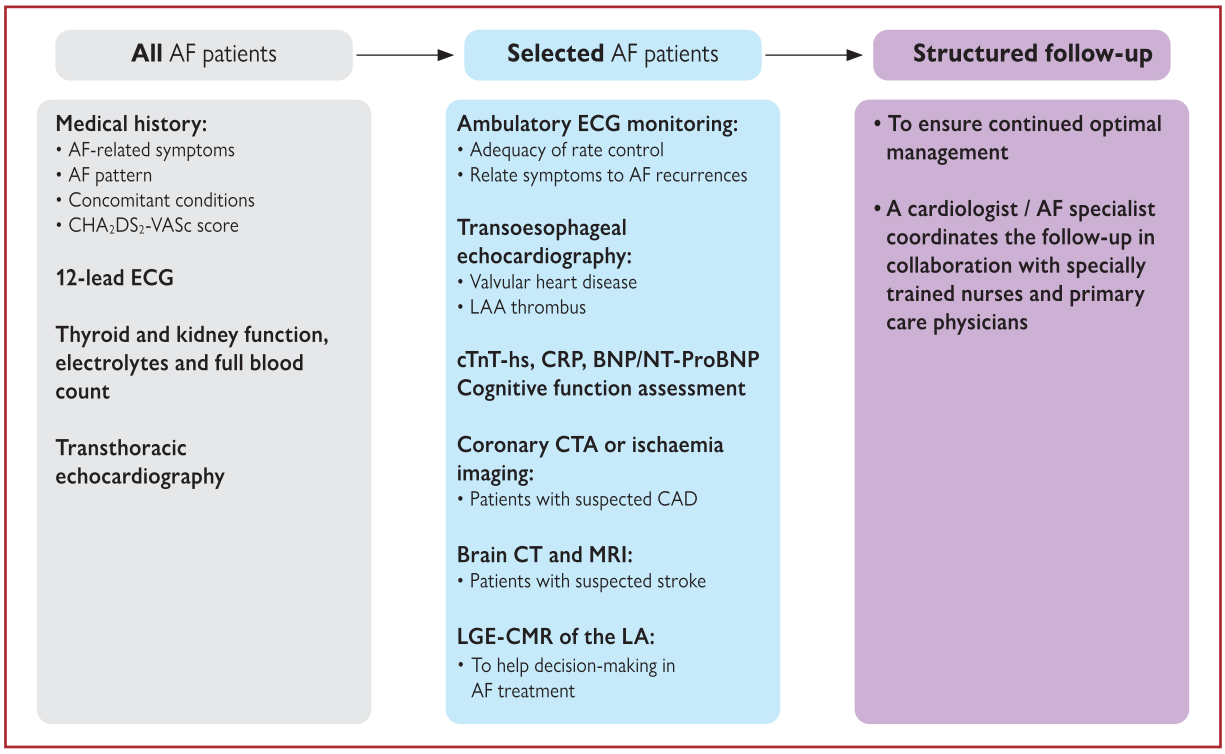


Figure 8 Diagnostic work-up and follow-up in AF patients. AF = atrial fibrillation; BNP = B-type natriuretic peptide; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CAD = coronary artery disease; CRP = C-reactive protein; CT = computed tomography; CTA = computed tomography angiography; cTnT-hs = high-sensitivity cardiac troponin T; ECG = electrocardiogram; LAA = left atrial appendage; LGE-CMR = late gadolinium contrast-enhanced cardiac magnetic resonance; MRI = magnetic resonance imaging; NT-ProBNP = N-terminal (NT)-prohormone B-type natriuretic peptide.

Table 6 EHRA symptom scale

Score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

Six symptoms, including palpitations, fatigue, dizziness, dyspnoea, chest pain, and anxiety during AF, are evaluated with regard to how it affects the patient's daily activity, ranging from none to symptom frequency or severity that leads to a discontinuation of daily activities.
To measure treatment effects, QoL and symptom questionnaires should be sensitive to changes in AF burden. The EHRA symptom scale is a physician-assessed tool for quantification of AF-related symptoms that is used to guide symptom-driven AF treatment decisions,[228] and has been related to adverse outcomes in more symptomatic patients (score 3 - 4) versus those with a score of 1 - 2.[228,230] However, it does not consider the symptom dimensions such as anxiety, treatment concerns, and medication adverse effects that are captured by general QoL scales,[230] or the patient-reported symptom-related outcomes. As discrepancies between patient-reported and physician-assessed outcomes are frequently observed,[231] the AF-related treatment decisions also need to be informed by a quantified patient perception of symptoms, but further research is needed to identify optimal tool(s) for capturing this information.
AF = atrial fibrillation; EHRA = European Heart Rhythm Association; QoL = quality of life.

Non-invasive, multimodality imaging can provide all needed information (*Figure 9*).[249,250]

In selected patients, transoesophageal echocardiography (TOE) can be used to evaluate valvular heart disease (VHD) or left atrial appendage (LAA) thrombus; CT coronary angiography can be performed for assessment of CAD; CT/MRI of the brain can be performed when stroke is suspected. Specific predictors of stroke have been suggested: LA dilation, spontaneous LA contrast, reduced LA strain, LAA thrombus, low peak LAA velocity (<20 cm/s), and LAA non-chicken wing configuration (on CT).[250]

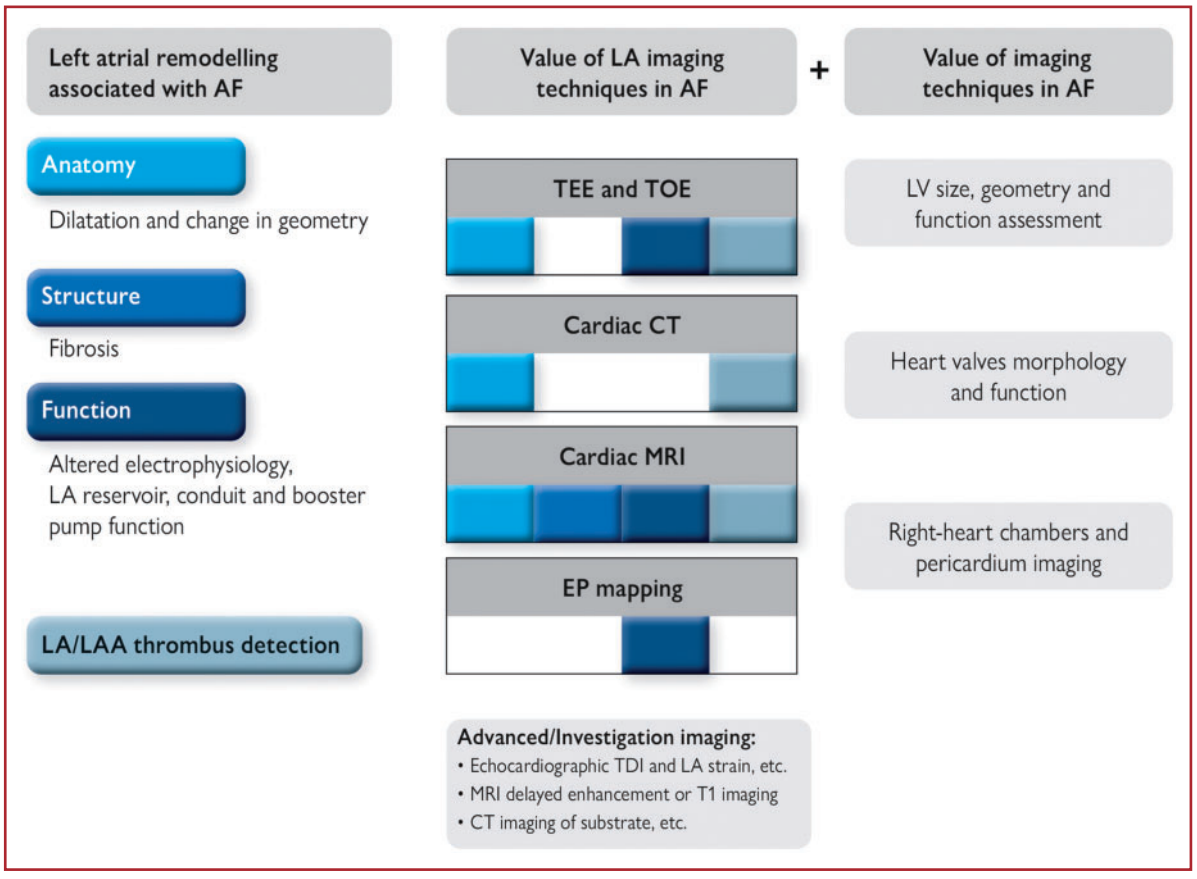


Figure 9 Imaging in AF. Anatomical imaging provides the LA size, shape, and fibrosis. Most accurate assessment of LA dilation is obtained by CMR or CT. For routine assessment, two-dimensional (2D) or (preferably) three-dimensional (3D) transthoracic echocardiography is used. The 3D echocardiographic normal volume values are 15 - 42 mL/m^2 for men and 15 - 39 mL/m^2 for women.[250] Assessment of LA fibrosis with LGE-CMR has been described but only rarely applied in clinical practice.[251] Functional imaging includes TDI and strain. TDI measures the velocities of the myocardium in diastole and systole, whereas LA strain reflects active LA contraction. The PA-TDI interval reflects the atrial electromechanical delay (total LA conduction time, the time interval between the P-wave on the ECG and the A' [atrial peak velocity] on TDI) and reflects LA strain.[252] LA wall infiltration by epicardial fat is a potential early marker of inflammation and can be detected with CT or cardiac MRI.[253] Before AF ablation, the pulmonary vein anatomy can be visualized with CT or CMR. AF = atrial fibrillation; CT = computed tomography; EP = electrophysiology; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; LGE-CMR = late gadolinium contrast-enhanced cardiac magnetic resonance; MRI = magnetic resonance imaging; TDI = tissue doppler imaging; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

Recommendations for diagnostic evaluation of patients with AF

Recommendation	Class[a]	Level[b]
In patients with AF, it is recommended to: • Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment.[230,232] • Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.[230,232]	I	C

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.
[a]Class of recommendation.
[b]Level of evidence.

9 Integrated management of patients with atrial fibrillation

9.1 Definitions and components of integrated management of atrial fibrillation patients

Integrated management of AF patients requires a coordinated and agreed patient-individualized care pathway to deliver optimized treatment (*Figure 10*) by an interdisciplinary team (*Figure 11*). Central to this approach is the patient; treatment options should be discussed, and the management plan agreed in discussion with healthcare professionals. Treatment is subject to change over time with the development of new risk factors, symptoms, disease progression, and the advent of new treatments.

9.2 Multidisciplinary atrial fibrillation teams

Integrated AF management requires a coordinated multidisciplinary team (*Figure 11*) composed according to individual patient needs and local availability of services. Complex patients would benefit from a multidisciplinary team that includes relevant specialists, as well as their primary care physician (for post-discharge care) and their family/carer. Involvement of patient and family/carers is integral to the success of AF management.

9.2.1 Role of healthcare systems and budget constraints

Optimized AF treatment requires a well-structured healthcare system and significant financial resources.[254] Allocation of resources will vary due to differing healthcare system structures and budget constraints in diverse geographies. The significant inequalities in the access to AF management-related resources are documented in the recent ESC Atlas on Cardiovascular Disease.[255] It is important to consider optimizing use of available resources to reduce stroke, improve symptoms, and treat comorbidities.

9.3 Patient involvement and shared decision making

9.3.1 Patient values and preferences

Exploring patient's values, goals, and preferences should be the first step of shared decision making.[256,257] Qualitative research demonstrates recurring discordance between caregivers reporting shared decision making and patients experiencing a paternalistic model,[109,258–261] and a misperception that many prefer not to be involved in decision making, rather deferring to their physician.[259,262–266] For shared decision making,[261] the importance attached by the patient to stroke prevention and rhythm control and the respective risk of death, stroke, and major bleeding, as well as the burden of treatment, should be thoroughly assessed and respected.[257,264,266–268]

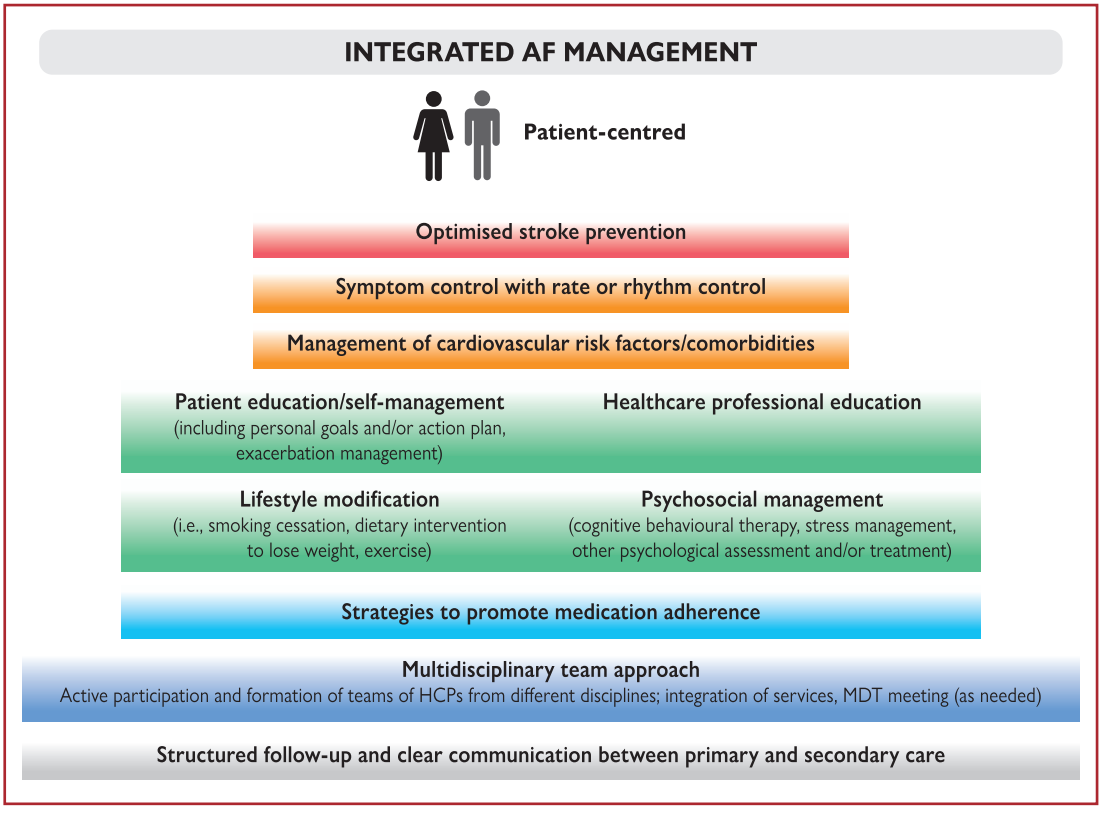


Figure 10 Components of integrated AF management. AF = atrial fibrillation; HCP = healthcare professional; MDT = multidisciplinary team.

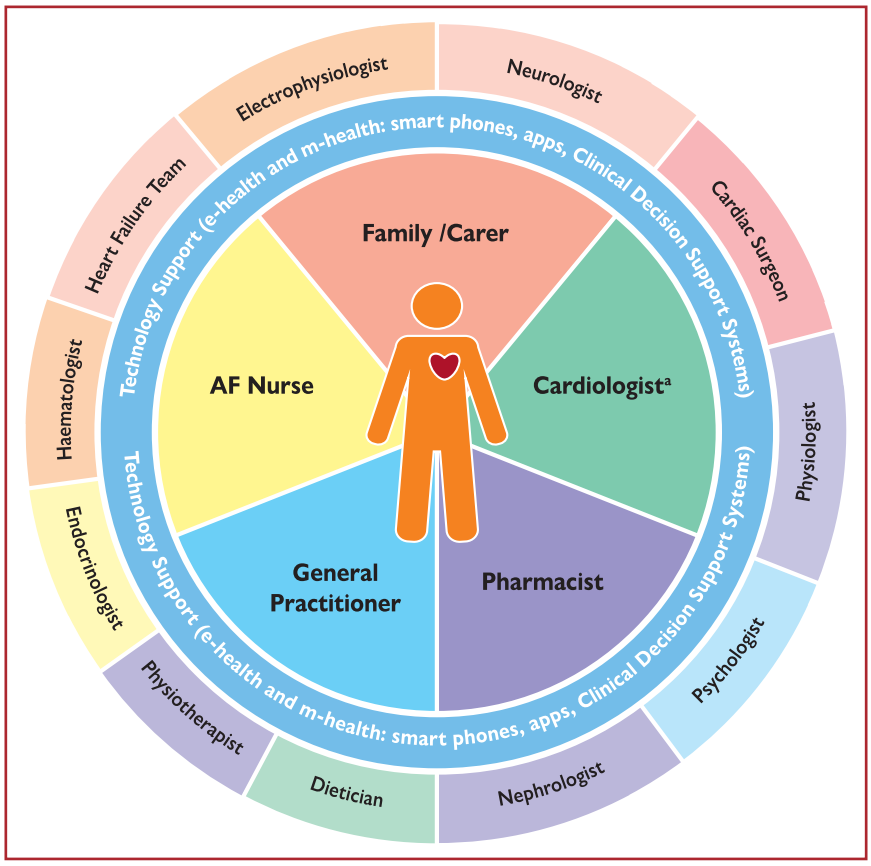


Figure 11 Integrated AF management team (an example). The figure gives an example on the potential composition of AF teams showing a variety of different specialists supporting individual patients as needed. AF = atrial fibrillation. [a]According to local standards, this could be a general cardiologist with special interest in arrhythmias/AF or an electrophysiologist.

9.3.2 Patient education

Patient knowledge about AF and its management is often limited[257,269–272] particularly when first diagnosed, when the majority of treatment decisions are discussed and made.

Information on useful resources to help educate AF patients[273] can be found in the *ESC Textbook of Cardiovascular Medicine*, but education alone is often insufficient to produce and maintain medication adherence and lifestyle modifications.

9.4 Healthcare professional education

A mixed-methods approach has been used when targeting healthcare professionals including individual needs assessment followed by bespoke education and training, whether by smart technology, online resources, or upskilling face-to-face workshops or a combination.[274] The mAFA, integrating clinical-decision support and education for healthcare professionals, has been successfully piloted and subsequently tested in an outcome RCT.[275] Education alone is insufficient to change healthcare-professional behaviour.[276] In the Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF) trial,[277] a multifaceted educational intervention including healthcare-professional education and feedback resulted in a significant increase in the proportion of patients treated with oral anticoagulant (OAC) therapy.

9.5 Adherence to treatment

Factors affecting adherence to treatment can be grouped into *patient-related* (e.g. demographics, comorbidities, cognitive impairment, polypharmacy, treatment side-effects, psychological health, patient understanding of the treatment regimen), *physician-related* (knowledge, awareness of guidelines, expertise, multidisciplinary team approach), and *healthcare system-related* (work-setting, access to treatments, cost) factors.[278]

Ensuring patients are appropriately informed about treatment options, how to adhere to treatment, potential consequences of non-adherence, in addition to managing patient's expectations of treatment goals, are crucial to promote adherence. Regular review by any member of the multidisciplinary team is important to identify non-adherence and implement strategies to improve adherence where appropriate.

9.6 Technology tools supporting atrial fibrillation management

Clinical decision support systems are intelligent systems that digitize and provide evidence-based guidelines, clinical pathways, and algorithms facilitating personalized, timely, and evidence-based treatment.

The MobiGuide project[279] and several applications[280–283] (*Supplementary Tables 5 and 6*) have been used to enhance patient

education, improve communication between patients and healthcare professionals, and encourage active patient involvement. The ESC/CATCH-ME (Characterizing AF by Translating its Causes into Health Modifiers in the Elderly) consortium also has a smartphone/tablet app[281] for AF patients, but this is yet to be tested prospectively. A Cochrane review[284] demonstrated that patient decision-support aids reduce decision conflict.[285–288] Nevertheless, contradictory results[277,289,290] illustrate the need for more carefully designed studies, including assessment of the intervention's effect on clinical events.

9.7 Advantages of integrated management of atrial fibrillation patients

Limited evidence exists on the effectiveness of integrated management of AF. Available intervention studies vary widely in number and content of 'integrated care' employed. Six studies—one cluster RCT,[291] four RCTs,[277,292–295] and one before-and-after study[294]—of integrated AF management have demonstrated mixed findings (*Supplementary Table 7*). Two studies[292,294] and one meta-analysis[296] report significantly lower rates of cardiovascular hospitalization and death with nurse-led, integrated care, whereas others reported no effect of integrated care on these outcomes. One multifaceted study[277] demonstrated improved OAC rates in the intervention group at 12 months. The IMPACT-AF study[277] found no significant difference in the composite efficacy outcome (unplanned emergency department visit or cardiovascular hospitalization) or the primary safety outcome of major bleeding between intervention and usual care.

9.8 Measures (or approaches) for implementation of integrated management

Integrated management of AF requires a change in the current approach to patient care, to focus on moving from a multidisciplinary team to interdisciplinary working, including behaviour change for all AF team members and key stakeholders including patients and their family[297,298] (*Supplementary Figure 3*).

To understand whether integrated AF management has been implemented into clinical practice and had an impact on important outcomes (mortality, stroke, hospitalization, QoL, symptom reduction, etc.), a specific international standard set of outcome measures should be collected (*Supplementary Figure 4*).[299] This would also highlight areas requiring further development.

9.9 Treatment burden

Patient-perceived treatment burden[300] is defined as the workload imposed by healthcare on patients and its effect on patient functioning and well-being apart from specific treatment side-effects.[301,302] It includes everything patients do for their health (drug management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes) and healthcare impact on their social relationships, potentially affecting adherence to treatment,[303,304] QoL, and outcomes (e.g. hospitalization and survival).[305,306] Patient-perceived treatment burden is influenced by their knowledge about disease.[302] Patients with similar treatment regimens may have very different treatment burden,[307] with only a weak agreement between patient's and physicians' treatment burden evaluation, suggesting that the patient's experience is not shared in depth during consultations.[302,308,309]

Treatment burden can be overwhelming for patients with multiple chronic conditions[301] (e.g. those with three chronic conditions would have to take 6 - 12 medications daily, visit a healthcare giver 1.2 - 5.9 times per month, and spend 49.6 - 71.0 h monthly in healthcare-related activities[310]). Treatment burden in AF patients is largely unknown. In a single-centre prospective study, AF patient-perceived total treatment burden was higher than in patients with other chronic conditions (27.6% vs. 24.3%, P =0.011), and 1 in 5 AF patients reported a high treatment burden that could question the sustainability of their treatment. Notably, AF patients attributed the highest proportion of treatment burden to healthcare system-related aspects (e.g. attending appointments etc.) and lifestyle modification requirements. Female sex and younger age were independently significantly associated with a higher treatment burden, whereas non-vitamin K antagonist oral anticoagulants (NOACs) and rhythm control reduced the odds for high treatment burden by >50%.[311]

The discussion of treatment burden should be an integral part of shared, informed treatment decision making, and treatment burden can be assessed using a validated questionnaire.[312]

9.10 Patient-reported outcomes

There is increasing advocacy for including patient-reported outcomes (PROs) as endpoints in clinical trials[313] and their routine collection[314–316] to improve care and assess treatment success from the patient's perspective. Patients' experience of AF and its management is highly subjective; AF management has become increasingly complex, potentially resulting in significant treatment burden and poorer health-related QoL.

Measuring outcomes that are important to patients, in addition to 'hard' clinical endpoints (death, stroke, major bleeding, etc.), can inform AF management. An international consortium of AF patients and healthcare professionals has identified the following PROs as important to measure for AF: health-related QoL, physical and emotional functioning, cognitive function, symptom severity, exercise tolerance, and ability to work (*Supplementary Figure 4*)[299]; PRO measures can be used to assess these factors and the international standard set of AF outcome measures proposes some tools for assessing PROs.[299] Health informatics systems could help capture PRO data. Despite increasing support for the role of PRO measures in healthcare management, few studies and registries report collecting PRO data using validated tools.[313] Implementation of PRO measures in the management of AF patients is addressed in a dedicated expert consensus paper developed in collaboration with patient representatives by the EHRA.[317]

Recommendations about integrated AF management

Recommendations	Class[a]	Level[b]
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that physicians: • Inform the patient about the advantages/limitations and benefit/risks associated with the treatment option(s) being considered; and • Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.	I	C
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I	C
Integrated management with a structured multidisciplinary approach including healthcare professionals, patients, and their family/carers, should be used in all AF patients to improve clinical outcomes.[277,292–294,296,297]	IIa	B

AF = atrial fibrillation; PRO = patient-reported outcome.
[a]Class of recommendation.
[b]Level of evidence.

10 Patient management: the integrated ABC pathway

The simple Atrial fibrillation Better Care (ABC) holistic pathway ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimization[318]) streamlines integrated care of AF patients across all healthcare levels and among different specialties. Compared with usual care, implementation of the ABC pathway has been significantly associated with lower risk of all-cause death, composite outcome of stroke/major bleeding/cardiovascular death and first hospitalization,[319] lower rates of cardiovascular events,[320,321] and lower health-related costs.[322] In the prospective, randomized mAFA-II trial, the composite outcome was significantly lowered with ABC pathway management intervention compared with usual care [1.9% vs. 6.0%; hazard ratio (HR) 0.39; 95% CI 0.22 - 0.67; *P* <0.001].[323]

10. 1 'A' – Anticoagulation/Avoid stroke

This section refers to AF in the absence of severe mitral stenosis or prosthetic heart valves (for AF with concomitant VHD see *section 11.7*).[148]

10.1.1 Stroke risk assessment

Overall, AF increases the risk of stroke five-fold, but this risk is not homogeneous, depending on the presence of specific stroke risk factors/modifiers. Main clinical stroke risk factors have been identified from non-anticoagulated arms of the historical RCTs conducted >20 years ago, notwithstanding that these trials only randomized <10% of patients screened, whereas many common risk factors were not recorded or consistently defined.[324] These data have been supplemented by evidence from large observational cohorts also studying patients who would not have been included in the RCTs. Subsequently, various imaging, blood, and urine biological markers (biomarkers) have been associated with stroke risk (*Table 7*).[324,325] In addition, non-paroxysmal AF is associated with an increase in thrombo-embolism (multivariable adjusted HR 1.38; 95% CI 1.19 - 1.61; *P* <0.001) compared with paroxysmal AF.[156] Notably, many of the risk factors for AF-related complications are also risk factors for incident AF.[33]

Common stroke risk factors are summarized in the clinical risk-factor-based CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female)] score (*Table 8*).[334]

Stroke risk scores have to balance simplicity and practicality against precision.[354–356] As any clinical risk-factor-based score, CHA_2DS_2-VASc performs only modestly in predicting high-risk patients who will sustain thrombo-embolic events, but those identified as low-risk [CHA_2DS_2-VASc 0 (males), or score of 1 (females)] consistently have low ischaemic stroke or mortality rates (<1%/year) and do not need any stroke prevention treatment.

Female sex is an age-dependent stroke risk modifier rather than a risk factor per se.[357,358] Observational studies showed that women with no other risk factors (CHA_2DS_2-VASc score of 1) have a low stroke risk, similar to men with a CHA_2DS_2-VASc score of 0.[359] The simplified CHA_2DS_2-VA score could guide the initial decision about OAC in AF patients, but not considering the sex component would underestimate stroke risk in women with AF.[360,361] In the presence of >1 non-sex stroke risk factor, women with AF consistently have significantly higher stroke risk than men.[353,362]

Many clinical stroke risk factors (e.g. renal impairment, OSA, LA dilatation[291,326,363–365]) are closely related to the CHA_2DS_2-VASc components, and their consideration does not improve its predictive value (the relationship of smoking or obesity to stroke risk in AF is also contentious).[366] Various biomarkers [e.g. troponin, natriuretic peptides, growth differentiation factor (GDF)-15, von Willebrand factor] have shown improved performance of biomarker-based over clinical scores in the assessment of residual stroke risk among anticoagulated AF patients[329,367]; notwithstanding, many of these biomarkers (as well as some clinical risk factors) are predictive of both stroke and bleeding[329] or non-AF and non-cardiovascular conditions, often (non-specifically) reflecting simply a sick heart or patient.

More complex clinical scores [e.g. Global Anticoagulant Registry in the FIELD - Atrial Fibrillation (GARFIELD-AF)][368] and those inclusive of biomarkers [e.g. Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA),[369,370] Intermountain Risk Score,[371] ABC-stroke (Age, Biomarkers, Clinical history)][372] improve stroke risk prediction modestly but statistically significantly. The ABC-stroke risk score that considers age, previous stroke/transient ischaemic attack (TIA), high-sensitivity troponin T (cTnT-hs) and N-terminal (NT)-prohormone

Table 7 Stroke risk factors in patients with AF

Most commonly studied clinical risk factors (a systematic review)[324]	Positive studies/All studies	Other clinical risk factors[325]	Imaging biomarkers[291,326–328]	Blood/urine biomarkers[329–332]
Stroke/TIA/systemic embolism	15/16	Impaired renal function/ CKD	*Echocardiography*	Cardiac troponin T and I Natriuretic peptides Cystatin C Proteinuria CrCl/eGFR CRP IL-6 GDF-15 von Willebrand factor D-dimer
Hypertension	11/20	OSA	LA dilatation Spontaneous contrast or thrombus in LA Low LAA velocities Complex aortic plaque	
Ageing (per decade)	9/13	HCM		
Structural heart disease	9/13	Amyloidosis in degenerative cerebral and heart diseases		
Diabetes mellitus	9/14	Hyperlipidaemia		
Vascular disease	6/17	Smoking	*Cerebral imaging*	
CHF/LV dysfunction	7/18	Metabolic syndrome[333]	Small-vessel disease	
Sex category (female)	8/22	Malignancy		

CHF = congestive heart failure; CKD = chronic kidney disease; CrCl = creatinine clearance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; GDF-15 = growth differentiation factor-15; IL-6 = interleukin 6; LA = left atrium; LAA = left atrial appendage; LV = left ventricular; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.

B-type natriuretic peptide has been validated in the cohorts of landmark NOAC trials.[373–375] A biomarker score-guided treatment strategy to reduce stroke and mortality in AF patients is being evaluated in an ongoing RCT (the ABC-AF Study, NCT03753490).

Whereas the routine use of biomarker-based risk scores currently would not substantially add to initial stroke prevention treatment decisions in patients already qualifying for treatment based on the CHA_2DS_2-VASc score (and a limited practicality would be accompanied by increased healthcare costs),[355,376,377] biomarkers could further refine stroke risk differentiation among patients initially classified as low risk and those with a single non-sex CHA_2DS_2-VASc risk factor.[378]

Studies of the CHA_2DS_2-VASc score report a broad range of stroke rates depending on study setting (community vs. hospital), methodology (e.g. excluding patients subsequently treated with OAC would bias stroke rates towards lower levels), ethnicity, and prevalence of specific stroke risk factors in the study population (different risk factors carry different weight, and age thresholds for initiating NOACs may even differ for patients with a different single non-sex stroke risk factor, as follows: age 35 years for HF, 50 years for hypertension or diabetes, and 55 years for vascular disease).[379,380] No RCT has specifically addressed the need for OAC in patients with a single non-sex CHA_2DS_2-VASc risk factor (to obtain high event rates and timely complete the study, anticoagulation trials have preferentially included high-risk patients), but an overview of subgroup analyses and observational data suggests that OAC use in such patients confers a positive net clinical benefit when balancing the reduction in stroke against the potential for harm with serious bleeding.[339,381]

For many risk factors (e.g. age), stroke risk is a continuum rather than an artificial low-, moderate-, or high-risk category. Risk factors are dynamic and, given the elderly AF population with multiple (often changing) comorbidities, stroke risk needs to be re-evaluated at each clinical review. Recent studies have shown that patients with a change in their risk profile are more likely to sustain strokes.[382,383] Many initially low-risk patients (>15%) would have ≥1 non-sex CHA_2DS_2-VASc risk factor at 1 year after incident AF,[384–386] and 90% of new comorbidities were evident at 4.4 months after AF was diagnosed.[387]

A Patient-Centred Outcomes Research Institute (PCORI)-commissioned systematic review of 61 studies compared diagnostic accuracy and impact on clinical decision making of available clinical and imaging tools and associated risk factors for predicting thrombo-embolic and bleeding risk in AF patients.[388] The authors concluded that the $CHADS_2$ (CHF history, Hypertension history, Age ≥75 y, Diabetes mellitus history, Stroke or TIA symptoms previously), CHA_2DS_2-VASc, and ABC risk scores have the best evidence for predicting thrombo-embolic risk (moderate strength of evidence for limited prediction ability of each score).

10.1.2 Bleeding risk assessment

When initiating antithrombotic therapy, potential risk for bleeding also needs to be assessed. Non-modifiable and partially modifiable bleeding risks (*Table 9*) are important drivers of bleeding events in synergy with modifiable factors.[389] Notably, a history of falls is not an independent predictor of bleeding on OAC (a modelling study estimated that a patient would need to fall 295 times per year for the benefits of ischaemic stroke reduction with OAC to be outweighed by the potential for serious bleeding).[390]

Modifiable and non-modifiable bleeding risk factors have been used to formulate various bleeding risk scores,[368,391–395] generally with a modest predictive ability for bleeding events.[396,397] Studies comparing specific bleeding risk scores provided conflicting findings.[393,394,398] Various biomarkers have been proposed as bleeding risk predictors, but many have been studied in anticoagulated trial cohorts (while bleeding risk assessment is needed at all parts of the patient pathway—when initially not using OAC, if taking aspirin, and, subsequently, on OAC). Additionally, biomarkers are non-specifically predictive of stroke, death, HF, etc.[399,400] or even non-cardiovascular conditions (e.g. glaucoma),[401] and the availability of some biomarkers is limited in routine clinical practice.

The biomarker-based ABC-bleeding risk score [Age, Biomarkers (GDF-15, cTnT-hs, haemoglobin) and Clinical history (prior

Table 8 CHA_2DS_2-VASc score[334]

CHA_2DS_2-VASc score Risk factors and definitions		Points awarded	Comment
C	**Congestive heart failure** Clinical HF, or objective evidence of moderate to severe LV dysfunction, or HCM	1	Recent decompensated HF irrespective of LVEF (thus incorporating HFrEF or HFpEF), or the presence (even if asymptomatic) of moderate-severe LV systolic impairment on cardiac imaging[335]; HCM confers a high stroke risk[336] and OAC is beneficial for stroke reduction.[337]
H	**Hypertension** or on antihypertensive therapy	1	History of hypertension may result in vascular changes that predispose to stroke, and a well-controlled BP today may not be well-controlled over time.[324] Uncontrolled BP - the optimal BP target associated with the lowest risk of ischaemic stroke, death, and other cardiovascular outcomes is 120 - 129/<80 mmHg.[338]
A	**Age 75 years or older**	2	Age is a powerful driver of stroke risk, and most population cohorts show that the risk rises from age 65 years upwards.[339] Age-related risk is a continuum, but for reasons of simplicity and practicality, 1 point is given for age 65 - 74 years and 2 points for age ≥75 years.
D	**Diabetes mellitus** Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL (7 mmol/L)	1	Diabetes mellitus is a well-established risk factor for stroke, and more recently stroke risk has been related to duration of diabetes mellitus (the longer the duration of diabetes mellitus, the higher the risk of thromboembolism[340]) and presence of diabetic target organ damage, e.g. retinopathy.[341] Both type 1 and type 2 diabetes mellitus confer broadly similar thromboembolic risk in AF, although the risk may be slightly higher in patients aged <65 years with type 2 diabetes mellitus compared to patients with type 1 diabetes mellitus.[342]
S	**Stroke**Previous stroke, TIA, or thromboembolism	2	Previous stroke, systemic embolism, or TIA confers a particularly high risk of ischaemic stroke, hence weighted 2 points. Although excluded from RCTs, AF patients with ICH (including haemorrhagic stroke) are at very high risk of subsequent ischaemic stroke, and recent observational studies suggest that such patients would benefit from oral anticoagulation.[343–345]
V	**Vascular disease** Angiographically significant CAD, previous myocardial infarction, PAD, or aortic plaque	1	Vascular disease (PAD or myocardial infarction) confers a 17 - 22% excess risk, particularly in Asian patients.[346–348] Angiographically significant CAD is also an independent risk factor for ischaemic stroke among AF patients (adjusted incidence rate ratio 1.29, 95% CI 1.08 - 1.53).[349] Complex aortic plaque on the descending aorta, as an indicator of significant vascular disease, is also a strong predictor of ischaemic stroke.[350]
A	**Age 65 – 74 years**	1	See above. Recent data from Asia suggest that the risk of stroke may rise from age 50 - 55 years upwards and that a modified CHA_2DS_2-VASc score may be used in Asian patients.[351,352]
Sc	**Sex category (female)**	1	A stroke risk modifier rather than a risk factor.[353]
Maximum score		**9**	

AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); CI = confidence interval; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICH = intracranial haemorrhage; LV = left ventricular; LVEF = left ventricular ejection fraction; OAC = oral anticoagulant; PAD = peripheral artery disease; RCT = randomized controlled trial; TIA = transient ischaemic attack.

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years	Extreme frailty ± excessive risk of falls[a]	Hypertension/elevated SBP	GDF-15
Previous major bleeding	Anaemia	Concomitant antiplatelet/NSAID	Cystatin C/CKD-EPI
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intake	cTnT-hs
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OAC	von Willebrand factor (+ other coagulation markers)
Malignancy	VKA management strategy[b]	Hazardous hobbies/occupations	
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with heparin	
Previous stroke, small-vessel disease, etc.		INR control (target 2.0 - 3.0), target TTR >70%[c]	
Diabetes mellitus		Appropriate choice of OAC and correct dosing[d]	
Cognitive impairment/dementia			

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

[b]Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioural interventions.

[c]For patients receiving VKA treatment.

[d]Dose adaptation based on patient's age, body weight, and serum creatinine level.

Table 10 Clinical risk factors in the HAS-BLED score[395]

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 μmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR[b]** TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SBP = systolic blood pressure; INR = international normalized ratio; NSAID = Non-steroidal anti-inflammatory drug; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Haemorrhagic stroke would also score 1 point under the 'B' criterion.
[b]Only relevant if patient receiving a VKA.
[c]Alcohol excess or abuse refers to a high intake (e.g. >14 units per week), where the clinician assesses there would be an impact on health or bleeding risk.

bleeding)][375,402] reportedly outperformed clinical scores, but in another study there was no long-term advantage of ABC-bleeding over HAS-BLED score (*Table 10*), whereas HAS-BLED was better in identifying patients at low risk of bleeding (HAS-BLED 0 - 2).[403] In the PCORI-commissioned systematic review,[388] encompassing 38 studies of bleeding risk prediction, the HAS-BLED score had the best evidence for predicting bleeding risk (moderate strength of evidence), consistent with other systematic reviews and meta-analyses comparing bleeding risk prediction approaches.[404–406]

A high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients. However, the formal assessment of bleeding risk informs management of patients taking OAC, focusing attention on modifiable bleeding risk factors that should be managed and (re)assessed at every patient contact, and identifying high-risk patients with non-modifiable bleeding risk factors who should be reviewed earlier (for instance in 4 weeks rather than 4 - 6 months) and more frequently.[389,407] Identification of 'high bleeding risk' patients is also needed when determining the antithrombotic strategy in specific AF patient groups, such as those undergoing percutaneous coronary intervention (PCI).

Overall, bleeding risk assessment based solely on modifiable bleeding risk factors is an inferior strategy compared with formal bleeding risk assessment using a bleeding risk score,[408–410] thus also considering the interaction between modifiable and non-modifiable bleeding risk factors. Bleeding risk is dynamic, and attention to the change in bleeding risk profile is a stronger predictor of major bleeding events compared with simply relying on baseline bleeding risk. In a recent study, there was a 3.5-fold higher risk of major bleeding in the first 3 months amongst patients who had a change in their bleeding risk profile.[389]

In the mAFA-II trial, prospective dynamic monitoring and reassessment using the HAS-BLED score (together with holistic App-based management) was associated with fewer major bleeding events, mitigated modifiable bleeding risk factors, and increased OAC uptake; in contrast, bleeding rates were higher and OAC use overall decreased by 25% in the 'usual care' arm when comparing baseline with 12 months.[411]

10.1.3 Absolute contraindications to oral anticoagulants

The few absolute contraindications to OAC include active serious bleeding (where the source should be identified and treated), associated comorbidities (e.g. severe thrombocytopenia <50 platelets/μL, severe anaemia under investigation, etc.), or a recent high-risk bleeding event such as intracranial haemorrhage (ICH). Non-drug options may be considered in such cases (*section 11.4.3*).

10.1.4 Stroke prevention therapies

10.1.4.1 Vitamin K antagonists

Compared with control or placebo, vitamin K antagonist (VKA) therapy (mostly warfarin) reduces stroke risk by 64% and mortality by 26%,[412] and is still used in many AF patients worldwide. VKAs are currently the only treatment with established safety in AF patients with rheumatic mitral valve disease and/or an artificial heart valve.

The use of VKAs is limited by the narrow therapeutic interval, necessitating frequent international normalized ratio (INR) monitoring and dose adjustments.[413] At adequate time in therapeutic range [(TTR) >70%], VKAs are effective and relatively safe drugs. Quality of VKA management (quantified using the TTR based on the Rosendaal method, or the percentage of INRs in range) correlates with haemorrhagic and thrombo-

embolic rates.[414] At high TTR values, the efficacy of VKAs in stroke prevention may be similar to NOACs, whereas the relative safety benefit with NOACs is less affected by TTR, with consistently lower serious bleeding rates (e.g. ICH) seen with NOACs compared with warfarin, notwithstanding that the absolute difference is small.[415,416]

Numerous factors (including genetics, concomitant drugs, etc.) influence the intensity of VKA anticoagulant effect; the more common ones have been used to derive and validate the SAMe-TT_2R_2 {Sex [female], Age [<60 years], Medical history of ≥2 comorbidities [hypertension, diabetes mellitus, CAD/myocardial infarction, peripheral artery disease (PAD), HF, previous stroke, pulmonary disease, and hepatic or renal disease], Treatment [interacting drugs, e.g. amiodarone], Tobacco use, Race [non-Caucasian]} score,[417] which can help to identify patients who are less likely to achieve a good TTR on VKA therapy (score >2) and would do better with a NOAC. If such patients with SAMe-TT_2R_2>2 are prescribed a VKA, greater efforts to improve TTR, such as more intense regular reviews, education/counselling, and frequent INR monitoring are needed or, more conveniently, the use of a NOAC should be reconsidered.[418]

10.1.4.2 Non-vitamin K antagonist oral anticoagulants

In four pivotal RCTs, apixaban, dabigatran, edoxaban, and rivaroxaban have shown non-inferiority to warfarin in the prevention of stroke/systemic embolism.[419–422] In a meta-analysis of these RCTs, NOACs were associated with a 19% significant stroke/systemic embolism risk reduction, a 51% reduction in haemorrhagic stroke,[423] and similar ischaemic stroke risk reduction compared with VKAs, but NOACs were associated with a significant 10% reduction in all-cause mortality (*Supplementary Table 8*). There was a non-significant 14% reduction in major bleeding risk, significant 52% reduction in ICH, and 25% increase in gastrointestinal bleeding with NOACs vs. warfarin.[423]

The major bleeding relative risk reduction with NOACs was significantly greater when INR control was poor (i.e. centre-based TTR<66%). A meta-analysis of the five NOAC trials [RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy), ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), J-ROCKET AF, ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), and ENGAGE AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48)] showed that, compared with warfarin, standard-dose NOACs were more effective and safer in Asians than in non-Asians.[424] In the AVERROES [Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment] trial of AF patients who refused or were deemed ineligible for VKA therapy, apixaban 5 mg b.i.d. (twice a day) significantly reduced the risk of stroke/systemic embolism with no significant difference in major bleeding or ICH compared with aspirin.[425]

Post-marketing observational data on the effectiveness and safety of dabigatran,[426,427] rivaroxaban,[428,429] apixaban,[430] and edoxaban[431] vs. warfarin show general consistency with the respective RCT. Given the compelling evidence about NOACs, AF patients should be informed of this treatment option.

Persistence to NOAC therapy is generally higher than to VKAs, being facilitated by a better pharmacokinetic profile of NOACs[432] (*Supplementary Table 9*) and favourable safety and efficacy, especially amongst vulnerable patients including the elderly, those with renal dysfunction or previous stroke, and so on.[433] Whereas patients with end-stage renal dysfunction were excluded from the pivotal RCTs, reduced dose regimens of rivaroxaban, edoxaban, and apixaban are feasible options for severe CKD [creatinine clearance (CrCl) 15 - 30 mL/min using the Cockcroft-Gault equation].[434,435] Considering that inappropriate dose reductions are frequent in clinical practice,[436] thus increasing the risks of stroke/systemic embolism, hospitalization, and death, but without decreasing bleeding risk,[437] NOAC therapy should be optimized based on the efficacy and safety profile of each NOAC in different patient subgroups (*Table 11*).

10.1.4.3 Other antithrombotic drugs

In the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was less effective than warfarin for prevention of stroke, systemic embolism, myocardial infarction, and vascular death (the annual risk of events was 5.6% vs. 3.9%, P =0.0003), with a similar rate of major bleeding.[438] In the ACTIVE-A trial, patients unsuitable for anticoagulation had a lower rate of thrombo-embolic complications when clopidogrel was added to aspirin compared with aspirin alone, but with a significant increase in major bleeding.[439] Aspirin monotherapy was ineffective for stroke prevention compared with no antithrombotic treatment and was

Table 11 Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: • Age ≥80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: • Age ≥80 years, • Body weight ≤60 kg, or • Serum creatinine ≥1.5 mg/dL (133 µmol/L)	If any of the following: • CrCl 15 - 50 mL/min, • Body weight ≤60 kg, • Concomitant use of dronedarone, ciclosporine, erythromycin, or ketoconazole

b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; o.d. = *omni die* (once daily).

associated with a higher risk of ischaemic stroke in elderly patients.[440]

Overall, antiplatelet monotherapy is ineffective for stroke prevention and is potentially harmful, (especially amongst elderly AF patients),[441,442] whereas DAPT is associated with a bleeding risk similar to OAC therapy. Hence, antiplatelet therapy should not be used for stroke prevention in AF patients.

10.1.4.4 Combination therapy with oral anticoagulant and antiplatelet drugs

The use of antiplatelet therapy remains common in clinical practice, often in patients without an indication (e.g. PAD, CAD, or cerebrovascular disease) beyond AF.[443] There is limited evidence to support the combination therapy solely for stroke prevention in AF, with no effect on reductions in stroke, myocardial infarction, or death, but with a substantial increase in the risk of major bleeding and ICH.[441,442]

10.1.4.5 Left atrial appendage occlusion and exclusion

10.1.4.5.1 Left atrial appendage occlusion devices. Only the Watchman device has been compared with VKA therapy in RCTs [the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy)],[444–446] where LAA occlusion was non-inferior to VKA stroke prevention treatment in AF patients with moderate stroke risk, with a possibility of lower bleeding rates on longer follow-up.[447] The LAA occlusion may also reduce stroke risk in patients with contraindications to OAC.[448,449]

A large European registry reported a high implantation success rate (98%), with an acceptable procedure-related complication rate of 4% at 30 days.[450] Nevertheless, the implantation procedure can cause serious complications (higher event rates have been reported in real-world analyses compared with industry-sponsored studies, possibly identifying some reporting bias) and device-related thrombosis may not be a benign finding.[451–454] Antithrombotic management after LAA occlusion has never been evaluated in a randomized manner and is based on historical studies, at least including aspirin (*Table 12*). For patients who do not tolerate any antiplatelet therapy, either an epicardial catheter approach (e.g. Lariat system) or thoracoscopic clipping of the LAA may be an option.[455,456]

Notably, the non-inferiority of LAA occlusion to VKA treatment was mostly driven by the prevention of haemorrhagic stroke, with a trend for more ischaemic strokes. The limitations of LAA occlusion as a strategy to reduce the risk of stroke associated with AF also include the consideration that AF acts as a risk marker of stroke. Withholding OAC after LAA occlusion is likely to result in undertreating the overall risk of stroke related to atrial cardiomyopathy.

10.1.4.5.2 Surgical left atrial appendage occlusion or exclusion. Multiple observational studies indicate the feasibility and safety of surgical LAA occlusion/exclusion, but only limited controlled trial data are available.[457–459] Residual LAA flow or incomplete LAA occlusion may be associated with an increased risk of stroke.[460] In most studies, LAA occlusion/exclusion was performed during other open heart surgery, and in more recent years in combination with surgical ablation of AF[459,461] or as an isolated thoracoscopic procedure. A large RCT in patients with an associated cardiac surgical procedure is ongoing.[462]

The most common justification for LAA occlusion/exclusion in clinical practice is a perceived high bleeding risk or, less often, contraindications for OAC.[450] However, LAA occluders have not been randomly tested in such populations. Most patients who some years ago would be considered unsuitable for OAC therapy with VKA now seem to do relatively well on NOAC,[433,463,464] and LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with surgical LAA occlusion/exclusion. Long-term aspirin is a common strategy in these patients,[465] and one may question whether a NOAC would not be a better strategy if aspirin is tolerated. There is the need for adequately powered trials to define the best indications of LAA occlusion/exclusion compared with NOAC therapy in patients with relative or absolute contraindications for anticoagulation, in those suffering from an ischaemic stroke on anticoagulant therapy, and for assessment of the appropriate antithrombotic therapy after LAA occlusion.

Table 12 Antithrombotic therapy after left atrial appendage occlusion

Device/patient	Aspirin	OAC	Clopidogrel	Comments
Watchman/low bleeding risk	75 - 325 mg/day indefinitely	Start warfarin after procedure (target INR 2 - 3) until 45 days or continue until adequate LAA sealing is confirmed[a] by TOE. NOAC is a possible alternative	Start 75 mg/day when OAC stopped, continue until 6 months after the procedure	Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)
Watchman/high bleeding risk	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing[a]	Clopidogrel often given for shorter time in very high-risk situations
ACP/Amulet	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing[a]	Clopidogrel may replace long-term aspirin if better tolerated

ACP = Amplatzer™ Cardiac Plug; INR = international normalized ratio; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant ; TOE = transoesophageal echocardiography.
Note: Load aspirin or clopidogrel before procedure if untreated. Heparin with activated clotting time >250 seconds before or immediately after trans-septal punctures for all patients, followed by LMWH when warfarin needed.
[a]Less than 5 mm leak.

10.1.4.6 Long-term oral anticoagulation per atrial fibrillation burden

Although the risk of ischaemic stroke/systemic embolism is higher with non-paroxysmal vs. paroxysmal AF, and AF progression is associated with an excess of adverse outcomes,[169,466] the clinically determined temporal pattern of AF should not affect the decision regarding long-term OAC, which is driven by the presence of stroke risk factors.[156] Management of patients with AHRE/subclinical AF is reviewed in *section 16*. Stroke risk in AHRE patients may be lower than in patients with diagnosed AF,[467] and strokes often occur without a clear temporal relationship with AHRE/subclinical AF,[179,226] underscoring its role as a risk marker rather than a stroke risk factor.[4,172] Whether AHRE and subclinical AF have the same therapeutic requirements as clinical AF[7] is presently unclear, and the net clinical benefit of OAC for AHRE/subclinical AF>24 h is currently being studied in several RCTs.[4]

Notably, patients with subclinical AF/AHRE may develop atrial tachyarrhythmias lasting more than 24 h[468] or clinical AF; hence careful monitoring of these patients is recommended, even considering remote monitoring, especially with longer AHRE and higher risk profile.[469] Given the dynamic nature of AF as well as stroke risk, a recorded duration in one monitoring period would not necessarily be the same in the next.

10.1.4.7 Long-term oral anticoagulation per symptom control strategy

Symptom control focuses on patient-centred and symptom-directed approaches to rate or rhythm control. Again, symptom control strategy should not affect the decision regarding long-term OAC, which is driven by the presence of stroke risk factors, and not the estimated success in maintaining sinus rhythm.

10.1.5 Management of anticoagulation-related bleeding risk

10.1.5.1 Strategies to minimize the risk of bleeding

Ensuring good quality of VKA treatment (TTR>70%) and selecting the appropriate dose of a NOAC (as per the dose reduction criteria specified on the respective drug label) are important considerations to minimize bleeding risk. As discussed in *section 10.1.2*, attention to modifiable bleeding risk factors should be made at every patient contact, and formal bleeding risk assessment is needed to help identify high-risk patients who should be followed up or reviewed earlier (e.g. 4 weeks rather than 4 - 6 months).[407] Concomitant regular administration of antiplatelet drugs or non-steroidal anti-inflammatory drug (NSAID) should be avoided in anticoagulated patients. Bleeding risk is dynamic, and attention to the change in bleeding risk profile is a stronger predictor of major bleeding events, especially in the first 3 months.[389]

10.1.5.2 High-risk groups

Certain high-risk AF populations have been under-represented in RCTs, including the extreme elderly (≥90 years), those with cognitive impairment/dementia, recent bleeding or previous ICH, end-stage renal failure, liver impairment, cancer, and so on. Observational data suggest that such patients are at high risk for ischaemic stroke and death, and many would benefit from OAC.

Patients with liver function abnormalities may be at higher risk of bleeding on VKA, possibly less so on NOACs. Observational data in cirrhotic patients suggest that ischaemic stroke reduction may outweigh bleeding risk.[470–472]

In patients with a recent bleeding event, attention should be directed towards addressing the predisposing pathology (e.g. bleeding ulcer or polyp in a patient with gastrointestinal bleeding), and the reintroduction of OAC as soon as feasible, as part of a multidisciplinary team decision. Consideration should be made for drugs such as apixaban or dabigatran 110 mg b.i.d., which are not associated with an excess of gastrointestinal bleeding compared with warfarin. Where OAC is not reintroduced, there is a higher risk of stroke and death compared with restarting OAC, although the risk of re-bleeding may be higher.[473] Similarly, thromboprophylaxis in cancer may require a multidisciplinary team decision balancing stroke reduction against serious bleeding, which may be dependent on cancer type, site(s), staging, anti-cancer therapy and so on.

Thromboprophylaxis in specific high-risk groups is discussed in detail throughout *section 11*.

10.1.6 Decision making to avoid stroke

In observational population cohorts, both stroke and death are relevant endpoints, as some deaths could be due to fatal strokes (given that endpoints are not adjudicated in population cohorts, and cerebral imaging or post-mortems are not mandated). As OAC significantly reduces stroke (by 64%) and all-cause mortality (by 26%) compared with control or placebo,[412] the endpoints of stroke and/or mortality are relevant in relation to decision making for thromboprophylaxis.

The threshold for initiating OAC for stroke prevention, balancing ischaemic stroke reduction against the risk of ICH and associated QoL, has been estimated to be 1.7%/year for warfarin and 0.9%/year for a NOAC (dabigatran data were used for the modelling analysis).[474] The threshold for warfarin may be even lower, if good-quality anticoagulation control is achieved, with average TTR>70%.[475]

Given the limitations of clinical risk scores, the dynamic nature of stroke risk, the greater risk of stroke and death among AF patients with ≥1 non-sex stroke risk factor, and the positive net clinical benefit of OAC among such patients, we recommend a risk-factor–based approach to stroke prevention rather than undue focus on (artificially defined) 'high-risk' patients. As the default is to offer stroke prevention unless the patient is low risk, the CHA_2DS_2-VASc score should be applied in a reductionist manner, to decide on OAC or not.[476]

Thus, the first step in decision making ('A' Anticoagulation/Avoid stroke) is to identify low-risk patients who do not need antithrombotic therapy. Step 2 is to offer stroke prevention (i.e. OAC) to those with ≥1 non-sex stroke risk factors (the strength of evidence differs, with multiple clinical trials for patients with ≥2 stroke risk factors, and subgroups from trials/observational data on patients with 1 non-sex stroke risk factor). Step 3 is the choice of OAC—a NOAC (given their relative effectiveness, safety and convenience, these drugs are generally first choice as OAC for stroke prevention in AF) or VKA (with good TTR at >70%). This 'AF 3-step' patient pathway[182,477] for stroke risk stratification and treatment decision making is shown in *Figure 12*.

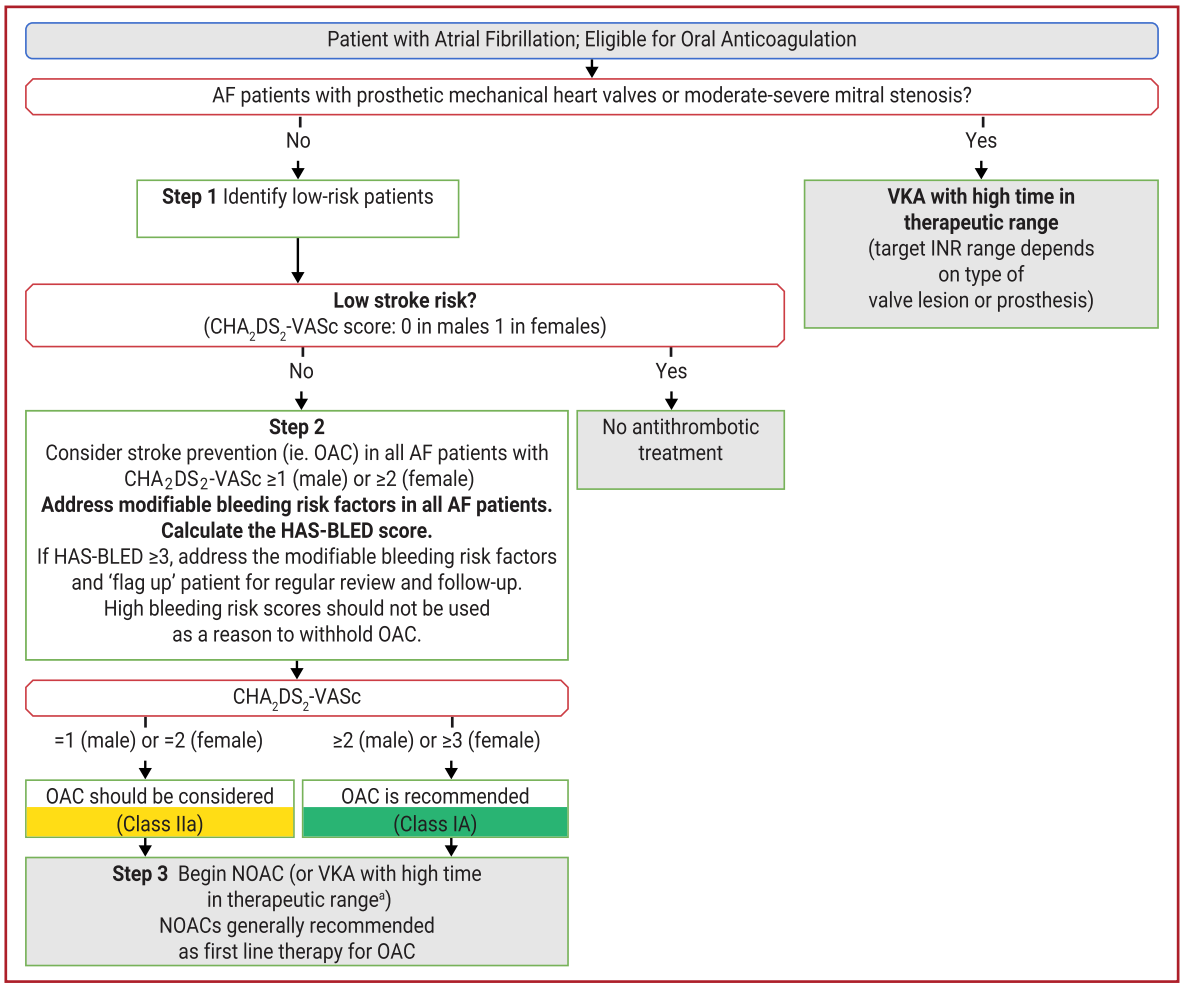


Figure 12 'A' - Anticoagulation/Avoid stroke: The 'AF 3-step' pathway. AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; SAMe-TT_2R_2 = Sex (female), Age (<60 years), Medical history, Treatment (interacting drug(s)), Tobacco use, Race (non-Caucasian) (score); TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]If a VKA being considered, calculate SAMe-TT_2R_2 score: if score 0−2, may consider VKA treatment (e.g. warfarin) or NOAC; if score >2, should arrange regular review/frequent INR checks/ counselling for VKA users to help good anticoagulation control, or reconsider the use of NOAC instead; TTR ideally >70%.

Recommendations for the prevention of thrombo-embolic events in AF

Recommendations	Class[a]	Level[b]
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).[423,424]	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA_2DS_2-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA_2DS_2-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy.[334,388]	I	A
OAC is recommended for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[412]	I	A
OAC should be considered for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences.[338,378,380]	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.[388,395,404,406]	I	B

Continued

For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥3) for early and more frequent clinical review and follow-up.[388,395,404,406]	IIa	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.[c389,478,479]	I	B
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation.[385–387]	IIa	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR≥70%.[414]	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), recommended options are: • Switching to a NOAC but ensuring good adherence and persistence with therapy[415,416]; or	I	B
• Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).[480]	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.[440,441,480,481]	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.[160]	III	B
Recommendations for occlusion or exclusion of the LAA		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).[448,449,481,482]	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.[459,483]	IIb	C

AF = atrial fibrillation; BP = blood pressure; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant ; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Including uncontrolled BP; labile INRs (in a patient taking VKA); alcohol excess; concomitant use of NSAIDs or aspirin in an anticoagulated patient; bleeding tendency or predisposition (e.g. treat gastric ulcer, optimize renal or liver function, etc.).

10.2 'B' – Better symptom control

10.2.1 Rate control

Rate control is an integral part of AF management, and is often sufficient to improve AF-related symptoms. Very little robust evidence exists to inform the best type and intensity of rate control treatment.[484–486]

10.2.1.1 Target/optimal ventricular rate range

The optimal heart-rate target in AF patients is unclear. In the RACE (Race Control Efficacy in Permanent Atrial Fibrillation) II RCT of permanent AF patients, there was no difference in a composite of clinical events, New York Heart Association (NYHA) class, or hospitalizations between the strict [target heart rate <80 beats per minute (bpm) at rest and <110 bpm during moderate exercise] and lenient (heart-rate target <110 bpm) arm,[487,488] similar to an analysis from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and RACE trials.[489] Therefore, lenient rate control is an acceptable initial approach, regardless of HF status (with the exception of tachycardia-induced cardiomyopathy), unless symptoms call for stricter rate control (*Figure 13*).

10.2.1.2 Drugs

Pharmacological rate control can be achieved with beta-blockers, digoxin, diltiazem, and verapamil, or combination therapy (*Table 13*). Some antiarrhythmic drugs (AADs) also have rate-limiting properties (e.g. amiodarone, dronedarone, sotalol) but generally they should be used only for rhythm control. The choice of rate control drugs depends on symptoms, comorbidities, and potential side-effects (*Table 13*).

Beta-blockers are often first-line rate-controlling agents, largely based on better acute rate control. Interestingly, the prognostic benefit of beta-blockers seen in HF with reduced ejection fraction (HFrEF) patients with sinus rhythm has been questioned in patients with AF.[491]

Non-dihydropyridine calcium channel blockers (NDCC) verapamil and diltiazem provide reasonable rate control[492] and can improve AF-related symptoms[486] compared with beta-blockers. In one small trial of patients with preserved LVEF, NDCC preserved exercise capacity and reduced B-type natriuretic peptide.[493,494]

Digoxin and digitoxin are not effective in patients with increased sympathetic drive. Observational studies have associated digoxin use with excess mortality in AF patients.[495–497] This finding was likely due to selection and prescription biases rather than harm caused by digoxin,[498–501] particularly as digoxin is commonly prescribed to sicker patients.[502] Lower doses of digoxin may be associated with

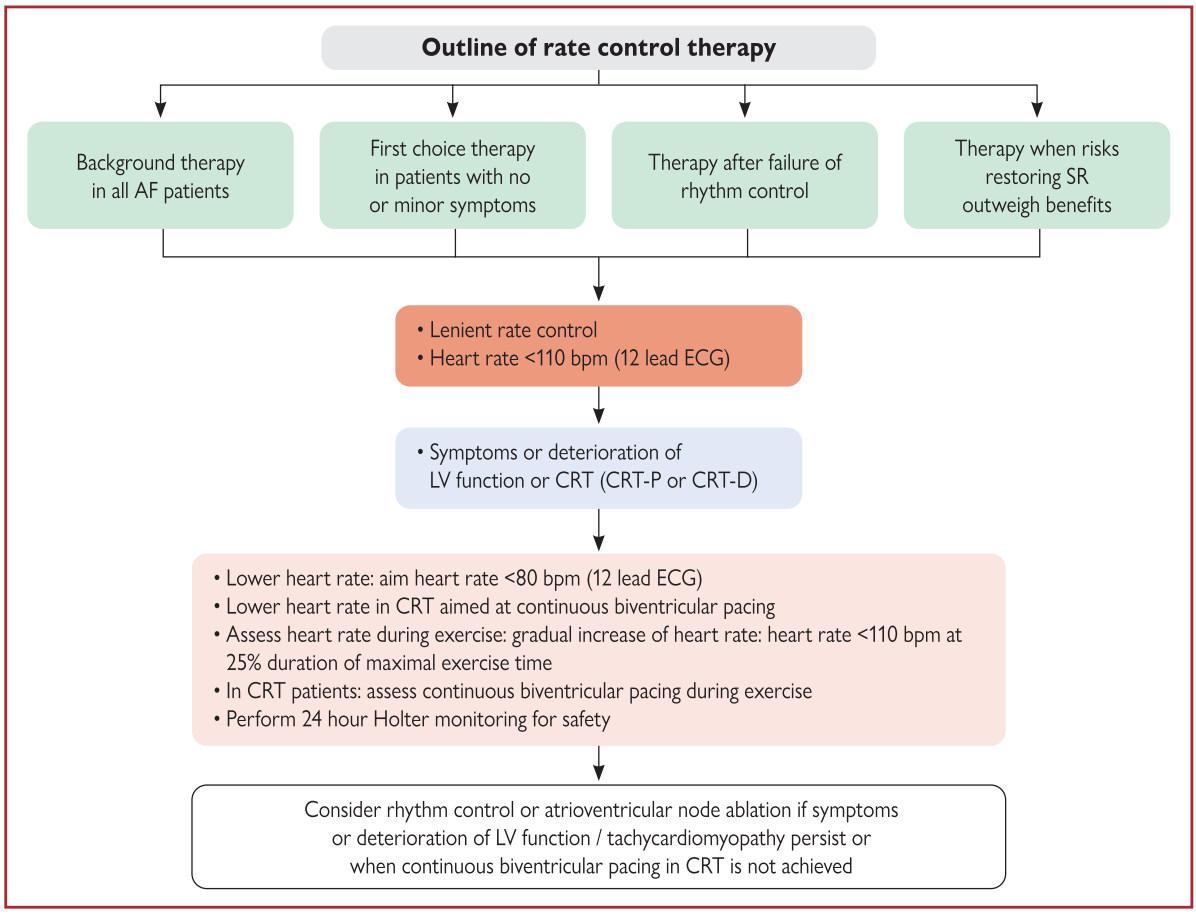


Figure 13 Outline of rate control therapy.[490] AF = atrial fibrillation; AVN = atrioventricular node; bpm = beats per minute; BV = biventricular; CRT = cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; ECG = electrocardiogram; LV = left ventricular; SR = sinus rhythm.

better prognosis.[502] An ongoing RCT is addressing digitoxin use in patients with HFrEF.[503]

Amiodarone can be useful as a last resort when heart rate cannot be controlled with combination therapy in patients who do not qualify for non-pharmacological rate control, i.e. atrioventricular node ablation and pacing, notwithstanding the extracardiac adverse effects of the drug[504] (*Table 13*).

10.2.1.3 Acute rate control

In acute settings, physicians should always evaluate underlying causes, such as infection or anaemia. Beta-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone.[507–511] The choice of drug (*Table 13* and *Figure 14*) and target heart rate will depend on the patient characteristics, symptoms, LVEF value, and haemodynamics, but a lenient initial rate control approach seems acceptable (*Figure 13*). Combination therapy may be required. In patients with HFrEF, beta-blockers, digitalis, or their combination should be used.[512,513] In critically ill patients and those with severely impaired LV systolic function, i.v. amiodarone can be used.[504,514,515] In unstable patients, urgent cardioversion should be considered (*section 11.1*).

10.2.1.4 Atrioventricular node ablation and pacing

Ablation of the atrioventricular node and pacemaker implantation can control ventricular rate when medication fails. The procedure is relatively simple and has a low complication rate and low long-term mortality risk,[516,517] especially when the pacemaker is implanted a few weeks before the atrioventricular node ablation and the initial pacing rate after ablation is set at 70–90 bpm.[518,519] The procedure does not worsen LV function[520] and may even improve LVEF in selected patients.[521–523] Most studies have included older patients with limited life expectancy. For younger patients, ablation of the atrioventricular node should only be considered if there is urgent need for rate control and all other pharmacological and non-pharmacological treatment options have been carefully considered. The choice of pacing therapy (right ventricular or biventricular pacing) will depend on patient characteristics.[524,525] His-bundle pacing after atrioventricular node ablation may evolve as an attractive alternative pacing mode,[526] as currently tested in ongoing clinical trials (NCT02805465, NCT02700425).

In severely symptomatic patients with permanent AF and at least one hospitalization for HF, atrioventricular node ablation combined with cardiac resynchronization therapy (CRT) may be preferred. In a small RCT, the primary composite outcome (death

Table 13 Drugs for rate control in AF[a]

	Intravenous administration	Usual oral maintenance dose	Contraindicated
Beta-blockers[b]			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg *b.i.d.*	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg *o.d.*	
Bisoprolol	N/A	1.25 - 20 mg *o.d.*	
Atenolol[c]	N/A	25 - 100 mg *o.d.*	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min, followed by 10 - 40 µg/kg/min; in patients with cardiac dysfunction: 1 - 10 µg/kg/min	N/A	
Nebivolol	N/A	2.5 - 10 mg *o.d.*	
Carvedilol	N/A	3.125 - 50 mg *b.i.d.*	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 - 10 mg i.v. bolus over 5 min	40 mg b.i.d. to 480 mg (extended release) o.d.	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg t.i.d. to 360 mg (extended release) o.d.	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75 - 1.5 mg over 24 hours in divided doses)	0.0625 - 0.25 mg o.d.	High plasma levels associated with increased mortality Check renal function before starting and adapt dose in CKD patients
Digitoxin	0.4 - 0.6 mg	0.05 - 0.1 mg o.d.	High plasma levels associated with increased mortality
Other			
Amiodarone	300 mg i.v. diluted in 250 mL 5% dextrose over 30 - 60 min (preferably via central venous cannula), followed by 900 - 1200 mg i.v. over 24 hours diluted in 500 - 1000 mL via a central venous cannula	200 mg o.d. after loading 3 × 200 mg daily over 4 weeks, then 200 mg daily[536] [d](reduce other rate controlling drugs according to heart rate)	In case of thyroid disease, only if no other options

AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); CKD = chronic kidney disease; HF = heart failure; HFrEF = HF with reduced ejection fraction; i.v. = intravenous; min = minutes; N/A = not available or not widely available; o.d. = *omni die* (once daily); t.i.d. = *ter in die* (three times a day).
[a]All rate control drugs are contraindicated in Wolff-Parkinson-White syndrome, also i.v. amiodarone.
[b]Other beta-blockers are available but not recommended as specific rate control therapy in AF and therefore not mentioned here (e.g. propranolol and labetalol).
[c]No data on atenolol; should not be used in HFrEF.
[d]Loading regimen may vary; i.v. dosage should be considered when calculating total load.

or hospitalization for HF, or worsening HF) was significantly less common in the ablation + CRT group vs. the drug arm (P =0.013), and ablation + CRT patients showed a 36% decrease in symptoms and physical limitations at 1-year follow-up (P =0.004).[527] Emerging evidence suggest that His-bundle pacing could be an alternative in these patients.[528]

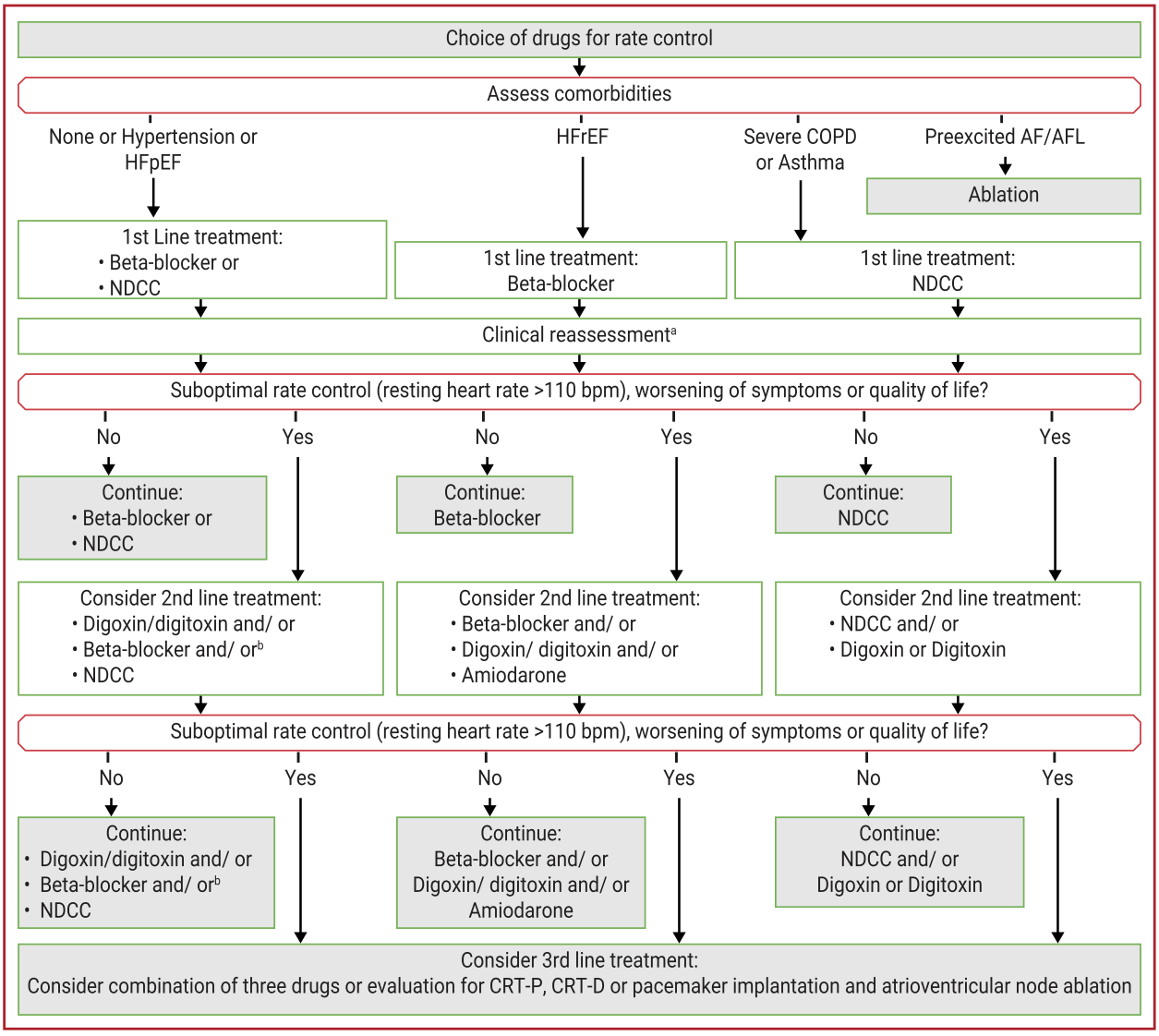


Figure 14 Choice of rate control drugs.[490] AF = atrial fibrillation; AFL = atrial flutter; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NDCC = Non-dihydropyridine calcium channel blocker. [a]Clinical reassessment should be focused on evaluation of resting heart rate, AF/AFL-related symptoms and quality of life. In case suboptimal rate control (resting heart rate >110 bpm), worsening of symptoms or quality of life consider 2nd line and, if necessary, 3rd line treatment options. [b]Careful institution of beta-blocker and NDCC, 24-hour Holter to check for bradycardia.

Recommendations for ventricular rate control in patients with AF[a]

Recommendations	Class[b]	Level[c]
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF≥40%.[492,507,511,529]	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF<40%.[486,491,502,512,530–532]	I	B
Combination therapy comprising different rate controlling drugs[d] should be considered if a single drug does not achieve the target heart rate.[533,534]	IIa	B
A resting heart rate of <110 bpm (i.e. lenient rate control) should be considered as the initial heart rate target for rate control therapy.[488]	IIa	B
Atrioventricular node ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, and not eligible for rhythm control by LA ablation, accepting that these patients will become pacemaker dependent.[516,523,535,536]	IIa	B
In patients with haemodynamic instability or severely depressed LVEF, intravenous amiodarone may be considered for acute control of heart rate.[504,514,515]	IIb	B

AF = atrial fibrillation; bpm = beats per minute; ECG = electrocardiogram; LA = left atrial; LVEF = left ventricular ejection fraction.
[a]See *section 11* for ventricular rate control in various concomitant conditions and AF populations
[b]Class of recommendation.
[c]Level of evidence.
[d]Combining beta-blocker with verapamil or diltiazem should be performed with careful monitoring of heart rate by 24-h ECG to check for bradycardia.[488]

10.2.2 Rhythm control

The 'rhythm control strategy' refers to attempts to restore and maintain sinus rhythm, and may engage a combination of treatment approaches, including cardioversion,[164,234] antiarrhythmic medication,[233,537,538] and catheter ablation,[539–541] along with an adequate rate control, anticoagulation therapy (*section 10.2.2.6*) and comprehensive cardiovascular prophylactic therapy (upstream therapy, including lifestyle and sleep apnoea management) (*Figure 15*).

10.2.2.1 Indications for rhythm control

Based on the currently available evidence from RCTs, the primary indication for rhythm control is to reduce AF-related symptoms and improve QoL (*Figure 15*). In case of uncertainty, an attempt to restore sinus rhythm in order to evaluate the response to therapy may be a rational first step. Factors that may favour an attempt at rhythm control should be considered[542,543] (*Figure 15*).

As AF progression is associated with a decrease in QoL[544] and, with time, becomes irreversible or less amenable to treatment,[176] rhythm control may be a relevant choice, although currently there is no substantial evidence that this may result in a different outcome. Reportedly, rates of AF progression were significantly lower with rhythm control than rate control.[545] Older age, persistent AF, and previous stroke/TIA independently predicted AF progression,[545] which may be considered when deciding the treatment strategy. For many patients, an early intervention to prevent AF progression may be worth considering,[546] including optimal risk-factor management.[245] Ongoing trials in patients with newly diagnosed symptomatic AF will assess whether early rhythm control interventions such as AF catheter ablation offer an opportunity to halt the progressive patho-anatomical changes associated with AF.[547] However, there is evidence that, at least in some patients, a successful rhythm control strategy with AF catheter ablation may not affect atrial substrate

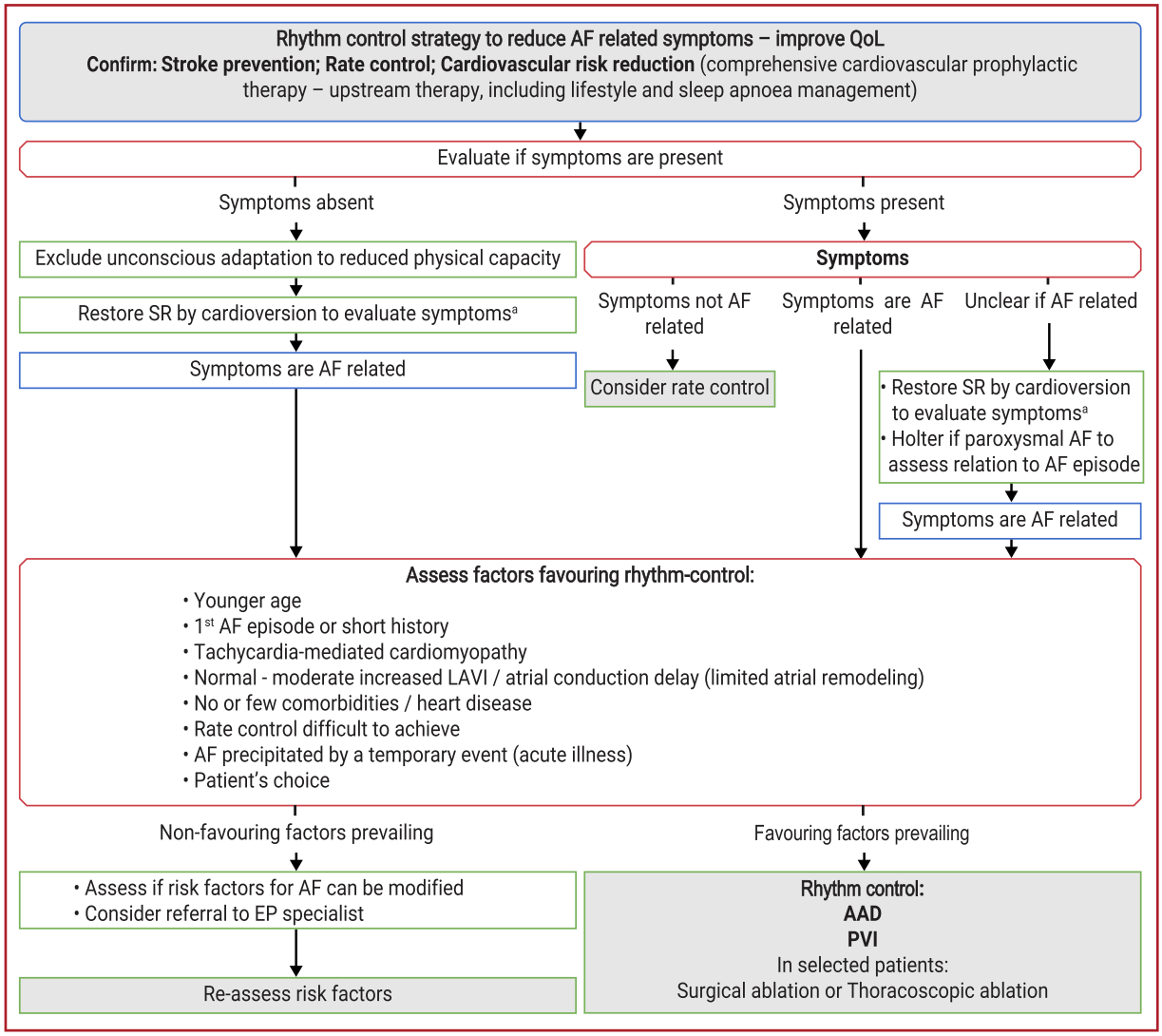


Figure 15 Rhythm control strategy. AAD = antiarrhythmic drug; AF = atrial fibrillation; CMP = cardiomyopathy; CV = cardioversion; LAVI = left atrial volume index; PAF = paroxysmal atrial fibrillation; PVI = pulmonary vein isolation; QoL = quality of life; SR = sinus rhythm. [a]Consider cardioversion to confirm that the absence of symptoms is not due to unconscious adaptation to reduced physical and/or mental capacity.

development.[548] Important evidence regarding the effect of early rhythm control therapy on clinical outcomes are expected in 2020 from the ongoing EAST (Early treatment of Atrial fibrillation for Stoke prevention Trial) trial.[549]

General recommendations regarding active informed patient involvement in shared decision making (*section 9*) also apply for rhythm control strategies. The same principles should be applied in female and male AF patients when considering rhythm control therapy.[550]

Recommendations for rhythm control

Recommendations	Class[a]	Level[b]
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF.[551–553]	I	A

AF = atrial fibrillation; QoL = quality of life.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.2 Cardioversion

10.2.2.2.1 Immediate cardioversion/elective cardioversion. Acute rhythm control can be performed as an emergency cardioversion in a haemodynamically unstable AF patient or in a non-emergency situation. Synchronized direct current electrical cardioversion is the preferred choice in haemodynamically compromised AF patients as it is more effective than pharmacological cardioversion and results in immediate restoration of sinus rhythm.[554,555] In stable patients, either pharmacological cardioversion or electrical cardioversion can be attempted; pharmacological cardioversion is less effective but does not require sedation. Of note, pre-treatment with AADs can improve the efficacy of elective electrical cardioversion.[556] A RCT showed maximum fixed-energy electrical cardioversion was more effective than an energy-escalation strategy.[557]

In a RCT, a wait-and-watch approach with rate control medication only and cardioversion when needed within 48 h of symptom onset was as safe as and non-inferior to immediate cardioversion of paroxysmal AF, which often resolves spontaneously within 24 h.[558]

Elective cardioversion refers to the situation when cardioversion can be planned beyond the nearest hours. Observational data[243] showed that cardioversion did not result in improved AF-related QoL or halted AF progression, but many of these patients did not receive adjunctive rhythm control therapies.[243] Other studies reported significant QoL improvement in patients who maintain sinus rhythm after electrical cardioversion and the only variable independently associated with a moderate to large effect size was sinus rhythm at 3 months.[232]

Factors associated with an increased risk for AF recurrence after elective cardioversion include older age, female sex, previous cardioversion, chronic obstructive pulmonary disease (COPD), renal impairment, structural heart disease, larger LA volume index, and HF.[164,559,560] Treatment of potentially modifiable conditions should be considered before cardioversion to facilitate maintenance of sinus rhythm (*Figure 15*).[245] In case of AF recurrence after cardioversion in patients with persistent AF, an early re-cardioversion may prolong subsequent duration of sinus rhythm.[561]

Non-emergency cardioversion is contraindicated in the presence of known LA thrombus. Peri-procedural thrombo-embolic risk should be evaluated and peri-procedural and long-term OAC use considered irrespective of cardioversion mode (i.e. pharmacological cardioversion or electrical cardioversion) (*section 10.2.2.6*). A flowchart for decision making on cardioversion is shown in *Figure 16*.

10.2.2.2.2 Electrical cardioversion. Electrical cardioversion can be performed safely in sedated patients treated with i.v. midazolam and/or propofol or etomidate.[562] BP monitoring and oximetry during the procedure should be used routinely. Skin burns may occasionally be observed. Intravenous atropine or isoproterenol, or temporary transcutaneous pacing, should be available in case of post-cardioversion bradycardia. Biphasic defibrillators are standard because of their superior efficacy compared with monophasic defibrillators.[563,564] Anterior–posterior electrode positions restore sinus rhythm more effectively,[554,555] while other reports suggest that specific electrical pad positioning is not critically important for successful cardioversion.[565]

10.2.2.2.3 Pharmacological cardioversion (including 'pill in the pocket'). Pharmacological cardioversion to sinus rhythm is an elective procedure indicated in haemodynamically stable patients. Its true efficacy is biased by the spontaneous restoration of sinus rhythm within 48 h of hospitalization in 76 - 83% of patients with recent onset AF (10 - 18% within first 3 h, 55 - 66% within 24 h, and 69% within 48 h).[566–568] Therefore, a 'wait-and-watch' strategy (usually for <24 h) may be considered in patients with recent-onset AF as a non-inferior alternative to early cardioversion.[558]

The choice of a specific drug is based on the type and severity of associated heart disease (*Table 14*), and pharmacological cardioversion is more effective in recent onset AF. Flecainide (and other class Ic agents), indicated in patients without significant LV hypertrophy (LVH), LV systolic dysfunction, or ischaemic heart disease, results in prompt (3 - 5 h) and safe[569] restoration of sinus rhythm in >50% of patients,[570–574] while i.v. amiodarone, mainly indicated in HF patients, has a limited and delayed effect but can slow heart rate within 12 h.[570,575–577] Intravenous vernakalant is the most rapidly cardioverting drug, including patients with mild HF and ischaemic heart disease, and is more effective than amiodarone[578–583] or flecainide.[584] Dofetilide is not used in Europe and is rarely used outside Europe. Ibutilide is effective to convert atrial flutter (AFL) to sinus rhythm.[585]

In selected outpatients with rare paroxysmal AF episodes, a self-administered oral dose of flecainide or propafenone is slightly less effective than in-hospital pharmacological cardioversion but may be preferred (permitting an earlier conversion), provided that the drug safety and efficacy has previously been established in the hospital setting.[586] An atrioventricular node-blocking drug should be instituted in patients treated with class Ic AADs (especially flecainide) to avoid transformation to AFL with 1:1 conduction.[587]

10.2.2.2.4 Follow-up after cardioversion. The goals of follow-up after cardioversion are shown in *Table 15*. When assessing the efficacy of a rhythm control strategy, it is important to balance symptoms and AAD side-effects. Patients should be reviewed after cardioversion to detect whether an alternative rhythm control strategy including AF catheter ablation, or a rate control approach is needed instead of current treatment.

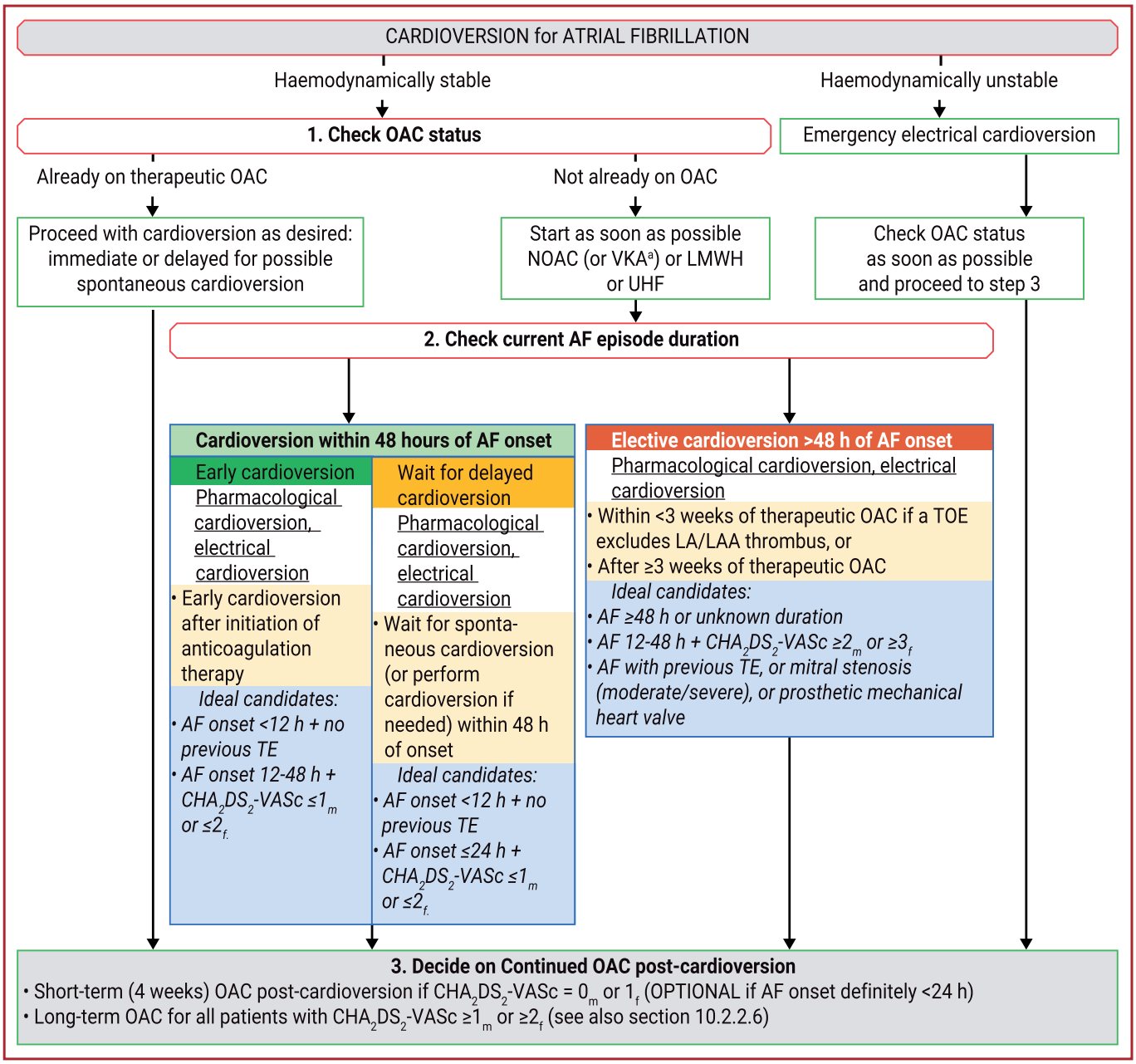


Figure 16 Flowchart for decision making on cardioversion of AF depending on clinical presentation, AF onset, oral anticoagulation intake, and risk factors for stroke. AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); cardioversion = cardioversion; ECV = electrical cardioversion; h = hour; LA = left atrium; LAA = left atrial appendage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TE = thromboembolism; TOE = transoesophageal echocardiography; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Table 14 **Antiarrhythmic drugs used for restoration of sinus rhythm**

Antiarrhythmic drugs for restoration of sinus rhythm (pharmacological cardioversion)					
Drug	**Administration route**	**Initial dose for cardioversion**	**Further dosing for cardioversion**	**Acute success rate and expected time to sinus rhythm**	**Contraindications/precautions/comments**
Flecainide[a]	Oral[b] i.v.	200–300 mg 2 mg/kg over 10 min	-	Overall: 59–78% (51% at 3 h, 72% at 8 h)	• Should not be used in ischaemic heart disease and/or significant structural heart disease • May induce hypotension, AFL with 1:1 conduction (in 3.5 - 5.0% of patients) • Flecainide may induce mild QRS complex widening • Do NOT use for pharmacological cardioversion of AFL
Propafenone[a]	Oral[b] i.v.	450–600 mg 1.5 - 2 mg/kg over 10 min	-	Oral: 45–55% at 3 h, 69–78% at 8 h; i.v.: 43–89% Up to 6 h	
Vernakalant[c]	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10 - 15 min after the initial dose)	<1 h (50% conversion within 10 min)	• Should not be used in patients with arterial hypotension (SBP <100 mmHg), recent ACS (within 1 month), NYHA III or IV HF, prolonged QT, or severe aortic stenosis • May cause arterial hypotension, QT prolongation, QRS widening, or non-sustained ventricular tachycardia
Amiodarone[a]	i.v.	5 - 7 mg/kg over 1 - 2 h	50 mg/h (maximum 1.2 g for 24 h)	44% (8–12 h to several days)	• May cause phlebitis (use a large peripheral vein, avoid i.v. administration >24 hours and use preferably volumetric pump) • May cause hypotension, bradycardia/atrioventricular block, QT prolongation • Only if no other options in patients with hyperthyroidism (risk of thyrotoxicosis)
Ibutilide[c]	i.v.	1 mg over 10 min 0.01 mg/kg if body weight <60 kg	1 mg over 10 min (10 - 20 min after the initial dose)	31–51% (AF) 63–73% (AFL) ≈1 h	• Effective for conversion of AFL • Should not be used in patients with prolonged QT, severe LVH, or low LVEF • Should be used in the setting of a cardiac care unit as it may cause QT prolongation, polymorphic ventricular tachycardia (torsades de pointes) • ECG monitoring for at least 4 hours after administration to detect a proarrhythmic event

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; AFL = atrial flutter; *b.i.d.* = bis in die (twice a day); CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; HCM = hypertrophic cardiomyopathy; HF = heart failure; i.v. = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = LV hypertrophy; NYHA = New York Heart Association; QRS = QRS interval; QT = QT interval; SA = sinoatrial; SBP = systolic blood pressure; VKA = vitamin K antagonist.

[a]Most frequently used for cardioversion of AF, available in most countries.

[b]May be self-administered by selected outpatients as a 'pill-in-the-pocket' treatment strategy.

[c]Not available in some countries.

For more details regarding pharmacokinetic or pharmacodynamic properties refer to EHRA AADs–clinical use and clinical decision making: a consensus document.[568]

Table 15 Goals of follow-up after cardioversion of AF

Goals
Early recognition of AF recurrence by ECG recording after cardioversion
Evaluation of the efficacy of rhythm control by symptom assessment
Monitoring of risk for proarrhythmia by regular control of PR, QRS, and QTc intervals in patients on Class I or III AADs
Evaluation of balance between symptoms and side-effects of therapy considering QoL and symptoms
Evaluation of AF-related morbidities and AAD-related side-effects on concomitant cardiovascular conditions and LV function
Optimization of conditions for maintenance of sinus rhythm including cardiovascular risk management (BP control, HF treatment, increasing cardiorespiratory fitness, and other measures, see *section 11*).

AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; ECG = electrocardiogram; HF = heart failure; LV = left ventricular; PR = PR interval; QoL = quality of life; QRS = QRS interval; QTc = corrected QT interval.

Recommendations for cardioversion

Recommendations	Class[a]	Level[b]
For pharmacological cardioversion of recent-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended.[569,573,579,582,588–590]	I	A
Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation.[515,591,592]	I	A
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent AF as part of rhythm control therapy.[232,233,593,594]	I	B
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thromboembolic risk.[595]	I	B
Pre-treatment with amiodarone, flecainide, ibutilide, or propafenone should be considered to facilitate the success of electrical cardioversion.[556,596–599]	IIa	B
In selected patients with infrequent and recent-onset AF and no significant structural or ischaemic heart disease, a single self-administered oral dose of flecainide or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment.[574,586,600,601]	IIa	B
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (>500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III	C

ACS = acute coronary syndrome; AF = atrial fibrillation; HF = heart failure; ms = milliseconds; i.v. = intravenous; QTc = corrected QT interval. Note: For cardioversion in various specific conditions and AF populations see *section 11*.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.3 Atrial fibrillation catheter ablation

AF catheter ablation is a well-established treatment for the prevention of AF recurrences.[1,602–604] When performed by appropriately trained operators, AF catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement.[165,235–242,246,247,605–618] It is advised to discuss the efficacy and complication rates of AF catheter ablation and AADs with the patient once rhythm control as long-term management has been selected.

10.2.2.3.1 Indications. In the following section, indications for AF catheter ablation are presented for paroxysmal and persistent AF in patients with and without risk factors for post-ablation AF recurrence. Differentiation of persistent and long-standing persistent AF was omitted because the latter only expresses the duration of persistent AF above an arbitrary and artificial cut-off at 12 months' duration. The significance of such a cut-off as a single measure has never been substantially proven.

A number of risk factors for AF recurrence after AF ablation have been identified, including LA size, AF duration, patient age, renal dysfunction, and substrate visualization by means of MRI.[619–625] Recent systematic reviews on prediction models for AF recurrence after catheter ablation showed the potential benefits of risk predictions, but a more robust evaluation of such models is desirable.[167,626] The model variables can be measured before ablation; therefore models could be used pre-procedurally to predict the likelihood of recurrence.[627–635] However, no single score has been presently identified as consistently superior to others. Thus, at present, for an improved and more balanced indication for ablation in patients with persistent AF and risk factors for recurrence, the most intensely evaluated risk predictors (including duration of AF) should be considered, and adjusted to the individual patient's situation including their preferences. Notably, patients must also be explicitly informed about the importance of treating modifiable risk factors to reduce risk of recurrent AF.[621,636–652]

The indications for AF catheter ablation are summarized in *Figure 17*. AF catheter ablation is effective in maintaining sinus rhythm in patients with paroxysmal and persistent AF.[165,235–242,605–616] The main clinical benefit of AF catheter ablation is the reduction of arrhythmia-related symptoms.[246,247,603,604,607,617,653,654] This has been confirmed in a recent RCT showing that the improvement in QoL was significantly higher in the ablation vs. medical therapy group,

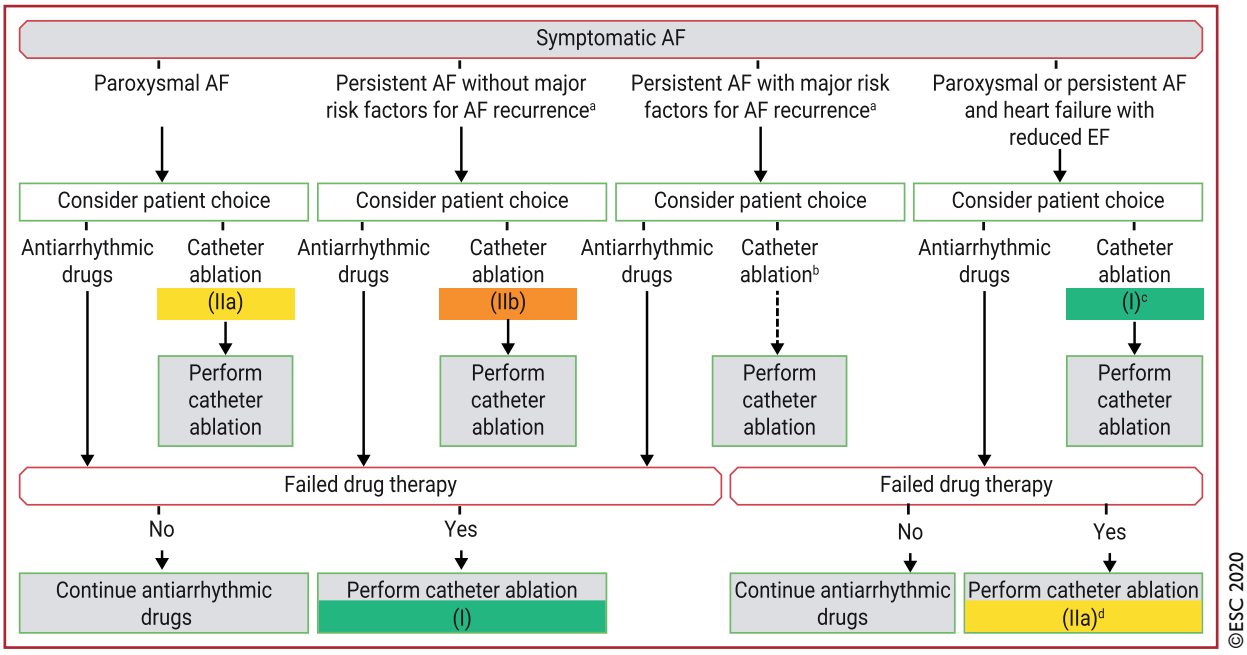


Figure 17 Indications for catheter ablation of symptomatic AF. The arrows from AAD to ablation indicate failed drug therapy. AAD = antiarrhythmic drug; AF = atrial fibrillation; EF = ejection fraction; LA = left atrial. [a]Significantly enlarged LA volume, advanced age, long AF duration, renal dysfunction, and other cardiovascular risk factors. [b]In rare individual circumstances, catheter ablation may be carefully considered as first-line therapy. [c]Recommended to reverse LV dysfunction when tachycardiomyopathy is highly probable. [d]To improve survival and reduce hospitalization.

as was the associated reduction in AF burden.[246] Symptom improvement has also been confirmed in the recent large CABANA (Catheter ABlation vs. ANtiarrhythmic Drug Therapy for Atrial Fibrillation) RCT,[655] but the trial showed that the strategy of AF catheter ablation did not significantly reduce the primary composite outcome of death, disabling stroke, serious bleeding, or cardiac arrest compared with medical therapy.[617] As no RCT has yet demonstrated a significant reduction in all-cause mortality, stroke, or major bleeding with AF catheter ablation in the 'general' AF population, the indications for the procedure have not been broadened beyond symptom relief,[617] and AF catheter ablation is generally not indicated in asymptomatic patients. Further important evidence regarding the impact of ablation on major cardiovascular events is expected from the EAST trial.[656]

In selected patients with HF and reduced LVEF, two RCTs have shown a reduction in all-cause mortality and hospitalizations with AF catheter ablation,[611,657] although combined mortality and HF hospitalization was a primary endpoint only in the CASTLE-AF (Catheter Ablation vs. Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation) trial.[657] The generalizability of the trial has recently been evaluated in a large HF patient population.[658] This analysis showed that only a small number of patients met the trial inclusion criteria (<10%) and patients who met the CASTLE-AF inclusion criteria had a significant benefit from treatment as demonstrated in the trial.[658] The smaller AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) RCT, which included patients with more advanced HFrEF, did not show benefits gained by AF catheter ablation at 1-year follow-up,[659] whereas a recent CABANA subgroup analysis supported the benefits of AF catheter ablation in patients with HFrEF, showing a significant reduction in the study primary endpoint (death, stroke, bleeding, cardiac arrest) and reduced mortality in the ablation group.[617,660] Overall, AF catheter ablation in patients with HFrEF results in higher rates of preserved sinus rhythm and greater improvement in LVEF, exercise performance, and QoL compared with AAD and rate control.[611,657,661–671] Accordingly, ablation should be considered in patients with HFrEF who have been selected for rhythm control treatment to improve QoL and LV function, and to reduce HF hospitalization and, potentially, mortality.

When AF-mediated tachycardia-induced cardiomyopathy (i.e. ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia) is highly suspected, AF catheter ablation is recommended to restore LV function.[672–676]

Ablation is recommended, in general, as a second-line therapy after failure (or intolerance) of class I or class III AADs. This recommendation is based on the results of multiple RCTs showing superiority of AF catheter ablation vs. AADs regarding freedom from recurrent arrhythmia or improvement in symptoms, exercise capacity, and QoL after medication failure.[235–239,246,247,605–607,609,611,613–617]

Clinical trials considering AF catheter ablation before any AAD suggest that AF catheter ablation is more effective in maintaining sinus rhythm, with comparable complication rates in experienced centres.[240–242,614] The 5-year follow-up in the MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) trial showed a significantly lower AF burden in the ablation arm that did not, however, translate into improved QoL compared with AAD treatment,[615] whereas the CAPTAF (Catheter Ablation compared with Pharmacological

Therapy for Atrial Fibrillation) study showed that, in AF patients mostly naive to class I and III AADs, the greater improvement in QoL in the ablation arm was directly associated with greater reduction in AF burden compared with the AAD arm.[246] Based on these studies and patient preferences, AF catheter ablation should be considered before a trial of AAD in patients with paroxysmal AF episodes (class IIa), or may be considered in patients with persistent AF without risk factors for recurrence (class IIb).

10.2.2.3.2 Techniques and technologies. The cornerstone of AF catheter ablation is the complete isolation of pulmonary veins by linear lesions around their antrum, either using point-by-point radiofrequency ablation or single-shot ablation devices.[235,237,239,607–609,612,613,654,677–686] Unfortunately, persistent pulmonary vein electrical isolation is difficult to achieve (pulmonary vein reconnection rates of >70% are reported[683,687–697], but could be significantly lower with the newer generation of catheters[698–700]).

Particularly in persistent and long-standing persistent AF, more extensive ablation has been advocated. This may include linear lesions in the atria, isolation of the LAA or of the superior vena cava, ablation of complex fractionated electrograms, rotors, non-pulmonary foci, or ganglionated plexi, fibrosis-guided voltage and/or MRI-mapping, or ablation of high dominant frequency sites.[701–710] However, additional benefit vs. pulmonary vein isolation (PVI) alone, justifying its use during the first procedure, is yet to be confirmed.[677,680,711–730] A RCT-based data suggest improved outcome with targeting extrapulmonary (particularly the LAA) foci and selective ablation of low-voltage areas as adjunct to PVI.[708,725] In patients with documented cavotricuspid isthmus (CTI)-dependent flutter undergoing AF catheter ablation, right isthmus ablation may be considered.[731–734] In case of non-CTI-dependent atrial tachycardia, the ablation technique depends on the underlying mechanism and tachycardia focus or circuit.[1,614]

Several RCTs and observational studies have compared point-by-point radiofrequency and cryoballoon ablation, mostly in the first procedure for paroxysmal AF.[612,681,735–755] They reported broadly similar arrhythmia-free survival and overall complications with either technique, with slightly shorter procedure duration but longer fluoroscopy time with cryoballoon ablation.[612,681,735–755] However, some studies showed reduced hospitalization and lower complication rates with cryoballoon ablation.[746,756,757] The choice of energy source may depend on centre availability, operator preference/experience, and patient preference. Alternative catheter designs and energy sources have been developed in an attempt to simplify the ablation procedure and improve outcomes,[613,755,758–761] but further evidence is required before changing current recommendations.

10.2.2.3.3 Complications. Prospective, registry-based data show that approximately 4 - 14% of patients undergoing AF catheter ablation experience complications, 2 - 3% of which are potentially life-threatening.[602–604,762–765] In the recent CABANA trial, mostly including experienced high-volume centres, complications occurred in the lower range of these rates.[617] Complications occur mostly within the first 24 h after the procedure, but some may appear 1 - 2 months after ablation[1,602–604] (*Table 16* and *Supplementary Table 10*). Periprocedural death is rare (<0.2%) and usually related to cardiac tamponade.[603,604,766–770]

10.2.2.3.4 AF catheter ablation outcome and impact of modifiable risk factors. Multiple RCTs have compared AADs with AF catheter ablation using different technologies/energy sources, either as 'first-line' therapy or after AAD failure, showing superiority of AF catheter ablation in arrhythmia-free survival.[165,235–242,605–616] However, many patients require several procedures and late recurrences are not infrequent.[248,639,772–780]

Key outcomes include QoL, HF, stroke, and mortality.[539–541,608,781,782] Compared with AADs, AF catheter ablation was associated with significant and sustained improvement in QoL scores in several RCTs and meta-analyses.[1,235,239–242,246,247,539–541,783,784] To date, there is no RCT sufficiently large to properly evaluate a reduction in stroke by catheter ablation.

Several factors, including AF type and duration,[235–237,239,607,609,612,613,654,680,682,785] and the presence of comorbidities such as hypertension,[621,639–641] obesity,[638,639,643,646,772,786–791] metabolic syndrome,[792–794] and sleep apnoea[643–645,647–652] may influence the outcome of catheter

Table 16 Procedure-related complications in catheter ablation and thoracoscopic ablation of AF[771]

Complication severity	Complication type	Complication rate	
		Catheter ablation	Thoracoscopic ablation
Life-threatening complications	Periprocedural death	<0.1%	<0.1%
	Oesophageal perforation/fistula	<0.5%	N/A
	Periprocedural thromboembolic event	<1.0%	<1.5%
	Cardiac tamponade	≈1%	<1.0%
Severe complications	Pulmonary vein stenosis	<1.0%	N/A
	Persistent phrenic nerve palsy	<1.0%	N/A
	Vascular complications	2-4%	N/A
	Conversion to sternotomy	N/A	<1.7%
	Pneumothorax	N/A	<6.5%
Moderate or minor complications	Various	1 - 2%	1 - 3%
Complications of unknown significance	Asymptomatic cerebral embolism	5 - 15%	N/A

NA = not available.

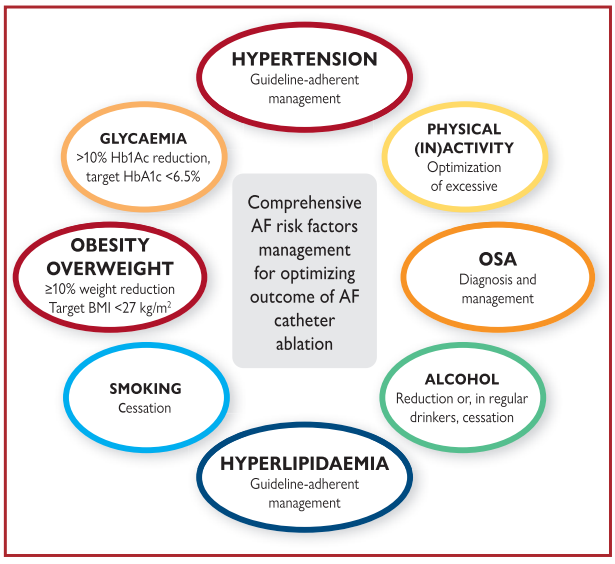


Figure 18 Risk factors for AF contributing to the development of an abnormal substrate translating into poorer outcomes with rhythm control strategies. AF = atrial fibrillation; BMI = body mass index; CPAP = continuous positive airway pressure; HbA_{1C} = haemoglobin A1c; OSA = obstructive sleep apnoea. Several AF risk factors may contribute to the development of LA substrates and thus affect the outcome of AF catheter ablation, predisposing to a higher recurrence rate. Aggressive control of modifiable risk factors may reduce recurrence rate.

ablation (*Figure 18* and *Supplementary Box 2*). Prospective cohort studies suggest that aggressive control of modifiable risk factors may improve arrhythmia-free survival after catheter ablation.[636]

10.2.2.3.5 Follow-up after atrial fibrillation ablation. AF catheter ablation is a complex procedure that may be associated with a range of specific post-procedural complications (*section 10.2.2.3.3*)[603,604,766–770]. Although mostly rare, potentially catastrophic complications may initially present with non-specific symptoms and signs to which managing physicians should be attuned. Key issues in follow-up are shown in *Table 17*.

10.2.2.3.6 Risk assessment for recurrence of atrial fibrillation post catheter ablation. Recurrence of AF after catheter ablation is driven by the complex interaction of various factors. These include increasing AF duration, age, and LA size,[619–624] and structural factors such as the abundance of epicardial fat tissue[807–810] and the presence of atrial substrate as evident from electrical or morphological markers.[811] A number of risk-prediction scores have been evaluated (for detailed description see *Supplementary Table 11* and *Supplementary Box 2*). Whereas these scores only moderately predict AF recurrence, one of the strongest predictors is early recurrent AF, indicating the need for further refinement of these scoring systems.[629]

Table 17 Key issues in follow-up after AF catheter ablation

Key issues
Recognition and management of complications
● Patients must be fully informed about the clinical signs and symptoms of rare but potentially dangerous ablation-related complications that may occur after hospital discharge (e.g. atrio-oesophageal fistula, pulmonary vein stenosis).
Follow-up monitoring:
Useful to assess procedural success and correlate symptom status with rhythm.[795,796] Recurrences beyond the first month post-ablation are generally predictive of late recurrences,[797,798] but recurrent symptoms may be due to ectopic beats or other non-sustained arrhythmia[640,799,800]; conversely the presence of asymptomatic AF after ablation is well described.[801–803]
Monitoring may be performed with intermittent ECG, Holter, Patch recordings, external or implanted loop recorder, or smart phone monitor (although the latter has not been validated for such use). Patients should be first reviewed at a minimum of 3 months and annually thereafter.[1]
Management of antiarrhythmic medication and treatment of AF recurrences
a. Continuing AAD treatment for 6 weeks to 3 months may reduce early AF recurrences, rehospitalizations and cardioversions during this period.[797,804] Clinical practice regarding routine AAD treatment after ablation varies and there is no convincing evidence that such treatment is routinely needed.
b. Subsequently, AADs may be weaned, ceased, or continued according to symptoms and rhythm status. Recent findings suggest that in AAD-treated patients remaining free of AF at the end of the blanking period, AAD continuation beyond the blanking period reduces arrhythmia recurrences.[805]
Management of anticoagulation therapy
a. In general, OAC therapy is continued for 2 months following ablation in all patients.[1,806] Beyond this time, a decision to continue OAC is determined primarily by the presence of CHA_2DS_2-VASc stroke risk factors rather than the rhythm status (*section 10.2.2.6*).

AAD = antiarrhythmic drug; AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); ECG=electrocardiogram; OAC = oral anticoagulant.

Recommendations for rhythm control/catheter ablation of AF

Recommendations	Class[a]	Level[b]
General recommendations		
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.[235–237,239,607,609,612,613,636,638,652,654,680,682,785,789]	I	B
Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI.[812–814]	IIa	B
AF catheter ablation after failure of drug therapy		
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with[235–238,247,605–609,612,613,615–617,654,677,678,680,682,685,758,779,780,815]:	I	
• Paroxysmal AF, or		A
• Persistent AF without major risk factors for AF recurrence, or		A
• Persistent AF with major risk factors for AF recurrence.		B
AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF.[246]	IIa	B
First-line therapy		
AF catheter ablation for PVI should/may be considered as first-line rhythm control therapy to improve symptoms in selected patients with symptomatic:		
• Paroxysmal AF episodes,[240–242,614,615] or	IIa	B
• Persistent AF without major risk factors for AF recurrence.[253–255,264,598–601,609,610,633,636,641,724,745,746,832]	IIb	C
as an alternative to AAD class I or III, considering patient choice, benefit, and risk.		
AF catheter ablation:		
• Is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.[666,675,676]	I	B
• Should be considered in selected AF patients with HF with reduced LVEF to improve survival and reduce HF hospitalization.[612,659,662–666,668–671,817–826]	IIa	B
AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation.[816–818]	IIa	C
Techniques and technologies		
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.[235–237,239,606,608–610,613,614,678,679,681,683,684,686,713,731,759,780]	I	A
If patient has history of CTI-dependent AFL or if typical AFL is induced at the time of AF ablation, delivery of a CTI lesion may be considered.[731–733,819–821]	IIb	B
Use of additional ablation lesions beyond PVI (low voltage areas, lines, fragmented activity, ectopic foci, rotors, and others) may be considered but is not well established.[677,680,708,711–730]	IIb	B
Lifestyle modification and other strategies to improve outcomes of ablation		
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.[636,638,639,643,646,772,786–791]	I	B
Strict control of risk factors and avoidance of triggers are recommended as part of a rhythm control strategy.[636,637]	I	B

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; CTI = cavotricuspid isthmus; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.4 Surgery for atrial fibrillation

With development of the maze procedure for surgical cure from AF, Cox *et al.* opened up a new window of therapeutic opportunities for AF patients.[822] The classical cut-and-sew maze procedure underwent several modifications and various device-based surgical ablation procedures have been developed.[823,824] More than 200 publications documented the application of these techniques and technologies in various clinical scenarios.[825] Most studies are retrospective and/or observational, but some RCTs and meta-analyses have also been published.[771,826–828] While the effects of surgical ablation on rhythm outcome (i.e. restoration of sinus rhythm/freedom from AF) have been clearly demonstrated, the effects on endpoints such as QoL, hospitalization, stroke, and mortality are not well established.[461,827,829,830] The only RCT with longer follow-up has shown a significant reduction in stroke risk at 5 years and a greater likelihood of maintaining sinus rhythm although the trial was underpowered for

stroke risk assessment.[828] The largest registry published, from the Polish National Health Service, describes better survival when ablation is performed concomitant to mitral or coronary surgery.[831,832] Close cooperation between cardiac surgeons and electrophysiologists (heart team) for proper patient selection and postoperative management, especially for handling of arrhythmia recurrences, seems advisable for high-standard quality care.

10.2.2.4.1 Concomitant surgery for atrial fibrillation: indications, outcome, complications. Most trials of concomitant AF ablation have been based mainly on patients undergoing mitral valve repair or replacement. While surgical PVI has been shown to be effective for maintaining sinus rhythm,[833] the most effective ablation treatment for AF isolates the pulmonary veins and the LA posterior wall, creates ablation lines that impede electrical impulses around the most important structures (mitral and tricuspid annuli, venae cavae and appendages), and excludes the LAA. Most evidence supports bipolar radiofrequency clamps and cryothermy to perform a maze.[834] For non-paroxysmal AF, a biatrial lesion pattern is more effective than left-sided only, performed by sternotomy or minimally invasive techniques.[826]

In general, the same preoperative risk factors for AF recurrence after concomitant AF surgery as for AF catheter ablation have been identified. These include LA size, patient age, AF duration, HF/reduced LVEF, and renal dysfunction.[379,636,835–841] The significant positive effects of concomitant surgical ablation on freedom from atrial arrhythmias is clearly documented. Most RCTs with 1-year follow-up show no effect on QoL, stroke, and mortality,[842–845] but some reported reduced event rates.[828,830,846]

Surgical AF ablation concomitant to other cardiac surgery significantly increases the need for pacemaker implantation with biatrial (but not left-sided) lesions,[827] being reported from 6.8% to 21.5%, while other complications are not increased.[827–830,846,847]

10.2.2.4.2 Stand-alone surgery for atrial fibrillation: indications, outcome, complications. Thoracoscopic radiofrequency ablation targets the pulmonary veins, LA posterior wall, and LAA closure in AF patients with no structural heart disease. Freedom from AF after the procedure is well documented, but only a few studies have reported improved QoL.[844,845,848–850] A recent meta-analysis of three RCTs showed a significantly higher freedom from atrial tachyarrhythmia and less need for repeat ablations after thoracoscopic ablation compared with AF catheter ablation for paroxysmal or persistent AF.[851] The FAST trial randomized patients who were prone to AF catheter-ablation failure (i.e. failed previous ablation or LA dilatation and hypertension) and reported common but substantially lower recurrence after thoracoscopic compared with AF catheter ablation (56% vs. 87%) at long-term follow-up (mean 7 years).[849] Hospitalization was longer and complication rates of surgical ablation were higher compared with catheter ablation[771] (*Table 16*). A systematic safety analysis of thoracoscopic ablation showed a 30-day complication rate of 11.3%, mainly self-limiting, whereas it was significantly lower (3.6%) in a multicentre registry.[456] In RCTs, thoracoscopic ablation proved more effective in rhythm control than catheter ablation; however, surgical ablation is more invasive, with higher complication rates and longer hospitalization.[461,852] Because of this risk-benefit ratio of surgical vs. catheter ablation, it seems reasonable to consider thoracoscopic surgery preferentially in patients with previous failed catheter ablation or with a high risk of catheter-ablation failure. There are no convincing data on the effects on stroke of surgical ablation as a stand-alone procedure or in combination with LAA occlusion or exclusion. Hence, OAC therapy should be continued after the procedure regardless of rhythm outcome in AF patients with stroke risk factors.

10.2.2.5 Hybrid surgical/catheter ablation procedures

Hybrid AF procedures combine a minimally invasive epicardial non-sternotomy ablation not using cardiopulmonary bypass with a percutaneous endocardial approach. They can be performed as a single intervention or sequentially, when the endocardial catheter mapping and, if needed, additional ablations are done within 6 months after the epicardial procedure.[853] There are no studies comparing these two hybrid strategies.

A systematic review on rhythm outcome and complications with a hybrid procedure or AF catheter ablation in patients with persistent or long-standing persistent AF showed that at 12 months or longer, a hybrid procedure achieved a significantly higher rate of freedom from atrial arrhythmias with and without the use of AAD compared with AF catheter ablation. Although the overall complication rate was low for both strategies, hybrid ablations had more complications (13.8% vs. 5.9%).[854] The difference in outcome could be explained by a long-lasting isolation of the pulmonary veins after bipolar radiofrequency clamping of the pulmonary veins, epicardial clipping of the LAA, and the add-on possibility of an endocardial touch-up.[855,856]

Recommendations for surgical ablation of AF

Recommendations	Class[a]	Level[b]
Concomitant AF ablation should be considered in patients undergoing cardiac surgery, balancing the benefits of freedom from atrial arrhythmias and the risk factors for recurrence (left atrial dilatation, years in AF, age, renal dysfunction, and other cardiovascular risk factors).[461,843,857–859]	IIa	A
Thoracoscopic—including hybrid surgical ablation—procedures should be considered in patients who have symptomatic paroxysmal or persistent AF refractory to AAD therapy and have failed percutaneous AF ablation, or with evident risk factors for catheter ablation failure, to maintain long-term sinus rhythm. The decision must be supported by an experienced team of electrophysiologists and surgeons.[860,861]	IIa	B
Thoracoscopic—including hybrid surgical ablation—procedures may be considered in patients with persistent AF with risk factors for recurrence, who remain symptomatic during AF despite at least one failed AAD and who prefer further rhythm control therapy.	IIb	C

AAD = antiarrhythmic drug; AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.6 Peri-procedural stroke risk management in patients undergoing rhythm control interventions

10.2.2.6.1 Management of stroke risk and oral anticoagulant therapy in atrial fibrillation patients undergoing cardioversion. Patients undergoing cardioversion of AF are at increased risk of stroke and thrombo-embolism, especially in the absence of OAC and if AF has been present for ≥12 h.[860–862] The exact duration of an AF episode before cardioversion may be difficult to ascertain, as many patients develop AF asymptomatically, seeking help only when symptoms or complications occur. If there is uncertainty over the exact onset of AF (i.e. unknown duration of AF), peri-cardioversion anticoagulation is managed as for AF of >12 h to 24 h. Mechanisms of the increased propensity to peri-cardioversion thrombo-embolism include the presence of pre-existing thrombus (especially if not anticoagulated), change in the atrial mechanical function with restoration of sinus rhythm, atrial stunning post-cardioversion, and a transient prothrombotic state.[863]

No RCT has evaluated anticoagulation vs. no anticoagulation in AF patients undergoing cardioversion with a definite duration of AF<48 h. Observational data suggest that the risk of stroke/thrombo-embolism is very low (0 - 0.2%) in patients with a definite AF duration of <12 h and a very low stroke risk (CHA_2DS_2-VASc 0 in men, 1 in women),[860,864,865] in whom the benefit of 4-week anticoagulation after cardioversion is undefined and the prescription of anticoagulants can be optional, based on an individualized approach.

Peri-cardioversion anticoagulation with a VKA results in a significant decrease of stroke and thrombo-embolism,[863] but achieving the necessary therapeutic anticoagulation (INR 2.0 - 3.0) for a minimum of 3 weeks before cardioversion may be difficult. This 3-week period is arbitrary, based on the time presumably needed for endothelialization or resolution of pre-existing AF thrombus. To shorten this time, TOE-guided cardioversion was introduced. If there is no atrial thrombus on TOE, cardioversion is performed after administration of heparin, and OAC is continued post-cardioversion.[866,867]

As NOACs act rapidly, cardioversion can be scheduled 3 weeks after NOAC initiation, provided that patients are counselled about the need for compliance to NOAC therapy[868–870]; NOACs have at least comparable efficacy and safety to warfarin in AF patients undergoing cardioversion.[871–874] A review of the three largest prospective trials (n =5203 patients) showed that the composite primary outcome (stroke/systemic embolism, myocardial infarction, or cardiovascular death) was significantly reduced with NOACs compared with VKA.[873]

Long-term OAC therapy after cardioversion should not be based on successful restoration of sinus rhythm, but on the stroke risk profile (using the CHA_2DS_2-VASc score), balanced against bleeding risk (e.g. HAS-BLED score).

For patients in whom a thrombus is identified on TOE, effective anticoagulation for at least 3 weeks before reassessment for cardioversion is recommended. A repeat TOE to ensure thrombus resolution should be considered before cardioversion.[875] Antithrombotic management for these patients is challenging and decided on an individual basis based on the efficacy (or inefficacy) of previous treatments.

Recommendations for stroke risk management peri-cardioversion

Recommendations	Class[a]	Level[b]
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety to warfarin.[868–873]	I	A
For cardioversion of AF/AFL, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.[866–870]	I	B
TOE is recommended to exclude cardiac thrombus as an alternative to 3-week pre-procedural anticoagulation when early cardioversion is planned.[866,868–870,875]	I	B
In patients at risk of stroke, it is recommended that OAC therapy is continued long term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion, the apparent maintenance of sinus rhythm, or characterization of AF as a 'first-diagnosed episode'.[412,872,876]	I	B
When thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks before cardioversion of AF.[875]	I	B
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	I	C
Effective anticoagulation should be initiated as soon as possible before every cardioversion of AF or AFL.[866–870]	IIa	B
Early cardioversion can be performed without TOE in patients with an AF duration of <48 h.[866]	IIa	B
In patients with AF duration of >24 h undergoing cardioversion, therapeutic anticoagulation should be continued for at least 4 weeks, even after successful cardioversion to sinus rhythm (beyond 4 weeks, the decision about long-term OAC treatment is determined by the presence of stroke risk factors).[860,861]	IIa	B
When thrombus is identified on TOE, a repeat TOE to ensure thrombus resolution should be considered before cardioversion.[875]	IIa	C
In patients with a definite duration of AF ≤24 h and a very low stroke risk (CHA_2DS_2-VASc of 0 in men or 1 in women) post-cardioversion anticoagulation for 4 weeks may be omitted.[871,876]	IIb	C

AF = atrial fibrillation; AFL = atrial flutter; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TOE = transoesophageal echocardiography.

[a]Class of recommendation.

[b]Level of evidence.

10.2.2.6.2 Management of stroke risk and oral anticoagulant therapy in atrial fibrillation patients undergoing atrial fibrillation catheter ablation. Although there is some variability in the peri-procedural OAC management in patients undergoing AF ablation, more recently operators have moved towards a strategy of performing the ablation under uninterrupted VKA or NOAC treatment, provided the INR is within therapeutic range. In non-anticoagulated patients, initiating therapeutic anticoagulation 3 - 4 weeks before ablation may be considered.[1]

In a meta-analysis of 12 studies,[877] uninterrupted anticoagulation using NOACs vs. VKAs for AF catheter ablation was associated with low rates of stroke/TIA (NOACs, 0.08%; VKA, 0.16%) and similar rates of silent cerebral embolic events (8.0% vs 9.6%). However, major bleeding was significantly reduced with uninterrupted NOACs (0.9%) compared with VKAs (2%).

In the largest RCT comparing peri-procedural NOAC vs. warfarin [the RE-CIRCUIT trial (Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of different peri-proCedUral antIcoagulation sTrategies)],[878] the incidence of major bleeding events during and up to 8 weeks after ablation was significantly lower with dabigatran vs. warfarin (1.6% vs. 6.9%). Other RCTs (VENTURE-AF with rivaroxaban,[879] AXAFA-AF NET 5 with apixaban,[880] and ELIMINATE-AF with edoxaban[881]) also showed similar event rates under uninterrupted NOACs vs. VKAs. Overall, uninterrupted peri-procedural NOACs were associated with a low incidence of stroke/TIA and a significant reduction in major bleeding compared with uninterrupted VKAs in patients undergoing AF catheter ablation. In contrast, heparin bridging increases the bleeding risk and should be avoided.

Frequently, the term 'uninterrupted' is used in clinical practice for the description of regimens where one or two NOAC doses are omitted before ablation, whereas in the RCTs comparing uninterrupted NOACs vs. warfarin, NOAC administration before ablation was truly uninterrupted.[869,878] Hence, there is no reason to recommend omitting one or two NOAC doses before ablation. After the procedure, administration of the first dose the evening after ablation or the next morning (if this corresponds to the timing of the next dose according to the patient's previous OAC regimen) appears to be safe.[878,881]

10.2.2.6.3 Postoperative anticoagulation after surgery for atrial fibrillation. Owing to endothelial damage during ablation, OAC is advisable in all patients after AF surgery, starting as soon as possible (balancing the risk of postoperative bleeding). There are no RCT data regarding interruption of OAC over the long term. Non-randomized studies with longer follow-up have shown better long-term freedom from stroke in patients with persistent sinus rhythm, but not in those with AF despite LAA exclusion.[824] Therefore, long-term OAC is recommended in all patients at risk of stroke despite a successful maze surgery and appendage closure.

Recommendations for postoperative anticoagulation after AF surgery

Recommendations	Class[a]	Level[b]
Long-term OAC therapy is recommended in patients after AF surgery and appendage closure, based on the patient's thrombo-embolic risk assessed with the CHA_2DS_2-VASc score.	I	C

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); OAC = oral anticoagulant.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.7 Long-term antiarrhythmic drug therapy for rhythm control

10.2.2.7.1 *Antiarrhythmic drugs.* The aim of AAD therapy is to improve AF-related symptoms.[484,882,883] Hence, the decision to initiate long-term AAD therapy needs to balance symptom burden, possible adverse drug reactions, and patient preferences. The principles of AAD therapy are shown in *Tables 18 and 19*.

Compared with no therapy, AAD therapy approximately doubles sinus rhythm maintenance,[883] but it is difficult to draw firm

Recommendations for stroke risk management peri-catheter ablation

Recommendations	Class[a]	Level[b]
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and:	I	C
• Preferably, therapeutic OAC for at least 3 weeks before ablation, or • Alternatively, the use of TOE to exclude LA thrombus before ablation.	IIa	C
For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended.[878,879,881]	I	A
After AF catheter ablation, it is recommended that: • Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and • Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.	I	C

AF = atrial fibrillation; LA = left atrial; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant therapy; TOE=transoesophageal echocardiography.
[a]Class of recommendation
[b]Level of evidence

conclusions from existing trials on their comparative efficacy.[884] In general, AAD therapy is less effective than AF catheter ablation,[114,611,615] but previously ineffective AADs can be continued after PVI, to reduce recurrent AF.[805] A shorter duration of AAD therapy would likely reduce the risk of side-effects[883,885] but late recurrences may occur.[595] Short-term AAD therapy is also used to prevent early AF recurrences after catheter ablation,[886] although the benefit is still debated[797,887]; this strategy may be reasonable in patients deemed at increased risk of AAD side-effects or in those with a low perceived risk of recurrent AF. Concomitant management of underlying cardiovascular conditions is pivotal to reduce AF symptom burden and facilitate the maintenance of sinus rhythm.[245,636,888,889]

Table 18 Principles of antiarrhythmic drug therapy[143]

Principles
AAD therapy aims to reduce AF-related symptoms
Efficacy of AADs to maintain sinus rhythm is modest
Clinically successful AAD therapy may reduce rather than eliminate AF recurrences
If one AAD 'fails', a clinically acceptable response may be achieved by another drug
Drug-induced proarrhythmia or extracardiac side-effects are frequent
Safety rather than efficacy considerations should primarily guide the choice of AAD

AAD = antiarrhythmic drug; AF = atrial fibrillation.

10.2.2.7.1 *Available antiarrhythmic drugs.* Several AADs have been shown to reduce AF recurrences (*Table 20*).[890] Class Ia (quinidine and disopyramide) and sotalol have been associated with increased overall mortality.[884] Again, safety should dictate both the initiation and continuation of AADs.

A flow chart for use of AADs for long-term rhythm control, depending on the underlying disease, is given in *Figure 19*.

10.2.2.7.2 *Non-antiarrhythmic drugs with antiarrhythmic properties (upstream therapy).* Either resulting from, or being a marker of structural atrial remodelling, AF is closely related to atrial cardiomyopathy. Drugs that affect the atrial-remodelling process could prevent new-onset AF acting as non-conventional AADs (i.e. upstream therapy) (*Table 21*).

Recently, the RACE 3 study[245] confirmed the importance of assessing underlying conditions and targeted upstream therapy for intense risk-factor control in AF patients with mild or moderate HF in optimizing rhythm control. The results showed that targeted therapy of underlying conditions improves maintenance of sinus rhythm in patients with persistent AF.

A list of new investigational antiarrhythmic drugs is provided in *Supplementary Box 3*.

Table 19 Rules to initiate antiarrhythmic drugs for long-term rhythm control in AF

Consideration	Criteria
Indication for AAD	• **Is the patient symptomatic?** • Are AF symptoms severe enough (EHRA class) to justify AAD use? • Are there associated conditions predicting poor tolerance of AF episodes?
When to start AAD	• **Usually not for the first episode, but it may enhance efficacy of cardioversion**

How to choose among AADs	• **Minimize proarrhythmic risk and organ toxicity**
	Evaluate for:
	  • basal ECG abnormalities (QRS duration, PR, QTc) and possible interference with AAD
	  • impact on LV function
	  • important pharmacokinetic and pharmacodynamic interactions (i.e. antithrombotic drugs)
	• **Risk factors for proarrhythmia may be dynamic and change over time**

How to minimize proarrhythmic risk	• **Evaluate ECG after the treatment, as indicated in these Guidelines** • Evaluate periodically for organ toxicity (amiodarone) • Long-term Holter monitoring and exercise test in selected cases • Avoid AAD combinations
How to verify efficacy	• **Estimate AF burden under therapy (ask patient for noting episodes)** • If the patient is already on AAD and it was effective but was stopped because of intolerance, choose preferably from the same class
Adjuvant interventions and hybrid therapy	• **In patients with atrioventricular conduction abnormalities and/or sinus node dysfunction, pacemaker implantation should be considered if AAD therapy is deemed necessary** • Short-term AAD therapy could prevent early recurrences after AF ablation

AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; LV = left ventricular; PR = PR interval; QRS = QRS interval; QTc = corrected QT interval.

Table 20 Antiarrhythmic drugs used for long-term maintenance of sinus rhythm in AF patients[890]

Drug	Administration route	Dose	Contraindications/precautions/comments
Amiodarone[233,506,891–896]	Oral	3 × 200 mg daily over 4 weeks, then 200 mg daily[506]	• The most effective AAD[890,897] • RCTs showed lower AF recurrence compared with sotalol and dronedarone[884] • Also reduces ventricular rate (for 10 - 12 bpm), safe in patients with HF[898–900] • Concomitant use with other QT-prolonging drugs with caution • Concomitant use with VKAs or digitalis (their dose should be reduced) • Increased risk of myopathy when used with statins • Requires regular surveillance for liver, lung, and thyroid toxicity • Has atrioventricular nodal-slowing properties, but should not be used as first intention for rate control • QT prolongation is common but rarely associated with torsades de pointes (<0.5%)[901] • Torsades de pointes occurs infrequently during treatment with amiodarone (the proarrhythmia caution requires QT-interval and TU-wave monitoring)[902] • Should be discontinued in case of excessive QT prolongation (>500 ms) • ECG at baseline, after 4 weeks • Contraindicated in manifest hyperthyroidism • Numerous and frequent extracardiac side-effects may warrant discontinuation of amiodarone, thus making it a second-line treatment when other choices are possible[903–907]
Flecainide Flecainide slow release[896,908,909]	Oral	100 - 200 mg b.i.d., or 200 mg once daily (flecainide slow release)	• Effective in preventing recurrence of AF[891,908,910] • Should not be used in patients with CrCl <35 mL/min/1.73 m^2 and significant liver disease • Both are contraindicated in patients with ischaemic heart disease or reduced LVEF[911–913] • Should be discontinued in case of QRS widening >25% above baseline and patients with left bundle-branch block or any other conduction block >120 ms • Caution when sinoatrial/atrioventricular conduction disturbances present[a] • CYP2D6 inhibitors increase concentration • May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate.[914] This risk can be reduced by concomitant administration of an atrioventricular nodal-blocking drug such as a beta-blocker or NDCC • In patients properly screened for propensity to proarrhythmias, both flecainide and propafenone are associated with a low proarrhythmic risk[915] • ECG at baseline, after 1 - 2 weeks
Propafenone Propafenone slow release[895,896,916–922]	Oral	150 - 300 mg three times daily, or 225 - 425 mg b.i.d. (propafenone slow release)	• Should not be used in patients with significant renal or liver disease, ischaemic heart disease, reduced LV systolic function, or asthma • Should be discontinued in case of QRS widening >25% above baseline and in patients left bundle-branch block and any other conduction block >120 ms • Caution when sinoatrial/atrioventricular conduction disturbances present[a] • Increases concentration of warfarin/acenocoumarin and digoxin when used in combination • May increase AFL cycle length, thus promoting 1:1 atrioventricular conduction and increasing ventricular rate • ECG at baseline and after 1 - 2 weeks

Continued

Table 20 ***Continued***

Drug	Administration route	Dose	Contraindications/precautions/comments
Dronedarone[923–927]	Oral	400 mg b.i.d.	• Less effective than amiodarone in rhythm control but has very few extracardiac side-effects[925,928–930] • Reduces cardiovascular hospitalizations and death in patients with paroxysmal or persistent AF or AFL and cardiovascular comorbidity[923,931] • Associated with increased mortality in patients with recent decompensated HF[927] or permanent AF[932] • Dronedarone has the most solid safety data and may thus be a preferable first choice,[933,934] however not indicated in patients with HF and permanent AF[935,936] • Should not be used in NYHA class III or IV or unstable HF, in combination with QT-prolonging drugs or with strong CYP3A4 inhibitors (e.g. verapamil, diltiazem) and in patients with CrCl <30 mL/min • Concomitant use with dabigatran is contraindicated • Combination with digoxin may significantly increase digoxin serum concentration • When used with digitalis or beta-blockers their doses should be reduced • Should be discontinued in case of excessive QT prolongation (>500 ms or >60 ms increase) • A modest increase in serum creatinine is common and reflects drug-induced reduction in CrCl rather than a decline in renal function[937] • Has atrioventricular nodal-slowing properties • ECG at baseline and after 4 weeks
Sotalol (d,l racemic mixture)[233,891,894,895,920,938–940]	Oral	80 - 160 mg b.i.d.	• Only class III effects if dosing >160 mg daily • Considering its safety and efficacy and potential drug alternatives, sotalol should be used with a caution • Should not be used in patients with HFrEF, significant LVH, prolonged QT, asthma, hypokalaemia, or CrCl <30 mL/min • Dose-related torsades de pointes may occur in >2% of patients[941] • Should be discontinued in case of excessive QT prolongation (>500 ms or >60 ms increase) • The potassium channel-blocking effect increases with increasing dose and, consequently, the risk of ventricular proarrhythmia (torsades de pointes) increases • Observational data and a recent meta-analysis revealed a correlation with an increased all-cause mortality[890,897,934] , whereas a nationwide registry analysis and two RCTs found no evidence for increased safety concerns with sotalol[233,933,942,943] • ECG at baseline, after 1 day and after 1 - 2 weeks
Disopyramide[944–946]	Oral	100 - 400 mg two or t.i.d. (maximum 800 mg/24 h)	• Associated with significantly increased mortality[890,947], and rarely used for rhythm control in AF.[948,949] Should not be used in patients with a structural heart disease. Rarely used for rhythm control in AF patients, due to increased mortality and frequent intolerance to side-effects • May be useful in 'vagal' AF occurring in athletes or during sleep[901] • Reduces LV outflow obstruction and symptoms in patients with HCM[950]

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; b.i.d. = *bis in die* (twice a day); bpm = beats per minute; CrCl = creatinine clearance; CYP2D6 = cytochrome P450 2D6; CYP34A = cytochrome 34A; ECG=electrocardiogram; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFrEF = HF with reduced ejection fraction; LV = left ventricular; LVEF = LV ejection fraction; LVH = LV hypertrophy; NDCC = non-dihydropyridinecalcium-channel blocker; NYHA = New York Heart Association; QRS = QRS interval; QT = QT interval; RCT=randomized controlled trial; SBP = systolic blood pressure; t.i.d. = *ter in die* (three times a day); VKA = vitamin K antagonist.
[a]Caution is needed when using any AAD in patients with conduction-system disease (e.g. sinoatrial or atrioventricular node disease).

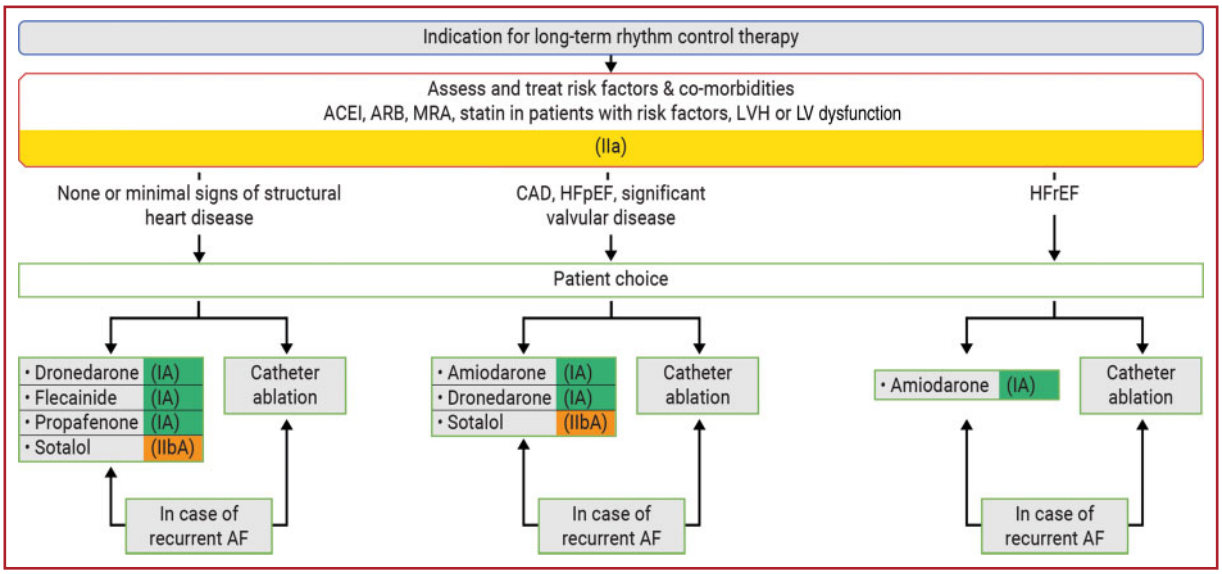


Figure 19 Long-term rhythm control therapy. ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CAD=coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = left ventricular hypertrophy; MRA=mineralocorticoid receptor antagonist.

Table 21 Non-antiarrhythmic drugs with antiarrhythmic properties (upstream therapy)

Drugs	Comment
ACEi, ARBs	Activated renin-angiotensin-aldosterone system is up-regulated in AF.[951,952] ACEi and ARBs showed encouraging results in preventing AF in preclinical studies.[953]
	As suggested by retrospective analyses and studies where AF was a prespecified secondary endpoint, ACEi/ARBs could prevent new-onset AF in patients with LV dysfunction, LVH, or hypertension.[954–961]
	As initial treatment, ACEi and ARBs seem to be superior to other antihypertensive regimens,[962] but ARBs did not reduce AF burden in patients without structural heart disease.[963] Despite several positive small-scale prospective studies and retrospective analyses, larger RCTs have shown controversial results and failed to confirm the role of ACEi or ARBs in secondary (post-cardioversion) prevention of AF.[964] The multifactorial pathways for AF promotion and study design could explain these negative results and should not discourage the use of ACEi or ARB to AAD in patients with structural heart disease.
MRAs	Aldosterone is implicated in inducibility and perpetuation of AF.[965–967] Evidence from RCTs showed that MRAs reduced new-onset atrial arrhythmias in patients with HFrEF in parallel with improvement of other cardiovascular outcomes.[968,969]
	Recently, the positive impact of MRAs was also shown in patients with HFpEF[970] irrespective of baseline AF status. Regarding other renin-angiotensin-aldosterone system inhibitors, the role of MRAs as upstream therapy in rhythm control strategy for patients with HF and AF has not been clarified. As AF is a marker of HF severity, the beneficial antiarrhythmic effect could be driven indirectly, through improvement of HF. A recent meta-analysis showed that MRAs significantly reduced new-onset AF and recurrent AF, but not postoperative AF.[971]
Beta-blockers	Several small studies suggested a lower AF recurrence rate with beta-blockers, with a comparable efficacy with sotalol.[939,972,973] However, most evidence pleads against a significant role of beta-blockers in preventing AF.[890] The observed beneficial effect could also result from transformation of clinically manifested AF to silent AF, because of the rate control with beta-blockers.
Statins	Statins are attractive candidates for upstream therapy, as the role of inflammation in AF is well established. However, in an adequately designed RCT,[974] statins failed to show a beneficial effect, and their preventive effect was not confirmed in other settings.[975,976] Specific patient groups in whom statins could induce reverse remodelling are not identified yet, but findings from the CARAF registry suggested that AF patients already on beta-blockers could benefit from statin therapy.[977] Polyunsaturated fatty acids also failed to show convincing benefit in preventing AF.[978–982]

AAD = antiarrhythmic drug; ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; ARB=angiotensin receptor blocker; CARAF = Canadian Registry of Atrial Fibrillation; HF = heart failure; HFrEF = HF with reduced ejection fraction; HFpEF = HF with preserved ejection fraction; LV = left ventricular; LVH = LV hypertrophy; MRA = mineralocorticoid receptor antagonist; RCT = randomized controlled trial.

Recommendations for long-term antiarrhythmic drugs

Recommendations	Class[a]	Level[b]
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.[233,570,884,942,983,985]	I	A
Dronedarone is recommended for long-term rhythm control in AF patients with: • Normal or mildly impaired (but stable) LV function, or • HFpEF, ischaemic, or VHD.[884,923,925,985]	I	A
Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia.[594,884,910,942,983,984]	I	A
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.[884,942]	I	B
In AF patients treated with flecainide for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered.	IIa	C
Sotalol may be considered for long-term rhythm control in patients with normal LV function or with ischaemic heart disease if close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is provided.[233,983]	IIb	A
AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C

AAD = antiarrhythmic drug; AF = atrial fibrillation; CrCl = Creatinine clearance; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVH = LV hypertrophy; VHD = valvular heart disease.
[a]Class of recommendation.
[b]Level of evidence.

10.2.2.7.3 *Assessment and long-term monitoring of the risk of proarrhythmia with antiarrhythmic drugs.* A variety of clinical, echocardiographic, and ECG criteria have been associated with a higher risk of proarrhythmia.[986–989] Increasing age, female sex, impaired renal and/or liver function, and known CAD have been variously identified as associated with higher risk.[890,990–992] Concomitant AAD use, hypokalaemia, or family history of sudden death have also been implicated.[990] Proarrhythmic events tend to cluster shortly after drug initiation, especially if a loading dose or a change in usual dosage is prescribed.[568] For quinidine, the risk is idiosyncratic independent of dosage. Impaired LV function and LVH are echocardiographic markers of increased proarrhythmic risk. Sotalol has a proarrhythmic risk even in the absence of structural heart disease. On the 12-lead ECG, prolonged corrected QT interval (QTc), widened QRS, and prolonged PR interval have all been associated with proarrhythmia.[993–995] Significant ion-channel mutations have been detected in only a minority of cases of drug-induced torsade.[996] Periodic ECG analysis for proarrhythmia signs has been used successfully in recent AAD trials[594,997]. Specifically, ECG monitoring was used systematically on days 1–3 in patients receiving flecainide, propafenone, or sotalol to identify those at risk of proarrhythmia[233,594,998]. The role of routine use of exercise stress testing in patients commencing 1C drugs who had no evidence of structural heart disease is still debatable[915,999].

10.3 'C' – Cardiovascular risk factors and concomitant diseases: detection and management

Cardiovascular risk-factor burden and comorbidities, including lifestyle factors and borderline conditions, significantly affect the lifetime risk for AF development (*Supplementary Figure 5*). The continuum of unhealthy lifestyle, risk factor(s), and cardiovascular disease can contribute to atrial remodelling/cardiomyopathy and development of AF that commonly results from a combined effect of multiple interacting factors (often without specific threshold values).

The 'C' component of the ABC pathway includes identification and management of concomitant diseases, cardiometabolic risk factors, and unhealthy lifestyle factors. Management of risk factors and cardiovascular disease complements stroke prevention and reduces AF burden and symptom severity. In a recent RCT, for example, targeted therapy of underlying conditions significantly improved maintenance of sinus rhythm in patients with persistent AF and HF.[245]

Whereas strategies on comprehensive risk-factor modification and interventions targeting underlying conditions have shown reduction of AF burden and recurrence, studies addressing isolated management of specific conditions alone (e.g. hypertension) yielded inconsistent findings,[1000] likely because the condition was not a sole contributor to AF.

10.3.1 Lifestyle interventions

10.3.1.1 Obesity and weight loss

Obesity increases the risk for AF progressively according to body mass index.[366,1001–1005] It may also increase the risk for ischaemic stroke, thrombo-embolism, and death in AF patients,[366] notwithstanding an obesity paradox in AF patients, especially regarding all-cause and cardiovascular death, with an inverse relationship between overweight/obesity and better cardiovascular prognosis in long-term follow-up.[1006]

Intense weight reduction with comprehensive management of concomitant cardiovascular risk factors resulted in fewer AF recurrences and symptoms than general advice in obese patients with AF[636,888,889]. Achieving a healthy weight may reduce blood pressure (BP), dyslipidaemia, and risk of developing type 2 diabetes mellitus,

thus improving the cardiovascular risk profile.[1007] Obesity may increase AF recurrence rates after AF catheter ablation (with OSA as a potential confounder).[638,643,789,1008] It has also been linked to a higher radiation dose and complication rate during AF ablation,[1009,1010] whereas symptom improvement after AF catheter ablation seems comparable in obese and normal-weight patients.[1008] Given the potential to reduce AF episodes by weight reduction, AF catheter ablation should be offered to obese patients in conjunction with lifestyle modifications for weight reduction (*Figure 18*).

10.3.1.2 Alcohol and caffeine use

Alcohol excess is a risk factor for incident AF[1011–1014] and bleeding[395] in anticoagulated patients (mediated by poor adherence, liver disease, variceal bleeding, and risk of major trauma), and high alcohol intake may be associated with thrombo-embolism or death.[1015] In a recent RCT, alcohol abstinence reduced arrhythmia recurrence in regular drinkers with AF.[1016]

By contrast, it is unlikely that caffeine consumption causes or contributes to AF.[47] Habitual caffeine consumption might be associated with lower risk of AF, but caffeine intake may increase symptoms of palpitations unrelated to AF.

10.3.1.3 Physical activity

Many studies have demonstrated beneficial effects of moderate exercise/physical activity on cardiovascular health.[1017–1019] Nevertheless, the incidence of AF appears to be increased among elite athletes, and multiple small studies reported a relationship between AF and vigorous physical activity, mainly related to long-term or endurance sport participation.[1020–1023] A non-linear relationship between physical activity and AF seems likely. Based on these data, patients should be encouraged to undertake moderate-intensity exercise and remain physically active to prevent AF incidence or recurrence, but maybe avoid chronic excessive endurance exercise (such as marathons and long-distance triathlons, etc.), especially if aged >50 years. Owing to few randomized patients and outcomes, the effect of exercise-based cardiac rehabilitation on mortality or serious adverse events is uncertain.[1024]

10.3.2 Specific cardiovascular risk factors/comorbidities

10.3.2.1 Hypertension

Hypertension is the most common aetiological factor associated with the development of AF, and patients with hypertension have a 1.7-fold higher risk of developing AF compared with normotensives.[26,1025]

Hypertension also adds to the complications of AF, particularly stroke, HF, and bleeding risk. AF patients with a longer hypertension duration or uncontrolled systolic BP (SBP) levels should be categorized as 'high-risk', and strict BP control in addition to OAC is important to reduce the risk of ischaemic stroke and ICH.

Given the importance of hypertension as a precipitating factor for AF, which should be regarded as a manifestation of hypertension target-organ damage, treatment of hypertension consistent with current BP guidelines[1026] is mandatory in AF patients, aiming to achieve BP≤130/80 mmHg to reduce adverse outcomes.[338,1027,1028] A recent randomized trial in patients with paroxysmal AF and hypertension reported fewer recurrences in patients undergoing renal denervation in addition to PVI compared with patients undergoing PVI only.[1029] Sotalol should not be used in the presence of hypertensive LVH or renal impairment, owing to the risk of proarrhythmia. There is some evidence of angiotensin converting enzyme or angiotensin receptor blocker use to improve outcomes in AF or reduce progression of the arrhythmia[26,1025] Other lifestyle changes, including obesity management, alcohol reduction, and attention to OSA, may also help in patients with AF and hypertension.

10.3.2.2 Heart failure

The interactions between AF and HF and the optimal management of patients with both AF and HF are discussed in *section 11.6*.

10.3.2.3 Coronary artery disease

The interactions between AF and CAD and the optimal management of patients with both AF and CAD are discussed in *section 11.3*.

10.3.2.4 Diabetes mellitus

In addition to shared risk factors (e.g. hypertension and obesity),[1004,1030] diabetes is an independent risk factor for AF, especially in young patients.[1031] Silent AF episodes are favoured by concurrent autonomic dysfunction,[1032] thus suggesting an opportunity for routine screening for AF in diabetes mellitus patients. The prevalence of AF is at least two-fold higher in patients with diabetes compared with people without diabetes,[1033] and AF incidence rises with increasing severity of microvascular complications (retinopathy, renal disease).[1034] Both type 1 and type 2 diabetes mellitus are the risk factors for stroke.[342,1035]

Intensive glycaemic control does not affect the rate of new-onset AF,[1036] but metformin and pioglitazone could be associated with lower long-term risk of AF in patients with diabetes,[1037] while this was not confirmed for rosiglitazone.[1038] Currently there is no evidence that glucagon-like peptide-1 agonists, sodium glucose co-transporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors affect the development of AF.[1039]

Previous meta-analyses showed no significant interaction between diabetes mellitus and NOAC effects in AF patients,[423,1040] but vascular mortality was lower in patients with diabetes treated with NOACs than in those on warfarin.[1040] Bleeding risk reduction with NOACs was similar in diabetic and non-diabetic patients except for apixaban, where a lower reduction in haemorrhagic complications was reported in the AF patients with diabetes compared with AF patients without diabetes.[1041] Regarding potential side-effects of OAC, there is no evidence that bleeding risk is increased in patients with diabetes and retinopathy.[341]

Optimal glycaemic control in 12 months before AF catheter ablation was associated with significant reduction in recurrent AF after ablation.[1042]

10.3.2.5 Sleep apnoea

The most common form of sleep-disordered breathing, OSA, is highly prevalent in patients with AF, HF, and hypertension, and is associated with increased risk of mortality or major cardiovascular events.[1043] In a prospective analysis, approximately 50% of AF patients had OSA compared with 32% of controls.[1044] The mechanisms facilitating AF include intermittent nocturnal hypoxemia/hypercapnia, intrathoracic pressure shifts, sympathovagal imbalance, oxidative stress, inflammation, and neurohumoral activation.[1045] OSA has been shown to reduce success rates of AADs, electrical cardioversion, and catheter ablation in AF.[1045]

Continuous positive airway pressure (CPAP) is the therapy of choice for OSA, and may ameliorate OSA effects on AF recurrences.[1046,1047] Observational studies and meta-analyses showed that appropriate CPAP treatment of OSA may improve rhythm control in AF patients.[648,649,1047–1051]

It seems reasonable to test for OSA before the initiation of rhythm control therapy in symptomatic AF patients, with the aim to reduce symptomatic AF recurrences (*Figure 18*). In the ARREST-AF (Aggressive Risk Factor Reduction Study – Implication for AF) and LEGACY (Long-term Effect of Goal-directed weight management on an Atrial fibrillation Cohort: a 5-Year follow-up study) studies, an aggressive risk-factor reduction programme focusing on weight management, hyperlipidaemia, OSA, hypertension, diabetes, smoking cessation, and alcohol-intake reduction significantly reduced AF burden after PVI.[636,1052] However, it remains unclear how and when to test for OSA and implement OSA management in the standard work-up of AF patients.

Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF

Recommendations	Class[a]	Level[b]
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.[888]	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.[245,636,887,889,1016,1052]	I	B
Opportunistic screening for AF is recommended in hypertensive patients.[26,172,222]	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.[26,1035]	I	B
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.[898,899,1011]	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for OAC therapy.[324,1012,1014,1016]	IIa	B
Physical activity should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.[1027–1033,1063]	IIa	C
Opportunistic screening for AF should be considered in patients with OSA.[172]	IIa	C
Optimal management of OSA may be considered, to reduce AF incidence, AF progression, AF recurrences, and symptoms.[650,651,1047–1051]	IIb	C

AF = atrial fibrillation; BP = blood pressure; OAC = oral anticoagulant; OSA = obstructive sleep apnoea.
[a]Class of recommendation.
[b]Level of evidence.

11 The ABC pathway in specific clinical settings/conditions/patient populations

In this section, the management of AF in patient populations with specific conditions is described. The principles of the ABC pathway apply in these settings as well. Additionally, specific considerations are given for each of these special conditions and populations.

11.1 Atrial fibrillation with haemodynamic instability

Acute haemodynamic instability (i.e. syncope, acute pulmonary oedema, ongoing myocardial ischaemia, symptomatic hypotension, or cardiogenic shock) in AF patients presenting with a rapid ventricular rate requires prompt intervention. In severely compromised patients, emergency electrical cardioversion should be attempted without delay, and anticoagulation should be started as soon as possible.

In critically ill patients and those with severely impaired LV systolic function, AF is often precipitated/exacerbated by increased sympathetic tone, inotropes, and vasopressors, and rhythm control is often unsuccessful. It is important to identify and correct precipitating factors and secondary causes and optimize background treatment. Owing to their rate-controlling effect during exertion and increased sympathetic tone, rather than only at rest, beta-blockers are preferred over digitalis glycosides for ventricular rate control in AF.[490] Beta-blockers and NDCC antagonists may exert a negative inotropic effect (the latter are contraindicated in HFrEF). Digoxin is often unsuccessful due to the increased sympathetic tone in these patients.

As conventional therapy is often ineffective or not well-tolerated,[490] electrical cardioversion should always be considered, even as initial therapy, whereas intravenous amiodarone may be instituted for rate control (or potential cardioversion to sinus rhythm), with or without electrical cardioversion.[504,514,515] Intravenous administration of amiodarone may lead to a further decrease in BP.

Recommendations for management of AF with haemodynamic instability

Recommendations	Class[a]	Level[b]
Emergency electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability.[1053,1054]	I	B
In AF patients with haemodynamic instability, amiodarone may be considered for acute control of heart rate.[503,511,512]	IIb	B

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

11.2 First-diagnosed (new-onset) atrial fibrillation

First-diagnosed or new-onset AF is a working diagnosis in a patient without a history of AF, until the pattern of AF can be defined more

precisely. Although the clinical profile and outcome of patients with first-diagnosed AF in AF registries were less favourable than those with paroxysmal AF, rather resembling permanent AF,[1055,1056] OAC prescription rates were the lowest in patients with first-diagnosed AF.[1057] In patients with first-diagnosed AF, the ABC pathway should resemble all steps outlined in the *Central Illustration*.

11.3 Acute coronary syndromes, percutaneous coronary intervention, and chronic coronary syndromes in patients with atrial fibrillation

The incidence of AF in acute coronary syndromes (ACS) ranges from 2 - 23%,[1058] the risk of new-onset AF is increased by 60 - 77%[1059] in myocardial infarction patients, and AF per se may be associated with an increased risk of ST-segment elevation myocardial infarction (STEMI) or non-STEMI ACS.[381,1060–1063] Overall, 10 - 15% of AF patients undergo PCI for CAD.[1064] In observational studies, patients with AF and ACS were less likely to receive appropriate antithrombotic therapy[1065] and more likely to experience adverse outcomes[1066] than ACS patients without AF.

Peri-procedural management of patients with an ACS or undergoing PCI is detailed in the respective ESC Guidelines on myocardial revascularization[1067] and chronic coronary syndromes (CCS).[1068]

Post-procedural management of atrial fibrillation patients with acute coronary syndrome and/or percutaneous coronary intervention

In AF patients having an ACS or undergoing PCI, concomitant risks of ischaemic stroke/systemic embolism, coronary ischaemic events, and antithrombotic treatment-related bleeding need to be carefully balanced when considering the use and duration of combined antithrombotic therapy.[1069] Overall, dual antithrombotic therapy including OAC (preferably NOAC) and a $P2Y_{12}$ inhibitor (preferably clopidogrel) is associated with significantly less major bleeding (and ICH) than triple therapy. However, available evidence suggests that at least a short course of triple therapy (e.g. ≤1 week) would be desirable in some AF patients after a recent ACS or undergoing PCI, especially in those at increased risk of ischaemic events[1070,1071] (*Figure 20*).

Box 1 About post-procedural management of patients with AF and ACS and/or PCI

Shorter courses of triple therapy (OAC + DAPT) may be safe in post-ACS/PCI patients requiring OAC.[1076] Observational data[1077] and the WOEST trial with warfarin (a safety RCT, underpowered for ischaemic outcomes)[1078] suggested better safety and similar efficacy with dual (OAC + clopidogrel) vs. triple therapy.

RCTs of NOACs in AF patients after a recent ACS/PCI

Four RCTs compared dual therapy with a $P2Y_{12}$ inhibitor (mostly clopidogrel) plus a NOAC—dabigatran 110 mg or 150 mg b.i.d. (RE-DUAL PCI),[1079] rivaroxaban 15 mg o.d. (PIONEER AF-PCI),[1080] apixaban 5 mg b.i.d. (AUGUSTUS),[1081] or edoxaban 60 mg o.d. (ENTRUST-AF PCI)[1082] —vs. triple therapy with a VKA in AF patients with a recent ACS or undergoing PCI. The two-by-two factorial AUGUSTUS trial design enabled the comparison of aspirin vs. placebo (see *Supplementary Table 12* for detailed information about these studies). All four trials had a primary safety endpoint (i.e. bleeding) and were underpowered to assess ischaemic outcomes.

Despite some heterogeneity among these trials, all have consistently:

- Included a proportion of patients with an ACS/PCI (37 - 52%); nevertheless, the highest risk patients (e.g. previous stent thrombosis or a complex PCI with stent-in-stent placement) were largely under-represented;
- Used triple therapy during PCI and until randomization (1 - 14 days post PCI);
- Most commonly used the $P2Y_{12}$ inhibitor clopidogrel (overall, >90%); and
- Reported a significant reduction of major/clinically significant bleeding, comparable rates of ischaemic stroke, similar or non-significantly higher rates of myocardial infarction and stent thrombosis, and a neutral effect on trial-defined major adverse cardiovascular events and all-cause mortality with dual (NOAC + $P2Y_{12}$) vs. triple (VKA + $P2Y_{12}$ + aspirin) therapy.

In AUGUSTUS,[1081] both placebo (vs. aspirin) and apixaban (vs. VKA) regimens were associated with significant reduction in bleeding, and apixaban (vs. VKA) was associated with significantly lower rates of stroke, death, or hospitalization.

Meta-analyses of RCTs

- **Bleeding outcomes:** Meta-analyses[1070,1071,1083,1084] consistently showed a significant reduction in major bleeding with dual vs. triple and NOAC- vs. VKA-based therapies (NOAC-based treatments were also associated with a significant reduction in ICH).
- **Ischaemic events:** Stroke rates were similar across all treatment arms, but the rates of myocardial infarction and stent thrombosis were numerically higher with dual vs. triple therapy. In two meta-analyses[1070,1071] stent thrombosis was statistically significantly increased on dual (i.e. no aspirin) vs. triple therapy. Also, the risk of myocardial infarction or stent thrombosis was slightly higher with dabigatran 110 mg but not dabigatran 150 mg.
- The trial-defined major adverse cardiovascular events and mortality rates were similar in all treatment arms, suggesting that the benefit from major bleeding and ICH reduction is counterbalanced by a higher risk for coronary (mainly stent-related) ischaemic events with dual therapy.

ACS = acute coronary syndromes; AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); DAPT = dual antiplatelet therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ICH = intracranial haemorrhage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; o.d. = *omni die* (once daily); PCI = percutaneous coronary intervention; PIONEER AF-PCI = (OPen-Label, Randomized, Controlled, Multicenter Study ExplorIng TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention; RCT = randomized controlled trial; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; VKA = vitamin K antagonist; WOEST = What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

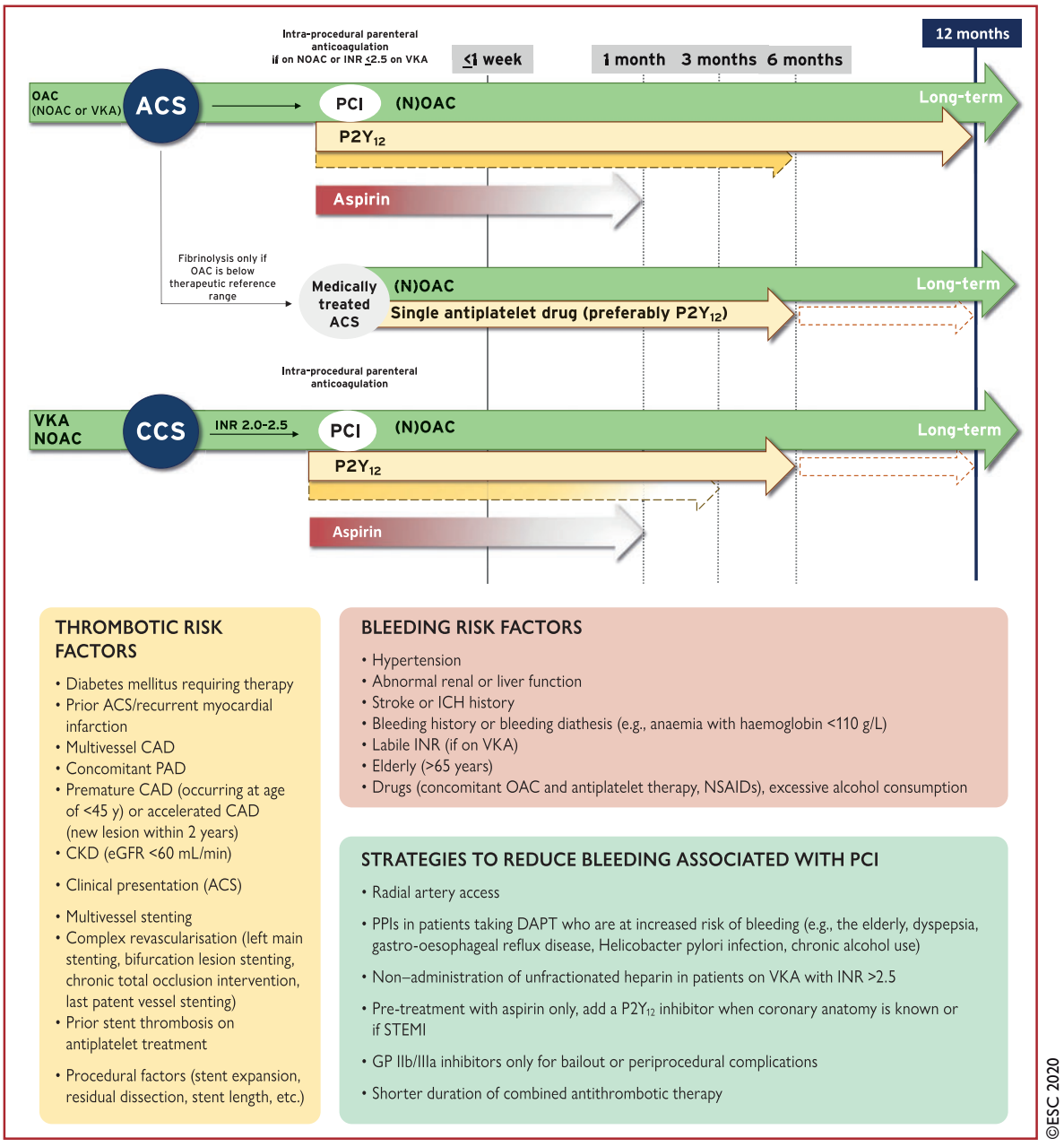


Figure 20 Post-procedural management of patients with AF and ACS/PCI (full-outlined arrows represent a default strategy; graded/dashed arrows show treatment modifications depending on individual patient's ischaemic and bleeding risks).

Pretreatment with a $P2Y_{12}$ inhibitor is recommended in STEMI patients or when coronary anatomy is known; it should be withheld in non-STEMI ACS until the time of coronary angiography in case of an early invasive strategy within 24 hours. Observational studies indicate that PCI on uninterrupted VKAs is generally safe compared with OAC interruption and heparin-bridging therapy,[1073] particularly with radial artery access; in contrast, studies on NOACs are conflicting, predominantly discouraging a PCI on fully uninterrupted NOAC therapy.[1074,1075] If urgent PCI is needed, administration of a parenteral anticoagulant (UFH, LMWH, or bivalirudin) is suggested, with temporary withdrawal of NOAC at least for the initial post-procedural period (e.g. 24 h) depending on the patient's thrombotic and bleeding risk profile. Where thrombolysis is being considered in a patient with STEMI, the initial step should be to assess the anticoagulation status (e.g. INR in a patient taking VKA; with a NOAC, assessing, for example, activated partial thromboplastin time on dabigatran or anti-factor Xa activity on factor Xa inhibitors). Thrombolytic therapy may be associated with an increased risk of bleeding in systemically anticoagulated patients, especially if parenteral heparin and antiplatelet drugs are coadministered. A balance between the potential benefit (e.g. large anterior myocardial infarction) and harm (e.g. ICH) is needed, as well as the reassessment of urgent transfer to a PCI centre. If the supposedly anticoagulated patient does not have evidence of a therapeutic anticoagulation effect (e.g. INR <2.0 on warfarin; or no NOAC anticoagulant effect detected), systemic thrombolysis may be considered if no access to primary PCI is possible.

ACS = acute coronary syndromes; ASA = acetylsalicylic acid; CAD = coronary artery disease; CCS = chronic coronary syndromes; CKD = chronic kidney disease; DAPT = dual antithrombotic therapy; eGFR = estimated glomerular filtration rate; ICH = intracranial haemorrhage; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

Whichever initial treatment plan was chosen, dual therapy with OAC and an antiplatelet drug (preferably clopidogrel) is recommended for the first 12 months after PCI for ACS, or 6 months after PCI in patients with CCS.[1067] Thereafter, OAC monotherapy is to be continued (irrespective of the stent type) provided that there were no recurrent ischaemic events in the interim. In 1-year event-free (i.e. 'stable') AF patients with CAD and no PCI, OAC monotherapy is also recommended.[1072]

Use of prasugrel or ticagrelor has been associated with a greater risk of major bleeding compared with clopidogrel[1085–1089] and should be avoided in ACS patients with AF. In the RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial, 12% of patients received ticagrelor with dabigatran, but experience with ticagrelor or prasugrel was minimal in PIONEER-AF (OPen-Label, Randomized, Controlled, Multicenter Study ExplorIng TwO TreatmeNt StratEgiEs of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), AUGUSTUS, and ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). In patients at potential risk of gastrointestinal bleeding, concomitant use of proton-pump inhibitors is reasonable.[1084]

In AF patients treated with surgical coronary revascularization, OAC should be resumed as soon as bleeding is controlled, possibly in combination with clopidogrel, and triple therapy should be avoided.

Poor ventricular rate control during AF may exacerbate symptoms of myocardial ischaemia and precipitate or worsen HF. Appropriate treatment may include a beta-blocker or rate-limiting calcium antagonist. In haemodynamic instability, acute cardioversion may be indicated. Vernakalant, flecainide, and propafenone should not be used for rhythm control in patients with known CAD (*section 10.2.2.2*).

In all AF patients with an ACS/CCS, optimized management of risk factors is needed, and cardiovascular prevention strategies such as good BP control,[338] lipid management, and other cardiovascular prevention interventions[1007] should be implemented as needed, once the acute presentation is stabilized.

Recommendations for patients with AF and an ACS, PCI, or CCS[1068]

General recommendations for patients with AF and an indication for concomitant antiplatelet therapy	Class[a]	Level[b]
In AF patients eligible for NOACs, it is recommended to use a NOAC[c] in preference to a VKA in combination with antiplatelet therapy.[1079,1081]	I	A
In patients at high bleeding risk (HAS-BLED ≥3), rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk.[1080]	IIa	B
In patients at high bleeding risk (HAS-BLED ≥3), dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk.[1079]	IIa	B
In AF patients with an indication for a VKA in combination with antiplatelet therapy, the VKA dosing should be carefully regulated with a target INR of 2.0 - 2.5 and TTR>70%.[1094,1095,1104,1105]	IIa	B
Recommendations for AF patients with ACS		
In AF patients with ACS undergoing an uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis[d] is low or if concerns about bleeding risk[e] prevail over concerns about risk of stent thrombosis,[d] irrespective of the type of stent used.[1090,1092–1095]	I	A
Triple therapy with aspirin, clopidogrel, and an OAC[f] for longer than 1 week after an ACS should be considered when risk of stent thrombosis[d] outweighs the bleeding risk,[e] with the total duration (≤1 month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge.	IIa	C
Recommendations in AF patients with a CCS undergoing PCI		
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis[d] is low or if concerns about bleeding risk[e] prevail over concerns about risk of stent thrombosis,[d] irrespective of the type of stent used.[1076,1078–1081]	I	A
Triple therapy with aspirin, clopidogrel, and an OAC[f] for longer than 1 week should be considered when risk of stent thrombosis[d] outweighs the bleeding risk,[e] with the total duration (≤1 month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge.	IIa	C

ACS = acute coronary syndrome; AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); CCS = chronic coronary syndrome; CKD = chronic kidney disease; DAPT = Dual antiplatelet therapy; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; o.d. = *omni die* (once daily); OAC = oral anticoagulant; PCI=percutaneous coronary intervention; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]See summary of product characteristics for reduced doses or contraindications for each NOAC in patients with CKD, body weight <60 kg, age >75 - 80 years, and/or drug interactions.

[d]Risk of stent thrombosis encompasses: (i) risk of thrombosis occurring, and (ii) risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include: stenting of left main stem or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

[e]Bleeding risk in AF patients may be assessed using the HAS-BLED score (*section 10.1.2*), which draws attention to modifiable bleeding risk factors; those at high risk (score ≥3) can have more frequent or early review and follow-up. Bleeding risk is highly dynamic and does not remain static, and relying on modifiable bleeding risk factors alone is an inferior strategy to evaluate bleeding risk.[389]

[f]When dabigatran is used in triple therapy, dabigatran 110 mg b.i.d may be used instead of 150 mg b.i.d, but the evidence is insufficient.

11.4 Acute stroke or intracranial haemorrhage in patients with atrial fibrillation

11.4.1 Patients with atrial fibrillation and acute ischaemic stroke or transient ischaemic attack

Management of acute stroke in AF patients is beyond the scope of this document. In AF patients presenting with acute ischaemic stroke while taking OAC, acute therapy depends on the treatment regimen and intensity of anticoagulation. Patients on VKA with an INR<1.7 are eligible for thrombolysis according to the neurological indication (if presenting with a clinically relevant neurological deficit within the appropriate time window and ICH is excluded with cerebral imaging). In patients taking NOACs, measurement of activated partial thromboplastin time or thrombin time (for dabigatran), or antifactor Xa levels (for factor Xa inhibitors) will provide information on whether the patient is systemically anticoagulated. Whenever possible, the time when the last NOAC dose was taken should be elucidated (generally, thrombolysis is considered to be safe in patients with last NOAC intake being ≥48 h, assuming normal renal function).[1090]

If the patient is systemically anticoagulated, thrombolysis should not be performed due to the risk of haemorrhage, and endovascular treatment should be considered. In patients taking dabigatran, systemic thrombolysis may be performed after reversal of the dabigatran action by idarucizumab.[1091]

Secondary prevention of stroke/systemic embolism in patients after acute AF-related ischaemic stroke or TIA includes early prevention of recurrent ischaemic stroke in the 2 weeks after the index event and long-term prevention thereafter.

Whereas infarct size/stroke severity is used clinically to guide timing of OAC initiation,[1090] the usefulness of such an approach in estimating the net benefit of early treatment may be limited. Robust data to inform optimal timing for (re)initiation of OAC after acute stroke are lacking. From the cardiological perspective, OAC should be (re)initiated as soon as considered possible from the neurological perspective (in most cases within the first 2 weeks). A multidisciplinary approach with involvement of stroke specialists, cardiologists, and patients is considered appropriate.

In AF patients who presented with acute ischaemic stroke despite taking OAC, optimization of OAC therapy is of key importance—if on VKA, optimize TTR (ideally >70%) or switch to a NOAC; if on NOAC, ensure appropriate dosing and good adherence to treatment. Inappropriate NOAC under-dosing using lower or reduced doses of specific NOACs has been associated with increased risk of stroke/systemic embolism, hospitalization, and deaths without appreciable reduction in major bleeding.[1107]

11.4.2 Cryptogenic stroke/embolic stroke with undetermined source

Currently available evidence including two recently completed RCTs[1108,1109] does not support *routine* OAC use in patients with acute ischaemic stroke of uncertain aetiology (cryptogenic stroke) or acute embolic stroke of undetermined source in patients *without documented AF* (*Supplementary Box 4*). Of note, subgroup

Box 2 About acute ischaemic stroke in patients with AF

AF-related ischaemic strokes are often fatal or disabling [106], with increased risk of early recurrence within 48 h [1092] to 2 weeks,[1092–1095] or haemorrhagic transformation,[1096] especially in the first days after large cardio-embolic lesions and acute recanalization therapy.[1097,1098] Notably, ICH is generally associated with higher mortality and morbidity than recurrent ischaemic stroke.

Timing of OAC (re)initiation after acute ischaemic stroke

- Early anticoagulation after acute ischaemic stroke might cause parenchymal haemorrhage, with potentially serious clinical consequences[1097,1099] Using UFH, LMWH, heparinoids, or VKAs <48 h after acute ischaemic stroke was associated with an increased risk of symptomatic ICH, without significant reduction in recurrent ischaemic stroke.[1095]
- Reportedly, the 90-day risk of recurrent ischaemic stroke outweighs the risk of symptomatic ICH in AF patients receiving a NOAC 4 - 14 days after the acute event[1100–1102] (ischaemic stroke recurrence rates after mild/moderate ischaemic stroke significantly increased with a later NOAC administration,[1101] e.g. >14 days).[1100] In a small RCT, rivaroxaban use within 5 days after mild ischaemic stroke in AF patients was associated with similar event rates compared with VKA.[1103]

As high-quality RCT-derived evidence to inform optimal timing of anticoagulation after acute ischaemic stroke is lacking, OAC use in the early post-stroke period is currently based on expert consensus.[505] Several ongoing RCTs [ELAN (NCT03148457), OPTIMAS (EudraCT, 2018-003859-3), TIMING (NCT02961348), and START (NCT03021928)] are investigating early (<1 week) vs. late NOAC initiation in patients with AF-related ischaemic stroke (first results are not expected before 2021).

Long-term secondary stroke prevention

- There is no evidence that the addition of aspirin to OAC or supratherapeutic INRs would improve outcomes in secondary stroke prevention.
- Compared with VKAs, NOACs were associated with better efficacy in secondary stroke prevention and better safety regarding ICH in a meta-analysis of landmark NOAC AF trial.[1104]
- Good adherence to OAC treatment is essential for effective secondary stroke prevention.

There is some evidence to support that strokes can induce AF through neurogenic mechanisms[1105,1106] The first study showed that damage to the insula increases the odds of AF detection after ischaemic stroke and is more prevalent in patients with AF diagnosed after stroke than among those without AF.[1105] The second study explained the reason why AFDAS detected soon after ischaemic stroke is associated with a low risk of ischaemic stroke recurrence.[1106]

AF = atrial fibrillation; ELAN = Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With AF; ICH = intracranial haemorrhage; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; OPTIMAS = OPtimal TIMing of Anticoagulation after Stroke; RCT = randomized controlled trial; START = Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in AF; TIMING = TIMING of Oral Anticoagulant Therapy in Acute Ischemic Stroke With AF; UFH = unfractionated heparin; VKA = vitamin K antagonist.

analyses of those two RCTs suggested that certain subgroups (i.e. age ≥75 years, impaired renal function,[1109] or enlarged LA[1110]) could benefit from OAC, but more data are needed to inform optimal use of NOACs among patients with a cryptogenic stroke. Two ongoing trials will study the use of apixaban in this setting [ATTICUS (Apixaban for treatment of embolic stroke of undetermined source)][1111] and ARCADIA [(AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) (NCT03192215)].

Efforts to improve detection of AF are needed in such patients (see also *section 8*). Clinical risk scores {e.g. C_2HEST [CAD/COPD (1 point each), Hypertension (1 point), Elderly (≥75 years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score)]} have been proposed for identification of 'high-risk' patients for AF diagnosis[1112] and facilitation of prolonged monitoring.

Recommendations for the search for AF in patients with cryptogenic stroke

Recommendations	Class[a]	Level[b]
In patients with acute ischaemic stroke or TIA and without previously known AF, monitoring for AF is recommended using a short-term ECG recording for at least the first 24 h, followed by continuous ECG monitoring for at least 72 h whenever possible.[1113–1116]	I	B
In selected[c] stroke patients without previously known AF, additional ECG monitoring using long-term non-invasive ECG monitors or insertable cardiac monitors should be considered, to detect AF.[1112]	IIa	B

AF = atrial fibrillation; C_2HEST = CAD/COPD (1 point each), Hypertension (1 point), Elderly (≥75 years, 2 points), Systolic heart failure (2 points), and Thyroid disease (hyperthyroidism, 1 point) (score); ECG=electrocardiogram; LA = left atrial; TIA=transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Not all stroke patients would benefit from prolonged ECG monitoring; those deemed at risk of developing AF (e.g. elderly, with cardiovascular risk factors or comorbidities, indices of LA remodelling, high C_2HEST score, etc.) or those with cryptogenic stroke and stroke characteristics suggestive of an embolic stroke should be scheduled for prolonged ECG monitoring.

11.4.3 Post-stroke patients without known atrial fibrillation

Detection of previously unknown AF after stroke has important implications for secondary prevention. Several RCTs have established the effectiveness of ECG monitoring for post-stroke AF detection, with numbers needed to screen of 8–14.[1117,1118]

Looking harder and longer and using more sophisticated monitoring may generally improve AF detection. In a meta-analysis[1118] of 50 post-stroke studies, the proportion of patients with post-stroke AF was 7.7% in the emergency room using admission ECG; 5.1% in the wards using serial ECG, continuous inpatient ECG monitoring/cardiac telemetry, and in-hospital Holter monitoring; 10.7% in the first ambulatory period using ambulatory Holter; and, after discharge, 16.9% using mobile cardiac outpatient telemetry and external or implantable loop recording. The overall post-stroke AF detection after all phases of cardiac monitoring reached 23.7%.[1118]

In patients with ischaemic stroke/TIA, monitoring for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 h, also considering a tiered longer ECG monitoring approach[1113] and insertion of an intracardiac monitor in case of cryptogenic stroke.[1114,1119] Post-stroke ECG monitoring is likely cost-effective[1120,1121]; however, RCTs have not been powered to assess the effect of prolonged ECG monitoring and subsequent prescription of OAC on stroke or mortality in patients with detected AF.

11.4.4 Management of patients with atrial fibrillation post-intracranial haemorrhage

As ICH is the most feared, often lethal, complication of anticoagulant and antiplatelet therapy, there is a considerable reluctance to (re)initiate OAC in AF patients who survived an ICH, despite their high estimated risk of AF-related ischaemic stroke.

Patients with a history of recent ICH were excluded from RCTs of stroke prevention in AF, but available observational data suggest than many AF patients would benefit from (re)institution of OAC, depending on the cause(s) of ICH and findings on brain CT and MRI (*Supplementary Box 5*).

Treatment decision to (re)start OAC in AF patients after an ICH requires multidisciplinary-team input from cardiologists, stroke specialists, neurosurgeons, patients, and their family/carers. After acute spontaneous ICH (which includes epidural, subdural, subarachnoid, or intracerebral haemorrhage), OAC may be considered after careful assessment of risks and benefits, and cerebral imaging may help. The risk of recurrent ICH may be increased in the presence of specific risk factors, shown in *Figure 21*. Of note, the risk of OAC-related ICH is increased especially in Asian patients.[1122]

Compared with VKAs, the use of NOACs in patients without previous ICH is associated with an approximately 50% lower risk of ICH,[423] whereas the size and outcome of OAC-related ICH is similar with NOACs and VKAs.[1124] Hence, NOACs should be preferred in NOAC-eligible ICH survivors with AF although there is no RCT to prove this.

The optimal timing of anticoagulation after ICH is unknown, but should be delayed beyond the acute phase, probably for at least 4 weeks; in AF patients at very high risk of recurrent ICH, LAA occlusion may be considered. Ongoing RCTs of NOACs and LAA occlusion may inform decision making in the future.

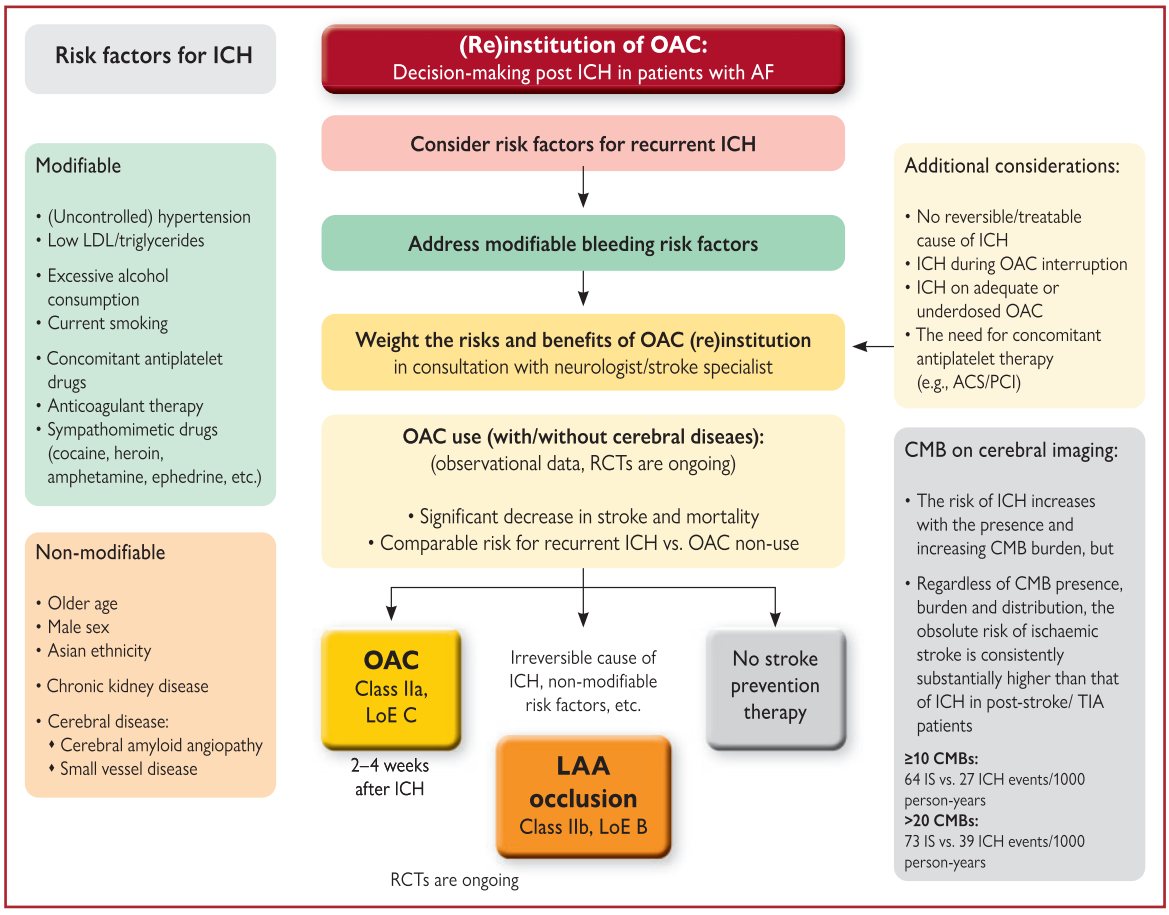


Figure 21 (Re-) initiation of anticoagulation post-intracranial bleeding.
A pooled analysis of individual patient data from cohort studies (n=20 322 patients; 38 cohorts; >35 225 patient-years) showed that although cerebral microbleeds can inform regarding the risk for ICH in patients with recent ischaemic stroke/TIA treated with antithrombotic therapy, the absolute risk of ischaemic stroke is substantially higher than that of ICH, regardless of the presence, burden, or location of cerebral microbleeds.[505,1123]
IS = ischaemic stroke;ACS = acute coronary syndrome; CMB = cerebral microbleeds; ICH = intracranial haemorrhage; LAA = left atrial appendage; LDL = low-density lipoprotein; LoE = level of evidence; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; TIA = transient ischaemic attack.

Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke	Class[a]	Level[b]
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients.[1125–1130]	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended.[1095]	III	B
Recommendations for stroke prevention in AF patients after intracranial haemorrhage		
In AF patients at high risk of ischaemic stroke, (re-)initiation of OAC, with preference for NOACs over VKAs in NOAC-eligible patients, should be considered in consultation with a neurologist/stroke specialist after: • A trauma-related ICH • Acute spontaneous ICH (which includes subdural, subarachnoid, or intracerebral haemorrhage), after careful consideration of risks and benefits.[c]	IIa	C

AF = atrial fibrillation; ICH = intracranial haemorrhage; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TIA = transient ischaemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]A more favourable net benefit is likely with deep ICH or without neuroimaging evidence of cerebral amyloid angiopathy or microbleeds.

11.5 Active bleeding on anticoagulant therapy: management and reversal drugs

Management of patients with active bleeding while on OAC is shown in *Figure 22*. General assessment should include detection of the bleeding site, assessment of bleeding severity, and evaluation of the time-point of last OAC intake. Concomitant antithrombotic drugs and other factors influencing bleeding risk (alcohol abuse, renal function) should be explored. Laboratory tests, such as INR, are useful in case of VKA therapy. More specific coagulation tests for NOACs include diluted thrombin time, ecarin clotting time, or ecarin chromogenic assay for dabigatran, and chromogenic anti-factor Xa assay for rivaroxaban, apixaban, and edoxaban.[1131] However, these tests or measurement of NOAC plasma levels are not always readily available in practice and are often unnecessary for bleeding management.[1132] An overview of reversal drugs for NOACs is given in *Supplementary Table 13* and *Supplementary Figure 6*.

Notably, the time of last drug ingestion combined with assessment of renal function, haemoglobin, haematocrit, and platelet count enable appropriate clinical decision making in most of the cases.

Minor bleeding events should be treated with supportive measures such as mechanical compression or minor surgery to achieve haemostasis. Withdrawal of VKAs is not associated with a prompt reduction of anticoagulant effect, while NOACs have a short plasma half-life and haemostasis can be expected within 12 - 24 h after an omitted dose.

Treatment of moderate bleeding events may require blood transfusions and fluid replacement. If the last intake of NOACs was less than 2 - 4 h before bleeding assessment, charcoal administration and/or gastric lavage will reduce further exposure. Specific diagnostic and treatment interventions to identify and manage the cause of bleeding (e.g. gastroscopy) should be performed promptly. Dialysis is effective in reducing dabigatran concentration and has been associated with reduction in the duration and/or severity of associated bleeding.[1133]

Severe or life-threatening bleeding requires immediate reversal of the antithrombotic effect of OACs. For VKAs, administration of fresh frozen plasma restores coagulation more rapidly than vitamin K, but prothrombin complex concentrates achieve even faster blood coagulation[1134] and are first-line therapy for VKA reversal.[1135] Specific reversal drugs are available for NOACs: idarucizumab (for dabigatran) and andexanet alfa (for factor Xa inhibitors) effectively reverse the anticoagulation action of NOACs and restore physiological haemostasis.[1136,1137] However, their use is often associated with subsequent non-reinitiation of OAC and increased rates of thrombotic events. These drugs can be effectively applied in case of severe life-threatening bleeding or urgent surgery, but their use is only very rarely necessary in daily clinical practice. Ciraparantag is an investigational synthetic drug that binds and inhibits direct factor Xa inhibitors, dabigatran, and heparin. The use of four-factor prothrombin complex concentrates may be considered as an alternative treatment for reversing the anticoagulant effect of rivaroxaban, apixaban, and edoxaban, although scientific evidence is very limited in this context and is frequently from healthy volunteers.[1138–1140]

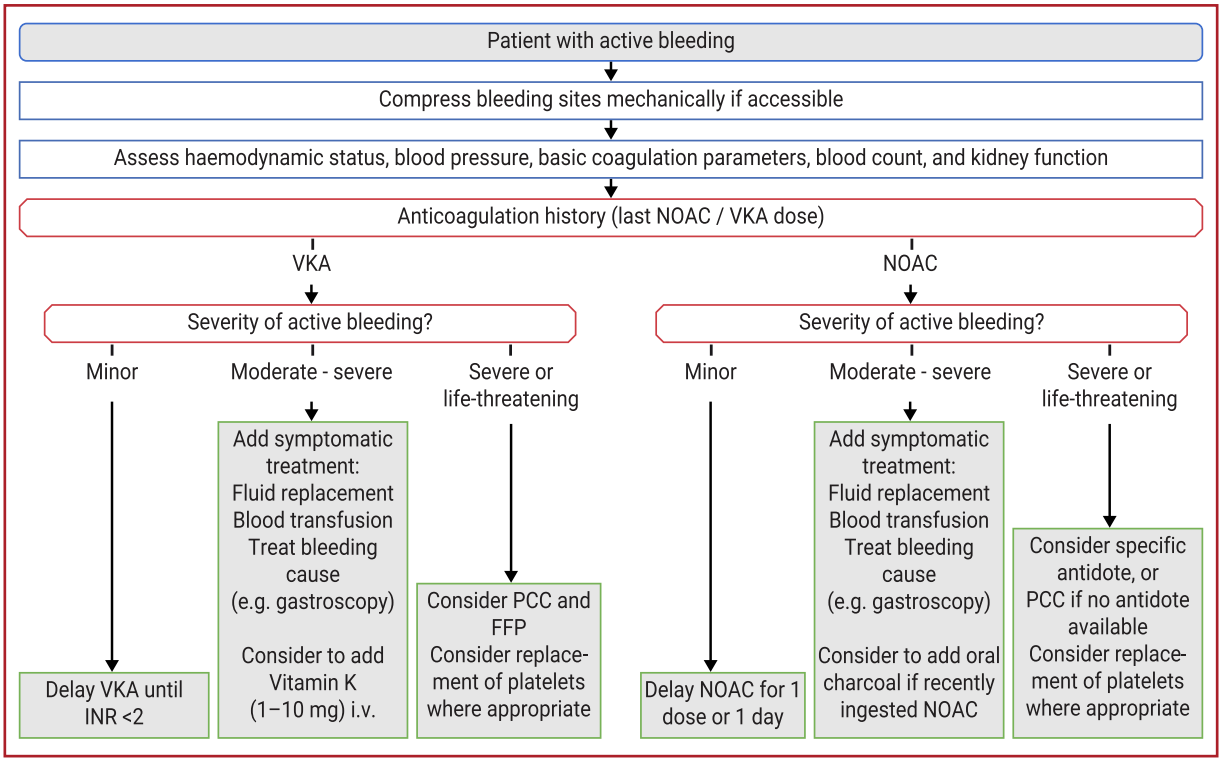


Figure 22 Management of active bleeding in patients receiving anticoagulation (institutions should have an agreed procedure in place).[143] FFP = fresh frozen plasma; INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation therapy; PCC = prothrombin complex concentrates; VKA = vitamin K antagonist.

Recommendations for the management of active bleeding on OAC

	Class[a]	Level[b]
In an AF patient with severe active bleeding, it is recommended to: • Interrupt OAC until the cause of bleeding is identified and active bleeding is resolved; and • Promptly perform specific diagnostic and treatment interventions to identify and manage the cause(s) and source(s) of bleeding.	I	C
Four-factor prothrombin complex concentrates should be considered in AF patients on VKA who develop a severe bleeding complication.	IIa	C

AF = atrial fibrillation; OAC = oral anticoagulant; VKA=vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

11.6 Atrial fibrillation and heart failure

Both AF and HF facilitate the occurrence and aggravate the prognosis of each other, and often coexist (see also *sections 4.2* and *5.3*); HF is also a thrombo-embolic risk factor in AF. The efficacy and safety of NOACs do not seem to differ in AF patients with and without HF.[1141,1142]

The management of patients with AF and HF is often challenging (*section 10.2*). The optimal heart-rate target in AF patients with HF remains unclear, but a rate of <100 - 110 bpm is usually recommended.[1143–1145] Pharmacological rate control strategies are different for patients with heart failure with preserved ejection fraction (HFpEF) and HFrEF. Beta-blockers, diltiazem, verapamil, and digoxin are all viable options in HFpEF, while beta-blockers and digoxin can be used in those with HFrEF. Amiodarone may be considered for rate control in both forms of HF, but only in the acute setting. Atrioventricular-node ablation and pacing can control ventricular rate when medication fails (*section 10.2.1.*). However, in an observation study, rhythm control strategies showed a lower 1-year all-cause death over rate control in older patients (≥65 years) with HFpEF.[1146]

Haemodynamic instability or worsening of HF may require emergency or immediate electrical cardioversion of AF, whereas pharmacological cardioversion using i.v. amiodarone may be attempted if a delayed cardioversion is consistent with the clinical situation (*section 10.2.2.2.2*). AF catheter ablation has been shown to improve symptoms, exercise capacity, QoL, and LVEF in AF patients with HF,[661] whereas the recent CASTLE-AF RCT showed a reduction in all-cause mortality and hospitalization for worsening HF after AF catheter ablation in patients with HFrEF[657] (*section 10.2.2.3*).

All patients with HF and AF should receive guideline-adherent HF therapy.[1145] The benefit of beta-blocker therapy in reducing mortality in AF patients with HFrEF has been questioned by some meta-analyses,[491] although this is not a universal finding, especially with some real-world studies supporting an improved prognosis.[1147,1148]

11.7 Atrial fibrillation and valvular heart disease

VHD is independently associated with AF[1149] and more than one-third of patients with AF have some form of VHD.[512]

Among patients with severe VHD, including those undergoing surgical and transcatheter aortic or mitral valve intervention, AF is associated with less favourable clinical outcomes.[1150–1155] Compared to AF patients without VHD, the risk of thrombo-embolism and stroke is increased among AF patients with VHD other than mitral stenosis and mechanical heart prostheses, mostly owing to older age and more frequent comorbidities.[1156,1157] While patients with moderate-to-severe mitral stenosis and mechanical prosthetic heart valves require anticoagulation with VKAs,[1158] there is no evidence that the presence of other VHDs including aortic stenosis/regurgitation, mitral regurgitation, bioprostheses, or valve repair should modify the choice of OAC.[1156,1159] In a meta-analysis of the four pivotal RCTs comparing NOACs with VKAs, the effects of NOACs vs. VKAs in terms of stroke/systemic embolism and bleeding risk in patients with VHD other than mitral stenosis and mechanical prosthetic heart valves were consistent with those in the main RCTs.[1160] In an observational study, NOACs were associated with better outcomes, with reduced rates of ischaemic stroke and major bleeding compared to warfarin in AF patients with mitral stenosis.[1161]

Recently, a functional categorization of VHD in relation to OAC use was introduced, categorizing patients with moderate-severe or rheumatic mitral stenosis as type 1 and all other VHD as type 2.[148,1157,1162] There are gaps in evidence on NOAC use in AF patients with rheumatic mitral valve disease, and during the first 3 months after surgical or transcatheter implantation of a bioprosthesis, and observational data regarding NOACs use after transcatheter aortic valve implantation are conflicting.[1163] An RCT in *non-AF* patients comparing rivaroxaban 10 mg daily with aspirin after transcatheter aortic valve implantation was stopped early due to higher risks of death or thrombo-embolic complications and bleeding in the rivaroxaban arm.[1164]

Recommendations for patients with valvular heart disease and AF

Recommendations	Class[a]	Level[b]
NOACs are contraindicated in patients with a prosthetic mechanical valve.[1165]	III	B
Use of NOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis.	III	C

AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant.
[a]Class of recommendation.
[b]Level of evidence.

11.8 Atrial fibrillation and chronic kidney disease

Independently of AF, CKD is a prothrombotic and prohaemorrhagic condition (*Supplementary Figure 7*),[1166,1167,1168] and AF may accelerate CKD progression. Coexisting in 15–20% of CKD patients,[1169] AF is associated with increased mortality,[1170] whereas CKD may be present in 40 - 50% of AF patients.[1171] In AF patients, renal function can deteriorate over time,[1172] and worsening CrCl is a better independent predictor of ischaemic stroke/systemic embolism and bleeding than renal impairment per se.[1172] In RCTs of OAC for stroke prevention in AF, renal function was usually estimated using the Cockcroft–Gault formula for CrCl, and a CrCl cut-off of <50 mL/min was used to adapt NOAC dosage.

In patients with mild-to-moderate CKD (CrCl 30 - 49 mL/min), the safety and efficacy of NOACs vs. warfarin was consistent with patients without CKD in landmark NOAC trials[1173–1176], hence the same considerations for stroke risk assessment and choice of OAC may apply.

In patients with CrCl 15 - 29 mL/min, RCT-derived data on the effect of VKA or NOACs are lacking. These patients were essentially excluded from the major RCTs. The evidence for the benefits of OAC in patients with end-stage kidney disease with CrCl≤15 mL/min or on dialysis is even more limited, and to some extent controversial. There are no RCTs, whereas observational data question the benefit of OAC in this patient population. Data from observational studies suggest possible bleeding risk reduction in patients with end-stage kidney disease taking a NOAC compared with VKA,[435,1177] but there is no solid evidence for a reduction in embolic events with either NOACs or VKAs, as recently shown in a systematic review.[1178] Notably, NOACs have not been approved in Europe for patients with CrCl ≤15 mL/min or on dialysis.

Several RCTs are currently assessing OAC use and comparing NOACs with VKAs in patients with end-stage renal disease (NCT02933697, NCT03987711). The RENAL-AF trial, investigating apixaban vs. warfarin in AF patients on haemodialysis, was terminated early with inconclusive data on relative stroke and bleeding rates.[1179]

There are no RCT data on OAC use in patients with AF after kidney transplantation. The prescription and dosing of NOACs should be guided by the estimated glomerular filtration rate of the transplanted kidney and taking into account potential interactions with concomitant medication.

Particular attention must be given to the dosing of NOACs in patients with CKD (*Supplementary Table 9*).

11.9 Atrial fibrillation and peripheral artery disease

Patients with AF often have atherosclerotic vascular disease. With the inclusion of asymptomatic ankle-brachial index≤0.90 in the definition PAD, the prevalence of vascular disease increased significantly.[1180] In a systematic review and meta-analysis, the presence of PAD was significantly associated with a 1.3- to 2.5-fold increased risk of stroke.[347] Complex aortic plaque in the descending aorta, as identified on TOE, is also a significant vascular stroke risk factor (*section 10.1.1*).

In patients with asymptomatic PAD, the risk of cardiovascular events progressively increases with increasing vascular disease burden.[470] Therefore, PAD patients should be opportunistically screened for AF. Patients with AF and PAD should be prescribed OAC, unless contraindicated. Those with stable vascular disease (arbitrarily defined as no new vascular event in the past 12 months) should be managed with OAC alone (*section 11.3*), as concomitant use of antiplatelet therapy has not been shown to reduce stroke or other cardiovascular events, but may increase serious bleeds, including ICH.

The principles of rate and rhythm control outlined in *section 10.2* also apply for AF patients with PAD. Special considerations include possibly limited exercise capacity in these patients, owing to intermittent claudication. Beta-blockers may exacerbate PAD symptoms in some patients, in whom NDCC blockers may be more appropriate for rate control.

11.10 Atrial fibrillation and endocrine disorders

Electrolyte disturbances and altered glucose and/or hormone levels in endocrine disorders such as thyroid disorders, acromegaly, pheochromocytoma, diseases of adrenal cortex, parathyroid disease, or pancreas dysfunction including diabetes mellitus may contribute to development of AF. Data on management of AF in these settings are limited.[3] Diabetes is discussed in *section 10.3.2.4*. Stroke prevention should follow the same principles as in other AF patients, with risk stratification using the CHA_2DS_2-VASc score.[3,1181] In AF patients with hyperthyroidism, spontaneous conversion of AF often occurs once a euthyroid state is achieved.[1182] Withdrawal of amiodarone is mandatory in hyperthyroidism. AF catheter ablation should be performed under stable electrolytic and metabolic conditions and should not be carried out during active hyperthyroidism.

11.11 Atrial fibrillation and gastrointestinal disorders

While gastrointestinal lesions can lead to bleeding events in anticoagulated AF patients, some gastrointestinal conditions such as active inflammatory bowel disease increase the risk of AF and stroke.[1183] Gastrointestinal bleeding is a well-known complication of OAC. Overall, NOAC use is associated with an increased risk of gastrointestinal bleeding,[1184,1185] but in patients treated with apixaban or dabigatran 110 mg the risk is similar to warfarin.[419,421] Bleeding lesions can be identified in more than 50% of cases of major gastrointestinal bleeding.[1186] After correction of the bleeding source, OAC should be restarted, as this strategy has been associated with decreased risks of thrombo-embolism and death.[1187]

Patients treated with dabigatran may experience dyspepsia (about 11% in the RE-LY trial, and 2% discontinued the drug because of gastrointestinal symptoms[419]). After-meal ingestion of dabigatran and/or the addition of proton-pump inhibitors improves symptoms.[1188]

Management of AF patients with liver disease is challenging, owing to increased bleeding risk (associated with decreased hepatic synthetic function in advanced liver disease, thrombocytopenia, and gastrointestinal variceal lesions), as well as increased ischaemic risk[1189,1190]). Patients with hepatic dysfunction were generally excluded from the RCTs,[1191] especially those with abnormal clotting tests, as such patients may be at higher risk of bleeding on VKA, possibly less so on NOACs. Despite the paucity of data, observational

studies did not raise concerns regarding the use of NOACs in advanced hepatic disease.[1192] In a recent study, AF patients with liver fibrosis had no increase in bleeding on NOACs compared with VKAs.[470] Other reassuring data for NOACs come from a large nationwide cohort.[472] A number of patients may be started on a NOAC while having unrecognized significant liver damage and, in cirrhotic patients, ischaemic stroke reduction may outweigh bleeding risk.[471] NOACs are contraindicated in patients within Child-Turcotte-Pugh C hepatic dysfunction, and rivaroxaban is not recommended for patients in the Child-Turcotte-Pugh B or C category.[1193]

11.12 Atrial fibrillation and haematological disorders

Anaemia is an independent predictor of OAC-related major bleeding.[393,402] In a population-based AF cohort, anaemia was associated with major bleeding and lower TTR, whereas OAC use in AF patients with moderate or severe anaemia was associated with more major bleeding but no reduction in thrombo-embolic risk.[1194] Thrombocytopenia is also associated with increased bleeding risk. Before and during anticoagulation treatment, both anaemia and thrombocytopenia should be investigated and corrected, if possible. Decision making on OAC use in patients with platelet counts <100/μL requires a multidisciplinary approach including haematologists, balancing thrombotic and bleeding risks and addressing modifiable bleeding risk factors. Some chemotherapeutic drugs may increase the risk of incident AF (e.g. ibrutinib, melphalan, anthracyclines)[1195–1197] or impair platelet function, thus increasing the risk of bleeding (e.g. ibrutinib).[1198,1199]

11.13 The elderly and frail with atrial fibrillation

The prevalence of AF increases progressively with age[67,1200–1206], and age is an independent risk factor for adverse outcomes in AF.[372,1200,1207,1208] Older people are less likely to receive OAC[1209–1216] despite sufficient evidence supporting the use of OAC in this population. Frailty, comorbidities, and increased risk of falls[1217–1219] do not outweigh the benefits of OAC given the small absolute risk of bleeding in anticoagulated elderly patients.[339,390,391,1220–1223] Evidence from RCTs,[441,1224] meta-analyses[423,1225] and large registries[339,433,1209,1226] support the use of OAC in this age group. Antiplatelets are neither more effective nor safer than warfarin and may even be harmful,[433] whereas NOACs appear to have a better overall risk–benefit profile compared with warfarin.[423,433,441,1035,1225,1227–1236] Prescribing a reduced dose of OAC is less effective in preventing AF adverse outcomes.[1107,1211,1237,1238]

Rate control is traditionally the preferred strategy, but evidence informing the choice between rate and rhythm control in the elderly is insufficient.[1239–1242] Limited evidence on other AF treatments supports the use of all rate and rhythm control options, including cardioversion, pacemaker implantation, and AF catheter ablation without any age discrimination. AF catheter ablation may be an effective and safe option in selected older individuals with success rates comparable to younger patients[1243–1255] and acceptable complication rates.[1243,1245–1247,1249–1260] Nevertheless, age was a predictor of complications in AF catheter ablation in some studies[1261–1263] and longer follow-up studies suggested an age-related increase in multivariable-adjusted risk for AF/AFL recurrence, death, and major adverse cardiac events.[1257]

11.14 Patients with cognitive impairment/dementia

Evidence regarding effective prevention of cognitive impairment in AF is derived mainly from observational studies, suggesting that OAC could play a protective role in AF patients with stroke risk factors, not only for stroke prevention but also for prevention of cognitive decline.[1264] The quality of anticoagulation with VKAs (i.e. TTR) seems to play an additional role: low TTR and supratherapeutic INR values were associated with higher risk of dementia.[1265,1266] Limited evidence suggests that NOACs may be superior to VKA for preventing cognitive impairment in some,[1267,1268] but not all, studies.[1269] Recent observational data indicate a protective effect of OAC even in low-risk AF patients who do not need OAC for stroke prevention.[1270] A number of RCTs with cognitive function as an endpoint are ongoing and will provide more insights into the role of anticoagulation (NOACs and VKAs) for prevention of cognitive impairment in AF.[86]

Conversely, cognitive impairment can influence treatment adherence,[1271,1272] thus affecting outcomes in AF patients. After AF catheter ablation, silent brain lesions are detected by MRI, but this has not led to cognitive impairment in the AXAFA–AFNET 5 trial, although underpowered.[880]

11.15 Atrial fibrillation and congenital heart disease

Survival of patients with congenital heart disease has increased over time, but robust data on the management of AF are missing and available evidence is derived mainly from observational studies and/or extrapolation from large clinical trials.

In patients with AF (or AFL or intra-atrial re-entrant tachycardia) and congenital heart disease, OAC treatment is recommended for all patients with intracardiac repair, cyanotic congenital heart disease, Fontan palliation, or systemic right ventricle.[1273] Patients with AF and other congenital heart diseases should follow the general risk stratification for OAC use in AF. Notably, NOACs are contraindicated in patients with mechanical heart valves,[1165] whereas they seem safe in those with a valvular bioprosthesis.[1274,1275]

Rate control drugs such as beta-blockers, verapamil, diltiazem, and digitalis can be used with caution due to the risk of bradycardia and hypotension. Rhythm control strategies (i.e. amiodarone) may be effective. In Fontan patients, sodium-channel blockers suppress half of the atrial arrhythmias, but caution is needed for proarrhythmia. When cardioversion is planned, both 3 weeks of anticoagulation and TOE may be considered as thrombi are common in patients with congenital heart disease and atrial tachyarrhythmias.[1276,1277]

In patients with atrial septal defect, closure may be considered before the fourth decade of life to decrease the risk of AF or AFL.[1278] Patients with stroke who underwent closure of the patent foramen ovale may have an increased risk of AF,[1279] but in patients with patent foramen ovale and AF, closure is not recommended for stroke prevention; and OAC use should be decided using the conventional stroke risk assessment tool. In patients with a history of AF, AF surgery or AF catheter ablation should be considered at the time of

closure of the septal defect.[1280–1282] AF catheter ablation of late atrial arrhythmias is likely to be effective after surgical atrial septal defect closure.[1283]

Recommendations for the management of AF in patients with congenital heart disease

Recommendations	Class[a]	Level[b]
• Oral anticoagulation should be considered in *all* adult patients with intracardiac repair, cyanosis, Fontan palliation, or systemic right ventricle and a history of AF, AFL, or intra-atrial re-entrant tachycardia.[1273] • In patients with AF and other congenital heart diseases, anticoagulation should be considered in the presence of one or more non-sex stroke risk factor(s).[1273]	IIa	C
Surgery for AF should be considered in patients: • Who need surgical closure of an atrial septal defect and who have a history of symptomatic atrial arrhythmia (atrial ablation should be considered at the time of surgical closure).[1280–1282] • Cox maze surgery should be considered in patients with symptomatic AF and an indication for corrective repair of congenital heart defects. The surgery should be done in experienced centres.[1280–1282]	IIa	C
AF catheter ablation of atrial arrhythmias associated with congenital heart defects may be considered when performed in experienced centres.[1283]	IIb	C
In patients with congenital heart disease, TOE may be considered together with 3-week anticoagulation therapy before cardioversion.[1292,1293]	IIb	C

AF = atrial fibrillation; AFL = atrial flutter; TOE = transoesophageal echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

11.16 Atrial fibrillation in inherited cardiomyopathies and primary arrhythmia syndromes

A higher incidence and prevalence of AF have been described in patients with inherited cardiomyopathies and primary arrhythmia syndromes.[1284–1318] Sometimes AF is the presenting or only clinically overt feature,[1319–1323] is often associated with adverse clinical outcomes,[1292,1299,1301,1307,1308,1310,1324–1329] and has important implications:

- The use of AADs may be challenging. In congenital long QT syndrome, many drugs are contraindicated owing to increased risk of QT prolongation and torsade de pointes (http://www.crediblemeds.org/); in Brugada syndrome, class I drugs are contraindicated (http://www.brugadadrugs.org/). Owing to its long-term adverse effects, chronic use of amiodarone is problematic in these typically young individuals.
- In patients with an implantable cardioverter defibrillator, AF is a common cause of inappropriate shocks.[1307,1311,1330–1333] Programming a single high-rate ventricular fibrillation zone ≥210 - 220 bpm with long detection time is safe,[1295,1296,1334] and is recommended in patients without documented slow monomorphic ventricular tachycardia. Implantation of an atrial lead may be considered in case of significant bradycardia under beta-blocker treatment.

Supplementary Table 14 summarizes the main clinical features of AF in patients with inherited cardiac diseases.

Patients with Wolff-Parkinson-White syndrome and AF are at risk of fast ventricular rates resulting from rapid conduction of atrial electrical activity to the ventricles via the accessory pathway, and at increased risk of ventricular fibrillation and sudden death.[1335,1336] Electrical cardioversion should be readily available for haemodynamically compromised patients with pre-excited AF, and atrioventricular node-modulating drugs (e.g. verapamil, beta-blockers, digoxin) should be avoided.[1337,1338] Pharmacological cardioversion can be attempted using ibutilide,[1339] whereas AADs class Ia (procainamide) and Ic (propafenone, flecainide) should be used with caution owing to their effect on the atrioventricular node.[1340–1343] Amiodarone may not be safe in pre-excited AF as it may enhance pathway conduction.[1343]

11.17 Atrial fibrillation during pregnancy

AF is one of the most frequent arrhythmias during pregnancy,[1344] especially in women with congenital heart disease[1345,1346] and in older gravidae,[1344,1347,1348] and is associated with increased risk of death.[1344] Rapid atrioventricular conduction may have serious haemodynamic consequences for mother and foetus.

Pregnancy is associated with a hypercoagulable state and increased thrombo-embolic risk. Given the lack of specific data, the same rules for stroke risk assessment should be used as in non-pregnant women.[1349] Detailed practical recommendations on oral and parenteral anticoagulation regimens depending on the pregnancy trimester, such as low- and high-dose VKA use during the second and third trimesters, timing of low-molecular-weight heparin (LMWH) to unfractionated heparin (UFH) relative delivery, and control of therapeutic effects are given in the recent ESC Pregnancy Guidelines.[1349] Immediate anticoagulation is required in clinically significant mitral stenosis, using LMWH at therapeutic doses in the first and last trimesters, and VKA with the usual INR targets or LMWH for the second trimester. Use of NOACs is prohibited during pregnancy. Vaginal delivery should be advised for most women but is contraindicated while the mother is on VKAs because of the risk of foetal intracranial bleeding.[1349]

Intravenous beta-blockers are recommended for acute rate control. Beta-1 selective blockers (e.g. metoprolol and bisoprolol) are generally safe and are recommended as the first choice.[1349] If beta-blockers fail, digoxin and verapamil should be considered for rate control.

Rhythm control should be considered the preferred strategy during pregnancy. Electrical cardioversion is recommended if there is haemodynamic instability or considerable risk for mother or foetus. It can be performed safely without compromising foetal blood flow[1350] and the consequent risk for foetal arrhythmias or preterm

labour is low.[1351,1352] The fetal heart rate should routinely be controlled after cardioversion.[1353] Cardioversion should generally be preceded by anticoagulation (*section 10.2.2.6*).[1349] In haemodynamically stable patients without structural heart disease, i.v. ibutilide or flecainide may be considered for termination of AF but experience is limited.[1354,1355] Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail. AF catheter ablation has no role during pregnancy.

Recommendations for the management of AF during pregnancy

Recommendations	Class[a]	Level[b]
Acute management		
Immediate electrical cardioversion[c] is recommended in case of haemodynamic instability or pre-excited AF.[1350,1351,1354]	I	C
In pregnant women with HCM, cardioversion[c] should be considered for persistent AF.[882]	IIa	C
Ibutilide or flecainide i.v. may be considered for termination of AF in stable patients with structurally normal hearts.[1355]	IIb	C
Long-term management (oral administration of drugs)		
Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF.[1349]	I	C
Beta-selective blockers are recommended for rate control in AF.[d]	I	C
Flecainide,[e] propafenone,[e] or sotalol[f] should be considered to prevent AF if atrioventricular nodal-blocking drugs[f] fail.	IIa	C
Digoxin[g] or verapamil[g] should be considered for rate control if beta-blockers fail.	IIa	C

AF = atrial fibrillation; ECG = electrocardiogram; US FDA = United States Food and Drug Administration; i.v. = intravenous; LV = left ventricular; HCM = hypertrophic cardiomyopathy; QTc = corrected QT interval; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Cardioversion of AF should generally be preceded by anticoagulation.
[d]Atenolol has been associated with higher rates of foetal growth retardation and is not recommended.[1356]
[e]Flecainide and propafenone should be combined with atrioventricular nodal-blocking drugs, but structural heart disease, reduced LV function, and bundle branch block should be excluded.
[f]Class III drugs should not be used in prolonged QTc.
[g]Atrioventricular nodal-blocking drugs should not be used in patients with pre-excitation on resting ECG or pre-excited AF.
Note that the former A to X categories of drugs—the classification system for counselling of pregnant women requiring drug therapy—was replaced by the Pregnancy and Lactation Labelling Rule, which provides a descriptive risk summary and detailed information on animal and clinical data, by the US FDA in June 2015.

11.18 Atrial fibrillation in professional athletes

Moderate physical activity improves cardiovascular health and prevents AF, whereas intense sports activity increases the risk of AF.[35,1357] Athletes have an approximate five-fold increased lifetime risk of AF compared with sedentary individuals despite a lower prevalence of conventional AF risk factors.[35,1020] Risk factors for AF in athletes include male sex, middle age, endurance sports, tall stature, and total lifetime exercise dose exceeding 1500 - 2000 hours.[1020,1358–1361] Endurance sports such as running, cycling, and cross-country skiing[35,1362] carry the highest risk.

In the absence of RCTs, recommendations for AF management in athletes are based largely on evidence in non-athletes, observational data, and expert consensus.[143] The need for anticoagulation is determined by clinical risk factors. Sports with direct bodily contact or prone to trauma should be avoided in patients on OAC. As athletes have a high prevalence of sinus bradycardia and sinus pauses, medical therapy is frequently contraindicated or poorly tolerated.[1021,1363] Digoxin and verapamil are often ineffective for rate control during exertional AF, whereas beta-blockers may not be well tolerated or are sometimes prohibited. Pill-in-the-pocket therapy has been used, but sports activity should be avoided after ingestion of flecainide or propafenone until AF ceases and two half-lives of the drug have elapsed.[586] AF catheter ablation is often preferred by athletes and was similarly efficacious in both the athletic and non-athletic populations in small studies.[1364,1365]

Recommendations for sports activity in patients with AF

Recommendation	Class[a]	Level[b]
It is recommended to counsel professional athletes that long-lasting intense sports participation may promote AF, while moderate physical activity is recommended to prevent AF.[35,38,1020,1360,1366–1368]	I	B

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

11.19 Postoperative atrial fibrillation

Perioperative AF describes the onset of the arrhythmia during an ongoing intervention. This is most relevant in patients undergoing cardiac surgery. While multiple strategies to reduce the incidence of perioperative AF with pretreatment or acute drug treatment have been described, there is lack of evidence from large RCTs. Amiodarone is the most frequently used drug for prevention of perioperative AF.[1369]

Postoperative AF, defined as new-onset AF in the immediate postoperative period, is a clinically relevant problem,[1370,1371] occurring in 20 - 50% of patients after cardiac surgery,[1372,1373] 10 - 30% after non-cardiac thoracic surgery,[1374] and in 5 - 10% after vascular or large colorectal surgery,[1375] with peak incidence between postoperative day 2 and 4.[1376] Intra- and postoperative changes affecting AF triggers and pre-existing atrial substrate may increase atrial vulnerability to AF. Many episodes of postoperative AF are self-terminating and some are asymptomatic, but postoperative AF has been associated with a four- to five-fold risk of recurrent AF in the next 5 years.[1377,1378] It has also been shown to be a risk factor for stroke,

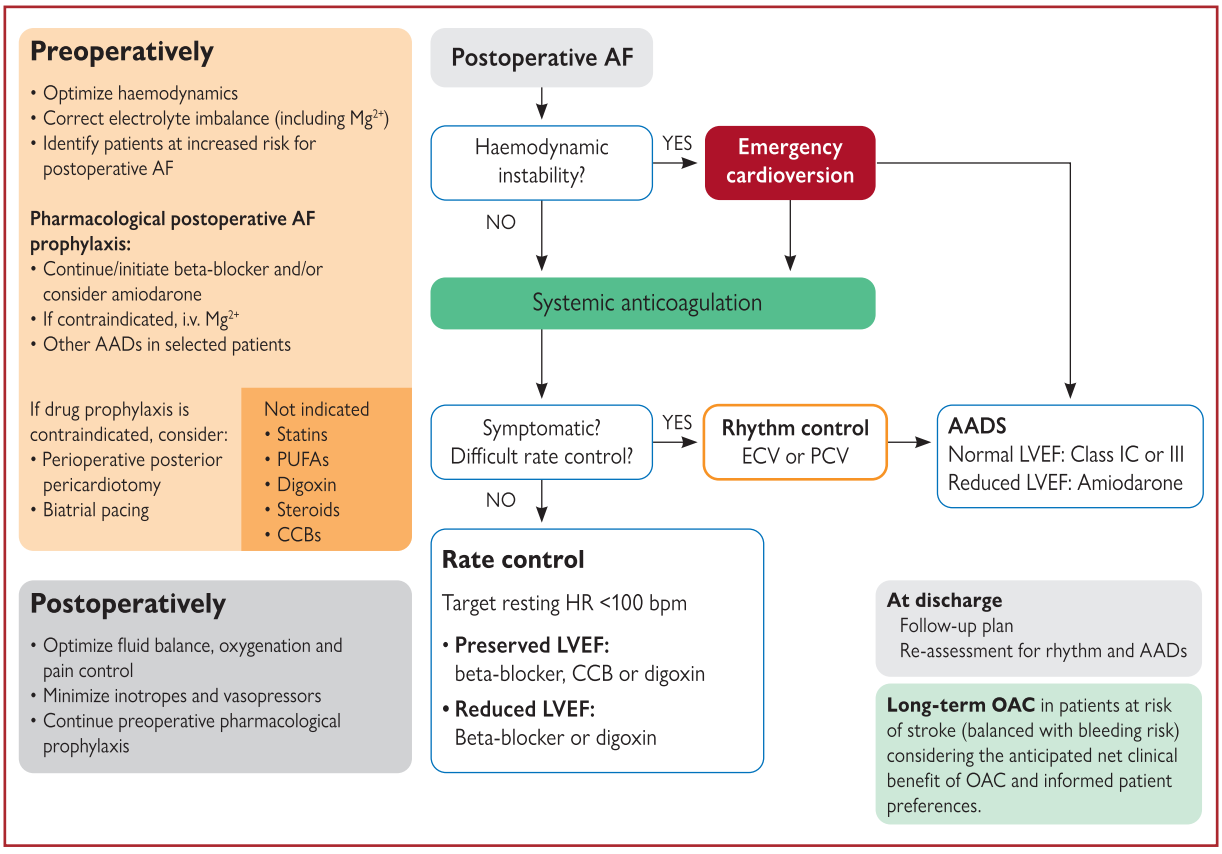


Figure 23 Management of postoperative AF. AAD = antiarrhythmic drug; bpm = beats per minute; CCB = calcium channel blocker; ECV = electrical cardioversion; LVEF = left ventricular ejection fraction; Mg^{2+} magnesium; OAC = oral anticoagulation; PCV = pharmacological cardioversion; PUFA=polyunsaturated fatty acid.

myocardial infarction, and death compared with non-postoperative AF patients.[1379,1380]

Other adverse consequences of postoperative AF include haemodynamic instability, prolonged hospital stay, infections, renal complications, bleeding, increased in-hospital death, and greater healthcare costs.[1371,1381,1382] Management of postoperative AF is shown in *Figure 23*.

11.19.1 Prevention of postoperative AF

Preoperative beta-blocker (propranolol, carvedilol plus N-acetyl cysteine) use in cardiac and non-cardiac surgery is associated with a reduced incidence of postoperative AF,[1383–1386] but not major adverse events such as death, stroke, or acute kidney injury.[1387] Notably, in non-cardiac surgery, perioperative metoprolol was associated with increased risk of death in a large RCT.[1388] In a meta-analysis, amiodarone (oral or i.v.), and beta-blockers were equally effective in reducing postoperative AF,[1389] but their combination was better than beta-blockers alone.[1390] Lower cumulative doses of amiodarone (<3000 mg) could be effective, with fewer adverse events.[1391–1393] Data for other interventions such as statins[974,1394] magnesium,[1395] sotalol,[1385] colchicine,[1396] posterior pericardiotomy,[1397,1398] (bi)atrial pacing,[1385] and corticosteroids[1399] are not robust. Two large RCTs showed no significant effect of i.v. steroids on the incidence of postoperative AF after cardiac surgery,[1400,1401] and colchicine is currently being investigated in the prevention of postoperative AF [COP-AF (Colchicine For The Prevention Of Perioperative Atrial Fibrillation In Patients Undergoing Thoracic Surgery): NCT03310125].

11.19.2 Prevention of thrombo-embolic events

In a large meta-analysis, patients with postoperative AF had a 62% higher odds of early and 37% higher risk of long-term stroke compared with those without postoperative AF (≥1-year stroke rates were 2.4% vs. 0.4%, respectively), as well as 44% higher odds of early and 37% higher risk of long-term mortality; long-term stroke risk was substantially higher with non-cardiac than cardiac postoperative AF (HR 2.00; 95% CI 1.70–2.35 for non-cardiac vs. HR 1.20; 95% CI 1.07–1.34 for cardiac postoperative AF; *P* for subgroup difference <0.0001).[1379]

Nevertheless, the evidence on OAC effects in patients with postoperative AF is not very robust.[1382,1402–1407] Observational data[1408] suggest that although coronary artery bypass graft-related postoperative AF might not be equivalent to non-surgery AF regarding the long-term risk of adverse outcomes, OAC use during follow-up was associated with a significantly lower risk of thrombo-embolic events in both postoperative AF and non-surgery AF compared with no OAC.[1408] Reportedly, postoperative AF occurring after non-cardiac surgery was associated with a similar long-term thrombo-embolic risk to non-surgery AF, and OAC therapy was associated with comparably lower risk of thrombo-embolic events and all-cause death in

both groups.[1409] Ongoing RCTs in cardiac [PACES (Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG); NCT04045665] and non-cardiac (ASPIRE-AF; NCT03968393) surgery will inform optimal long-term OAC use among patients developing postoperative AF.

In haemodynamically unstable patients with postoperative AF, emergency electrical cardioversion (or i.v. administration of amiodarone[1385] or vernakalant,[583] if consistent with the clinical situation) is indicated. In a recent RCT of postoperative AF patients after cardiac surgery, neither rate nor rhythm control showed net clinical advantage over each other.[1373] Hence, rate or rhythm control treatment decisions should be based on symptoms, and non-emergency cardioversion should follow the principles of peri-cardioversion anticoagulation outlined in *section 10.2*.

Recommendations for postoperative AF

Recommendations	Class[a]	Level[b]
Perioperative amiodarone or beta blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery.[1390,1492]	I	A
Long-term OAC therapy to prevent thromboembolic events should be considered in patients at risk for stroke with postoperative AF after non-cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.[1404,1405,1408,1409]	IIa	B
Long-term OAC therapy to prevent thromboembolic events may be considered in patients at risk for stroke with postoperative AF after cardiac surgery, considering the anticipated net clinical benefit of OAC therapy and informed patient preferences.[1404,1405,1408,1409]	IIb	B
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery.[1410]	III	B

AF = atrial fibrillation; OAC = oral anticoagulant.
[a]Class of recommendation.
[b]Level of evidence.

12 Prevention of atrial fibrillation

12.1 Primary prevention of atrial fibrillation

Primary prevention of AF refers to the implementation of preventive measures in patients at risk but without previous documentation of AF. This strategy relies on the identification and management of risk factors and comorbidities predisposing to AF, before the development of atrial remodelling and fibrosis[964,1411] Upstream therapy refers to the use of non-AADs that modify the atrial substrate or target-specific mechanisms of AF to prevent the occurrence or recurrence of the arrhythmia. The key targets of upstream therapy are structural changes in the atria (e.g. fibrosis, hypertrophy, inflammation, oxidative stress), but effects on atrial ion channels, gap junctions, and calcium handling are also evident.[964]

Adequate management of hypertension and HF may prevent AF by reducing atrial stretch, but inhibition of the renin-angiotensin-aldosterone system may exert an additional protective role by suppressing electrical and structural cardiac remodelling.[964,1411,1412] Large RCTs and meta-analyses have yielded equivocal results, either in favour[1413–1416] or against[1417–1421] statin use for primary prevention of AF. Controversial results have also been reported for the effects of fish oils on primary prevention of AF.[1422]

For primary prevention of postoperative AF after cardiac and non-cardiac surgery, see *section 11.19*.

12.2 Secondary prevention of atrial fibrillation

For secondary AF prevention see *section 11.3* and *Supplementary section 12*.

13 Sex-related differences in atrial fibrillation

Female patients are generally under-represented in RCTs, including AF trials. Sex-related differences in the epidemiology, pathophysiology, clinical presentation, and prognosis of AF that are consistently reported[19,107,124,1423,1424] may influence the effectiveness of AF treatment, and hence should be considered in a personalized, individual patient-centred approach to AF management in clinical practice.[1425] Understanding the underlying pathophysiological mechanisms and biology may help to improve personalized treatments. Adequate representation of women in future AF trials is recommended, as well as the identification and resolution of sex-specific barriers to implementation of guideline-recommended treatments for AF.

Women presenting with AF are older, have a higher prevalence of hypertension, VHD, and HFpEF, and a lower prevalence of CAD compared with men. Women with AF are more often symptomatic than men with AF, with greater symptom severity.[1423,1426]

Female sex is a stroke risk modifier that increases the risk of AF-associated stroke in the presence of other stroke risk factors.[353] Women with AF have a greater stroke severity and permanent disability than men with AF.[1427] Anticoagulation with warfarin may be less well controlled in women, and they have a greater residual stroke risk even with well-controlled VKAs.[1428] The efficacy and safety of NOACs in landmark RCTs were consistent in both sexes, but women were largely under-represented.[423]

In women with AF, the use of AADs for rhythm control is associated with significantly higher rates of life-threatening adverse events (e.g. acquired long QT syndrome with class Ia or III AADs)[1429,1430] or sinus-node disease/bradyarrhythmia requiring pacemaker implantation[19] compared with male patients. Women with AF are less likely to undergo electrical cardioversion,[1426] and are referred for AF catheter ablation later than men, possibly reflecting AF occurrence later in life among women.[107,1431,1432] The result of PVI may be less favourable in women,[1431,1432] with higher rates of procedure-related complications.[1431] Women are more likely to undergo atrioventricular nodal ablation for AF than men.[124] Sex-specific data on cardiovascular risk management in women with AF are lacking. Principles outlined in *section 11.3* apply to women with AF.

Recommendations pertaining to sex-related differences in AF

Recommendation	Class[a]	Level[b]
It is recommended that women and men with AF are equally offered diagnostic assessment and therapies to prevent stroke and other AF-related complications.[423,1433]	I	A
Women with symptomatic paroxysmal or persistent AF should be offered timely access to rhythm control therapies, including AF catheter ablation, when appropriate for medical reasons.[1448,1451]	IIa	B

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

14 Implementation of the atrial fibrillation guidelines

Guideline-adherent care (i.e. the implementation of guideline-recommended management to individual AF patients) aims to improve patient outcomes and reduce healthcare costs,[1238,1434,1435] but adherence to guidelines is modest worldwide.[124,1436–1439,1440,1441] Reportedly, the adoption of NOACs as first-line therapy has been associated with increasing guideline-adherent stroke prevention.[1442,1443]

Guideline non-adherence is multifactorial,[1215,1444,1445] including physician/healthcare professional- and healthcare system-related factors.[1446] Integrated AF management may facilitate adherence to guidelines. Various educational interventions[280,284,290,1447,1448] based on guideline-provided recommendations[284] and tailored to close specific knowledge gaps among healthcare professionals and/or AF patients[1446] may facilitate the implementation of guideline-based AF management to improve patient outcomes.[277,1449–1452] Further research is needed to identify the cost-effective intervention type(s) that would more effectively improve patient clinical outcomes, medication adherence, and QoL.

15 Quality measures and clinical performance indicators in the management of atrial fibrillation

Measurable service quality has been identified as a cornerstone for optimal AF management and is a mandatory step towards value-based healthcare. Quality and performance indicator sets should provide practitioners and institutions with the tools to measure the quality of care (e.g. adherence to guideline class I recommendations upon discharge/end of visit, complications after procedures, access/waiting list times) and identify opportunities for improvement. They should capture important aspects of care quality, including structure, process, outcome measures, and patient-centrednes, while the reporting burden for hospitals, practices, and practitioners should be kept to a minimum.[658,1453–1455]

A collaborative effort involving the ESC, EHRA, Asia Pacific Heart Rhythm Society, Heart Rhythm Society, and Latin American Heart Rhythm Society was put in place to develop quality indicators for the diagnosis and management of AF; a summary form of these quality indicators is provided in *Table 22*, with the full set published separately.[317] The ESC quality indicators are intended for quality improvement and performance measurement through meaningful surveillance, as well as for integration within registries that specifically aim to identify areas for improvement in clinical practice and are not intended for ranking healthcare professionals/providers or payment incentives.

Recommendations for quality measures in patients with AF

Recommendations	Class[a]	Level[b]
The introduction of tools to measure quality of care and identify opportunities for improved treatment quality and AF patient outcome should be considered by practitioners and institutions.[317]	IIa	B

AF = atrial fibrillation.
[a]Class of recommendation.
[b]Level of evidence.

16 Epidemiology, clinical implications, and management of atrial high-rate episodes/ subclinical atrial fibrillation

The incidence of AHRE/subclinical AF in patients with a pacemaker/implanted device is 30–70%, but it may be lower in the general population.[1458] Very short episodes (≤10 - 20 s/day) are considered clinically irrelevant, as they are not significantly associated with longer episodes or an increased risk of stroke or systemic embolism.[1459] However, longer episodes of AHRE/subclinical AF (minimum of 5 - 6 min) are associated with an increased risk of clinical AF,[467,469] ischaemic stroke,[168,467] major adverse cardiovascular events,[1460] and cardiovascular death.[1461]

Overall, the absolute risk of stroke associated with AHRE/subclinical AF may be lower than with clinical AF.[160,168,226,467] The temporal dissociation from acute stroke suggests that AHRE/subclinical AF may represent a marker rather than a risk factor for stroke[4,7,1462] (*Supplementary Box 6*).

Whereas current data were obtained mostly from pacemakers/implantable cardioverter defibrillators or post-stroke patients, AHRE/subclinical AF is increasingly reported in a variety of patients undergoing cardiac monitoring. Clinical AF will reportedly develop in 1 in 5 - 6 of patients within 2.5 years after diagnosing AHRE/subclinical AF.[168] Notwithstanding that more high-quality evidence is needed to inform optimal management of these patients, more intense

Table 22 Summary of quality indicators for the diagnosis and management of AF

Domain: Patient assessment (at baseline and follow-up)
Main quality indicator: CHA_2DS_2-VASc cardioembolic risk assessment.
Main quality indicator: bleeding risk assessment using a validated method such as the HAS-BLED score.
Numerator: Number of AF patients who have their respective score documented at the time of diagnosis and at every follow-up appointment.
Denominator: Number of AF patients.
Domain: Anticoagulation
Main quality indicator: inappropriate prescription of anticoagulation to patients with a CHA_2DS_2-VASc score of 0 for men and 1 for women.
Numerator: number of AF patients with CHA_2DS_2-VASc score of 0 for men and 1 for women, who are inappropriately prescribed anticoagulation.
Denominator: number of AF patients with CHA_2DS_2-VASc score of 0 for men and 1 for women who do not have other indication for anticoagulation.
Main quality indicator: proportion of patients with a CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women who are prescribed anticoagulation.
Numerator: Number of AF patients with CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women who are prescribed anticoagulation.
Denominator: Number of AF patients with CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women who are eligible for anticoagulation with no contraindication or refusal.
Domain: rate control
Main quality indicator: inappropriate prescription of AADs[a] to patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned).
Numerator: Number of patients with permanent AF who are prescribed one or more AADs[a] for rhythm control.
Denominator: Number of patients with permanent AF.
Domain: rhythm control
Main quality indicator: inappropriate prescription of class IC AADs to patients with structural heart disease.
Numerator: number of AF patients with structural heart disease who are inappropriately prescribed class IC AADs.
Denominator: number of AF patients with structural heart disease.
Main quality indicator: proportion of patients with symptomatic paroxysmal or persistent AF who are offered AF catheter ablation after failure of/intolerance to one class I or class III AAD.
Numerator: Number of patients with paroxysmal or persistent AF who are offered catheter ablation after the failure of, or intolerance to, at least one class I or class III AAD.
Denominator: Number of patients with paroxysmal or persistent AF with no contraindications (or refusal) to catheter ablation who remain symptomatic on, or intolerant to at least one class I or class III AAD.
Domain: risk factor management
Main quality indicator: Proportion of patients who have their modifiable risk factors identified.
Numerator: number of AF patients who have their modifiable risk factors (e.g. BP, obesity, OSA, alcohol excess, lack of exercise, poor glycaemic control and smoking) identified
Denominator: number of AF patients.
Domain: outcomes
Main quality indicator: ischaemic stroke or TIA.
Main quality indicator: life-threatening or major bleeding events.[b]
Numerator: number of AF patients who have a documented ischaemic or bleeding event
Denominator: number of AF patients or number of patients prescribed an OAC, respectively.

AAD = antiarrhythmic drug; AF = atrial fibrillation; BP = blood pressure; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly; OAC = oral anticoagulant; OSA = obstructive sleep apnoea; TIA = transient ischaemic attack.
[a]Flecainide, propafenone, amiodarone, dronedarone, sotalol and disopyramide.
[b]Using the definitions of the International Society of Thrombosis and Haemostasis.[1456,1457]

follow-up and monitoring to detect clinical AF early is prudent (preferably with the support of remote monitoring). Notably, the AHRE/subclinical AF burden is not static but may change on daily basis,[469] hence should be regularly reassessed—the greater the AHRE/subclinical AF burden at diagnosis, the higher the risk of subsequent progression to longer episodes[469] (*Figure 24*).

Whereas available evidence is insufficient to justify routine OAC use in patients with AHRE/subclinical AF, modifiable stroke risk factors should be identified and managed in each patient.

The use of OAC may be considered in selected patients with longer durations of AHRE/subclinical AF (≥24 h) and an estimated high individual risk of stroke,[4,1462] accounting for the anticipated net

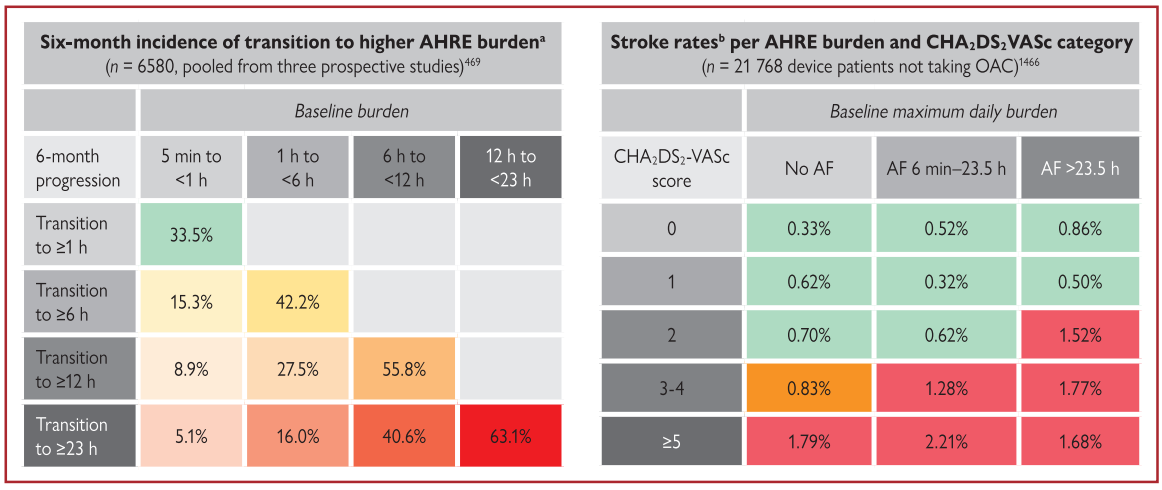


Figure 24 Progression of atrial high-rate episode burden (left panel) and stroke rates according to AHRE daily burden and CHA_2DS_2-VASc score (right panel). AHRE = atrial high-rate episodes; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); OAC = oral anticoagulant. [a]The higher the burden at diagnosis, the greater the incidence of progression in the next 6 months and thereafter. [b]Stroke rates above the threshold for OAC are shown in red.

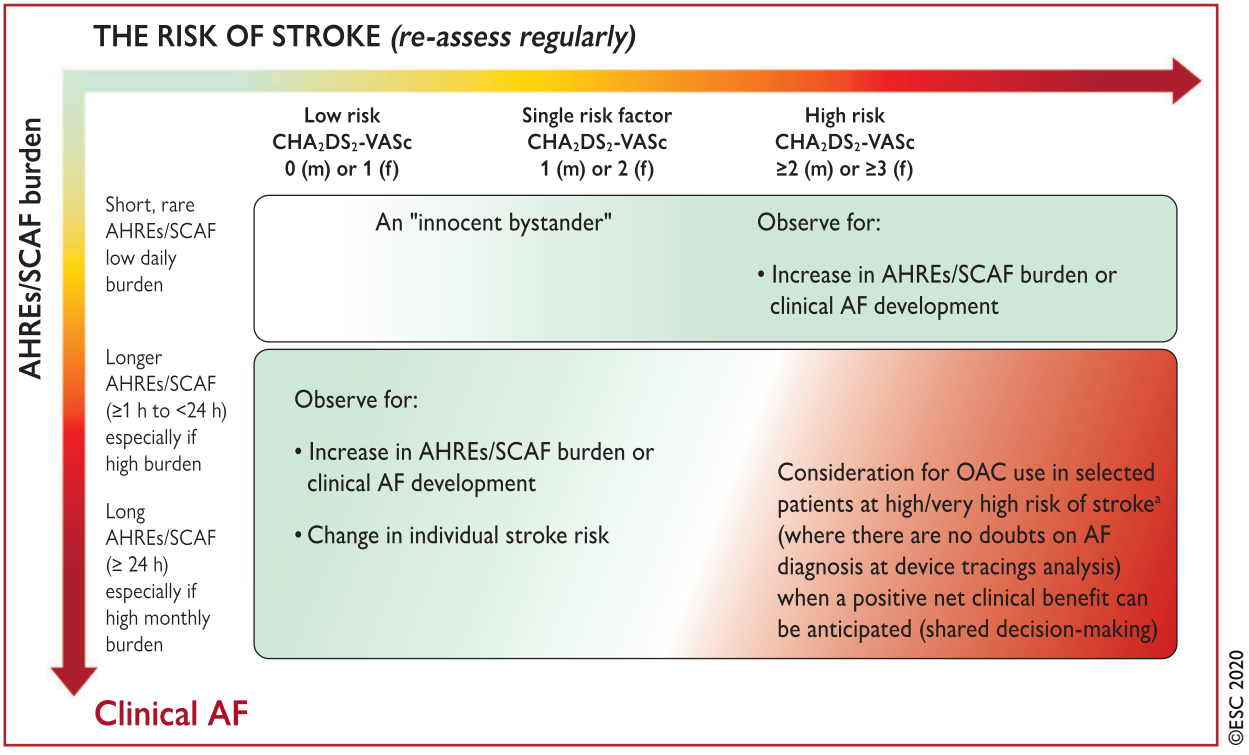


Figure 25 Proposed management of AHRE/subclinical AF. AF = atrial fibrillation; AHRE = atrial high-rate episode; CKD = chronic kidney disease; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); f = female; LA = left atrium; LoE = level of evidence; m = male; OAC = oral anticoagulant; SCAF = subclinical atrial fibrillation. [a]Highly selected patients (e.g. with previous stroke and/or age ≥75 years, or ≥3 CHA_2DS_2-VASc risk factors, and additional non-CHA_2DS_2-VASc stroke factors such as CKD, elevated blood biomarkers, spontaneous echo contrast in dilated LA, etc); selected patients (e.g. with previous stroke and/or age ≥75 years, or ≥3 CHA_2DS_2-VASc risk factors , etc).

clinical benefit and informed patient's preferences (*Figures 24 and 25*). In the recent trials, OAC was initiated in 76.4% and 56.3% of patients with ≥2 clinical stroke risk factors and insertable cardiac monitor-detected physician-confirmed AF≥6 min, but follow-up bleeding rates were not reported.[1463,1464] In a large retrospective cohort study using remote monitoring data about daily AF burden, there was large practice variation in OAC initiation. Across increasing AF burden strata (from >6 min to >24 h) the risk of stroke in untreated

patients increased numerically, and the strongest association of OAC with reduction in stroke was observed among patients with device-detected AF episodes of >24 h.[5]

Recommendations for management of patients with AHRE

Recommendations	Class[a]	Level[b]
In patients with AHRE/subclinical AF detected by CIED or insertable cardiac monitor, it is recommended to conduct: • Complete cardiovascular evaluation with ECG recording, clinical risk factors/comorbidity evaluation, and thrombo-embolic risk assessment using the CHA_2DS_2-VASc score.[469] • Continued patient follow-up and monitoring (preferably with the support of remote monitoring) to detect progression to clinical AF, monitor the AHRE/subclinical AF burden (especially transition to ≥24 h), and detect changes in underlying clinical conditions.[469]	I	B

AF = atrial fibrillation; AHRE = atrial high-rate episode; CIED = cardiac implantable electronic device; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

17 Atrial fibrillation and other atrial tachyarrhythmias (atrial flutter and atrial tachycardias)

Although AFL may exist as a solitary atrial arrhythmia, a significant proportion of patients will subsequently develop AF.[1466–1470] Typical AFL may occur in those taking class IC AADs or amiodarone.[1467,1468,1471] The ABC pathway for integrated AF management largely applies to patients with AFL. It is recommended that stroke-prevention strategies in patients with solitary AFL, including periprocedural management of stroke risk, follow the same principles as in patients with AF.[1472]

Rate control should be the first step in symptom management. However, cardioversion to sinus rhythm may be more effective, especially electrical cardioversion or (where feasible) high-rate stimulation.[1473,1474] Of note, the class III AADs dofetilide and ibutilide i.v. are very effective in interrupting AFL, whereas the class Ic drugs flecainide and propafenone[1475–1478] should not be used in the absence of atrioventricular-blocking drugs as they may slow the atrial rate, thus facilitating 1 : 1 atrioventricular conduction with a rapid ventricular rate.[1479,1480] AF catheter ablation of the CTI is the most effective rhythm control treatment for CTI-dependent AFL.[732,1481,1482] When typical AFL develops in AF patients during treatment with class Ic drugs or amiodarone, CTI ablation should be considered to ensure that AADs can be continued for AF rhythm control.[732,1481]

Atypical AFL (i.e. macro re-entrant atrial tachycardia) most commonly occurs in diseased or scarred atrial myocardium. Clinical management of atypical AFL/macro re-entrant atrial tachycardia broadly follows the principles of typical AFL management, but the use of AADs is often limited by significant structural heart disease, and ablation is more complex.[1336]

Notably, the intervention to treat atrial tachycardias (AFL/macro re-entrant atrial tachycardia) occurring early after AF catheter ablation (or surgery) should be delayed, and initial rate control or the use of AADs should be considered instead, as some of these tachyarrhythmias are transient and cease after maturation of the lesions deployed by the index procedure.[1483–1485] For additional details about AFL, see *Supplementary Box 7* and the 2019 ESC Guidelines on supraventricular tachycardias.[1336]

18 Key messages

(1) The diagnosis of AF needs to be confirmed by a conventional 12-lead ECG tracing or rhythm strip showing AF for ≥30 s.
(2) Structured characterization of AF, including stroke risk, symptom severity, severity of AF burden, and AF substrate, helps improve personalized treatment of AF patients.
(3) Novel tools and technologies for screening and detection of AF such as (micro-)implants and wearables substantially add to the diagnostic opportunities in patients at risk for AF. However, appropriate management pathways based on such tools are still incompletely defined.
(4) Integrated holistic management of AF patients is essential to improving their outcomes.
(5) Patient values need to be considered in treatment decision making and incorporated into the AF management pathways; the structured assessment of PRO measures is an important element to document and measure treatment success.
(6) The ABC pathway streamlines integrated care of AF patients across healthcare levels and among different specialties.
(7) Structured, clinical, risk-score-based assessment of individual thrombo-embolic risk, using the CHA_2DS_2-VASc score, should be performed as the first step in optimal thrombo-embolic risk management in AF patients.
(8) Patients with AF and risk factors for stroke need to be treated with OAC for stroke prevention. In NOAC-eligible patients, NOACs are preferred over VKAs.
(9) A formal structured risk-score-based bleeding risk assessment using, for example, the HAS-BLED score, helps to identify non-modifiable and address modifiable bleeding risk factors in AF patients.
(10) An elevated bleeding risk should not automatically lead to withholding OAC in patients with AF and stroke risk. Instead, modifiable bleeding risk factors should be addressed, and high-risk patients scheduled for a more frequent clinical review and follow-up.
(11) Rate control is an integral part of AF management and is often sufficient to improve AF-related symptoms.
(12) The primary indication for rhythm control using cardioversion, AADs, and/or catheter ablation is reduction in AF-related symptoms and improvement of QoL.
(13) The decision to initiate long-term AAD therapy needs to balance symptom burden, possible adverse drug reactions, particularly drug-induced proarrhythmia or extracardiac side-effects, and patient preferences.

(14) Catheter ablation is a well-established treatment for prevention of AF recurrences. When performed by appropriately trained operators, catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement.

(15) Major risk factors for AF recurrence should be assessed and considered in the decision making for interventional therapy.

(16) In patients with AF and normal LVEF, catheter ablation has not been shown to reduce total mortality or stroke. In patients with AF and tachycardia-induced cardiomyopathy, catheter ablation reverses LV dysfunction in most cases.

(17) Weight loss, strict control of risk factors, and avoidance of triggers for AF are important strategies to improve outcome of rhythm control.

(18) Identification and management of risk factors and concomitant diseases is an integral part of the treatment of AF patients.

(19) In AF patients with ACS undergoing uncomplicated PCI, an early discontinuation of aspirin and switch to dual antithrombotic therapy with OAC and a $P2Y_{12}$ inhibitor should be considered.

(20) Patients with AHRE should be regularly monitored for progression to clinical AF and changes in the individual thrombo-embolic risk (i.e. change in CHA_2DS_2-VASc score). In patients with longer AHRE (especially >24 h) and a high CHA_2DS_2-VASc score, it is reasonable to consider the use of OAC when a positive net clinical benefit from OAC is anticipated in a shared, informed, treatment decision-making process.

19 Gaps in evidence

Whereas some progress has been made since publication of the 2016 ESC AF Guidelines, major gaps identified in those guidelines persist in 2020, calling for more intense research. In 2019, the EHRA published a white paper that covers major gaps in the field of AF in detail.[1486] The following bullet-list gives the most important knowledge gaps:

☐ **Major health modifiers causing atrial fibrillation**

Mechanisms of AF are not yet fully understood. Improvement in understanding of these mechanisms in individual patients, e.g. patients with cardiac structural remodelling or HF, would allow better selection of treatments including the best rate and rhythm control strategies and OAC.

It is uncertain how educational interventions translate into actual behavioural change (patients and physicians) that leads to improvements in clinical management and outcomes, especially in the multimorbid AF patient.

☐ **Implementation of digital technologies for screening, diagnosis, and risk stratification in the atrial fibrillation patient**

New techniques for digital ECG analysis (e.g. machine learning and artificial intelligence) and new technologies (e.g. wearables and injectables) have opened up potentially significant opportunities for the detection and diagnosis of AF. These innovations may help to personalize therapy and risk stratification. Studies are needed to evaluate such opportunities and to define for which groups of patients this is worthwhile.

☐ **Type of atrial fibrillation**

There is a gap in knowledge regarding classification of AF. Recent data suggest that paroxysmal AF is not one entity. According to the pattern, type of therapy and outcome may differ.[1487] More studies are needed.

☐ **How much atrial fibrillation constitutes a mandate for therapy?**

The threshold of AF burden at which to initiate OAC therapy needs to be defined more clearly. This knowledge gap has resulted in substantial variation in physician attitudes and practice patterns.[5]

We are still waiting for the results of two ongoing RCTs in subclinical AF patients who are detected with cardiac implantable electronic device (CIED) [(Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) (NCT 01938248) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) (NCT 02618577)].

☐ **Role of biomarkers in atrial fibrillation management**

Although some studies have demonstrated an effective role of biomarkers (including natriuretic peptides and troponin) in AF risk assessment, there is uncertainty over the exact time point of biomarker assessment, optimal cut-offs, and the effect on management decision making based on changes in biomarker levels over time, especially with increasing age and incident comorbidities.

☐ **Stroke risk in specific populations**

Some studies have tested the effect of biomarkers in predicting risk of AF-related complications, including stroke, in specific populations. However, it is unknown if biomarkers and biomarker-based scores practically help physicians in refining stroke risk, especially in prospective non-anticoagulated cohorts, particularly given the dynamic nature of stroke risk and how many current biomarkers are non-specific for AF or AF-related outcomes.

There is uncertainty of actual stroke risk in AHRE, compared with actual stroke risk in overt AF, in properly matched cohorts in similar settings, and the effect of appropriate management pathways.

The effect of sex in AF patients has been more investigated. Men with AF are less likely to have hypertension or VHD vs. women.[1488] Women often present with atypical symptoms related to AF. Further comparative studies are needed in different settings and ethnic groups on the effect of different stroke risk factors and female sex on stroke and bleeding risks.

☐ **Anticoagulant therapy in specific patients**

There is a gap in knowledge regarding optimal NOAC dosing in specific groups, including those with mild-to-moderate CKD, with very low/high body mass index, and patients receiving medications with a high risk of metabolic interaction.[1489]

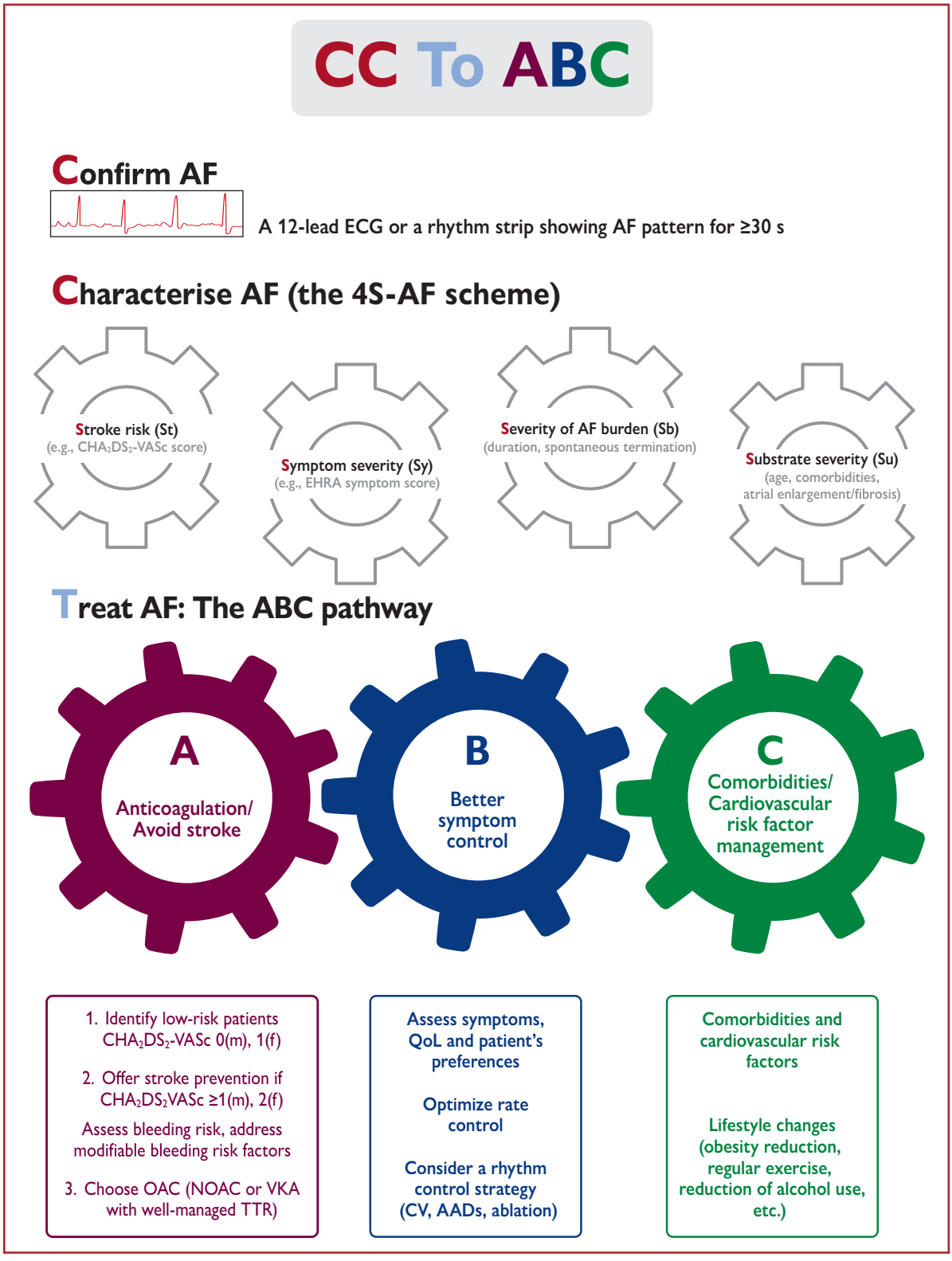
In patients with CrCl ≤25 mL/min, RCT-derived data on the effect of VKA or NOACs is still lacking, due to the exclusion of these patients from the major RCTs. However, two RCTs (NCT02933697, NCT03987711) are currently assessing OAC use and comparing NOACs with VKAs in patients with end-stage renal disease.

☐ **Anticoagulation in patients with heart valve diseases**

There are gaps in evidence on NOAC use in AF patients with rheumatic mitral valve disease and during the first 3 months after surgical or transcatheter implantation of a bioprosthesis; observational data regarding the use of NOACs after transcatheter aortic valve implantation are conflicting.[1163]

☐ **Anticoagulation in atrial fibrillation patients after a bleeding or stroke event**

As high-quality RCT-derived evidence to inform optimal timing of anticoagulation after acute ischaemic stroke is lacking, OAC use in the early post-stroke period is currently based on expert consensus. Several ongoing RCTs [ELAN (NCT03148457), OPTIMAS



Central Illustration Management of AF. AAD = antiarrhythmic drug; AF = atrial fibrillation; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; CHA_2DS_2-VASc = Congestive HF, Hypertension, Age ≥75 years, diabetes mellitus, Stroke, Vascular disease, Age 65 - 74 years, Sex category (female); CV = cardioversion; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist.

(EudraCT, 2018-003859-3), TIMING (NCT02961348), and START (NCT03021928)] will try to assess the differences between the two approaches, including early (<1 week) vs. late NOAC initiation in patients with AF-related ischaemic stroke.

☐ **Left atrial appendage occlusion for stroke prevention**

More studies have been conducted in this field. There is clearer evidence of the safety and possible complications of the LAA closure procedure.[450–454] However, there are still knowledge gaps to be addressed: (i) antithrombotic management after LAA occlusion has not been evaluated in a randomized manner; and (ii) the efficacy and safety of LAA closure vs. OAC therapy needs to be assessed in randomized trials.

LAA occluders have not been compared with NOAC therapy in patients at risk for bleeding, or with surgical LAA occlusion/exclusion.

☐ **Surgical exclusion of Left atrial appendage**

Only limited RCT data are available[457–459] on surgical exclusion of the LAA. Although a large RCT in patients with an associated cardiac surgical procedure is ongoing,[462] adequately powered RCTs are needed.

There is the need for adequately powered trials to define the best indications for LAA occlusion/exclusion compared with NOAC therapy in patients with relative or absolute contraindications for anticoagulation, in those with an ischaemic stroke on anticoagulant therapy, and for assessment of the appropriate antithrombotic therapy after LAA occlusion.

☐ **Atrial fibrillation catheter ablation technique**

The best approach to safely and expeditiously achieve permanent PVI in a single procedure is still one of the knowledge gaps in relation to emerging technologies for catheter ablation of AF. Moreover, it remains unknown if ablating additional targets will improve the outcomes of AF catheter ablation.[1490]

☐ **Outcome of atrial fibrillation catheter ablation**

The following issues need to be addressed in further studies:

- The value of early AF ablation to prevent AF progression.
- The optimal outcome measure (AF 30 s, AF burden, etc.) for AF-related outcome.
- How much reduction in AF burden is needed to achieve an effect on hard endpoints, including survival, stroke, and comorbidity.
- The main mechanism of PVI translating into freedom of AF.
- The potential effect of cardiac structure and function on the likelihood of success of AF ablation.

Despite the publication of CABANA and CASTLE-AF, more data are needed on the effect of AF catheter ablation on clinical outcomes, including death, stroke, serious bleeding, AF recurrence, QoL, and cardiac arrest.

The relationship between the degree of atrial dilation/fibrosis and successful ablation of AF needs to be addressed. Additionally, the impact of specific components of structural heart disease, including LA structure/function, LV structure, etc., on the success of AF catheter ablation and the likelihood of recurrence requires further investigation.

☐ **Who may benefit less from atrial fibrillation catheter ablation**

There are gaps in knowledge about subgroups of patients who may benefit less from AF catheter ablation, including (i) persistent and long-standing persistent AF; (ii) patients with enlarged atrial size and/or atrial fibrosis; (iii) patients with atypical AFL; and (iv) patients with risk factors for AF recurrence, including obesity or sleep apnoea.

☐ **Thoracoscopic 'stand-alone' atrial fibrillation surgery**

There are no convincing data on the effects on stroke of surgical ablation as a stand-alone procedure or in combination with LAA occlusion or exclusion on various outcomes including QoL, stroke, and death.

☐ **Personalized therapy**

The arrhythmia phenotype may differ among patients. Improved assessment of the pathophysiological process involved in the individual patient by using clinical characteristics, blood biomarkers, and non-invasive substrate determination (echo/MRI/CT) may improve personalized therapy (e.g. selection of rhythm control, yes or no; treatment of risk factors and comorbidities; type of antiarrhythmic drug; atrial ablation; and which type/techniques used for AF).

20 'What to do' and 'what not to do' messages from the Guidelines

Recommendations	Class[a]	Level[b]
Recommendations for diagnosis of AF		
ECG documentation is required to establish the diagnosis of AF. • A standard 12-lead ECG recording or a single-lead ECG tracing of ≥30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals (when atrioventricular conduction is not impaired) is diagnostic of clinical AF.	I	B
Recommendations for screening of AF		
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.	I	B
When screening for AF it is recommended that: • The individuals undergoing screening are informed about the significance and treatment implications of detecting AF. • A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF. • Definite diagnosis of AF in screen-positive cases is established only after the physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.	I	B

Continued

Recommendations for diagnostic evaluation of patients with AF		
In patients with AF, it is recommended to: • Evaluate AF-related symptoms (including fatigue, tiredness, exertional shortness of breath, palpitations, and chest pain) and quantify the patient symptom status using the modified EHRA symptom scale before and after initiation of treatment. • Evaluate AF-related symptoms before and after cardioversion of persistent AF to aid rhythm control treatment decisions.	I	C
In patients with AHRE/subclinical AF detected by CIED or insertable cardiac monitor, it is recommended to conduct: • Complete cardiovascular evaluation with ECG recording, clinical risk factors/comorbidity evaluation, and thrombo-embolic risk assessment using the CHA_2DS_2-VASc score. • Continued patient follow-up and monitoring (preferably with the support of remote monitoring) to detect progression to clinical AF, monitor the AHRE/subclinical AF burden (especially transition to ≥24 h), and detect changes in underlying clinical conditions.	I	B
Recommendations about integrated AF management		
To optimize shared decision making about specific AF treatment option(s) in consideration, it is recommended that physicians: • Inform the patient about the advantages/limitations and benefit/risks associated with the treatment option(s) being considered; and • Discuss the potential burden of the treatment with the patient and include the patient's perception of treatment burden in the treatment decision.	I	C
It is recommended to routinely collect PROs to measure treatment success and improve patient care.	I	C
Recommendations for the prevention of thrombo-embolic events in AF		
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis).	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA_2DS_2-VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA_2DS_2-VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy.	I	A
OAC is recommended for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.	I	A
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up.	I	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors.	I	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR≥70%.	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR<70%), switching to a NOAC but ensuring good adherence and persistence with therapy is recommended.	I	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.	III	B
Recommendations for stroke risk management peri-cardioversion		
In patients with AF undergoing cardioversion, NOACs are recommended with at least similar efficacy and safety as warfarin.	I	A
For cardioversion of AF/AFL, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion.	I	B
TOE is recommended to exclude cardiac thrombus as an alternative to 3-week pre-procedural anticoagulation when early cardioversion is planned.	I	B
In patients at risk of stroke, it is recommended that OAC therapy is continued long term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion, the apparent maintenance of sinus rhythm, or characterization of AF as a 'first-diagnosed episode'.	I	B
When thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks before cardioversion of AF.	I	B
It is recommended that the importance of adherence and persistence to NOAC treatment both before and after cardioversion is strongly emphasized to patients.	I	C
Recommendations for stroke risk management peri-catheter ablation		
In AF patients with stroke risk factors not taking OAC before ablation, it is recommended that pre-procedural management of stroke risk includes initiation of anticoagulation and, preferably, therapeutic OAC for at least 3 weeks before ablation.	I	C

Continued

For patients undergoing AF catheter ablation who have been therapeutically anticoagulated with warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without OAC interruption is recommended.	I	A
After AF catheter ablation, it is recommended that: • Systemic anticoagulation with warfarin or a NOAC is continued for at least 2 months post ablation, and • Long-term continuation of systemic anticoagulation beyond 2 months post ablation is based on the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure.	I	C
Recommendations for postoperative anticoagulation after AF surgery		
Long-term OAC is recommended in patients after AF surgery and appendage closure, based on the patient's thrombo-embolic risk assessed with the CHA_2DS_2-VASc score.	I	C
Recommendations for patients with AF and an ACS, PCI, or CCS		
In AF patients eligible for NOACs, it is recommended to use a NOAC in preference to a VKA in combination with antiplatelet therapy.	I	A
In AF patients with ACS undergoing an uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and a $P2Y_{12}$ inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I	A
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespective of the type of stent used.	I	A
Recommendations for secondary stroke prevention in AF patients after acute ischaemic stroke		
In AF patients with an ischaemic stroke or TIA, long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients.	I	A
In AF patients presenting with acute ischaemic stroke, very early anticoagulation (<48 h) using UFH, LMWH, or VKAs is not recommended.	III	B
Recommendations for patients with valvular heart disease and AF		
NOACs are contraindicated in patients with a prosthetic mechanical valve.	III	B
Use of NOACs is not recommended in patients with AF and moderate-to-severe mitral stenosis.	III	C
Recommendations for the management of AF during pregnancy		
Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF.	I	C
Recommendations for the management of active bleeding on OAC		
In an AF patient with severe active bleeding, it is recommended to: • Interrupt OAC until the cause of bleeding is identified and active bleeding is resolved; and • Promptly perform specific diagnostic and treatment interventions to identify and manage the cause(s) and source(s) of bleeding.	I	C
Recommendations for ventricular rate control in patients with AF		
Beta-blockers, diltiazem, or verapamil are recommended as first-choice drugs to control heart rate in AF patients with LVEF≥40%.	I	B
Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF<40%.	I	B
Recommendations for the management of AF during pregnancy		
Beta-selective blockers are recommended for rate control in AF.	I	C
Recommendations for rhythm control		
Rhythm control therapy is recommended for symptom and QoL improvement in symptomatic patients with AF.	I	A
Recommendations for cardioversion		
For pharmacological cardioversion of new-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or flecainide or propafenone (excluding patients with severe structural heart disease) is recommended.	I	A
Intravenous amiodarone is recommended for cardioversion of AF in patients with HF or structural heart disease, if delayed cardioversion is consistent with clinical situation.	I	A
Cardioversion of AF (either electrical or pharmacological) is recommended in symptomatic patients with persistent or long-standing persistent AF as part of rhythm control therapy.	I	B
Pharmacological cardioversion of AF is indicated only in a haemodynamically stable patient, after consideration of the thrombo-embolic risk.	I	B

Continued

Emergency electrical cardioversion is recommended in AF patients with acute or worsening haemodynamic instability.	I	B
For patients with sick-sinus syndrome, atrioventricular conduction disturbances or prolonged QTc (>500 ms), pharmacological cardioversion should not be attempted unless risks for proarrhythmia and bradycardia have been considered.	III	C
Recommendations for the management of AF during pregnancy		
Immediate electrical cardioversion is recommended in case of haemodynamic instability or pre-excited AF.	I	C
Recommendations for rhythm control/catheter ablation of AF		
For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient.	I	B
AF catheter ablation after failure of drug therapy		
AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with:	I	
• Paroxysmal AF, or		A
• Persistent AF without major risk factors for AF recurrence, or		A
• Persistent AF with major risk factors for AF recurrence.		B
First-line therapy		
AF catheter ablation is recommended to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, independent of their symptom status.	I	B
Techniques and technologies		
Complete electrical isolation of the pulmonary veins is recommended during all AF catheter-ablation procedures.	I	A
Lifestyle modification and other strategies to improve outcomes of ablation		
Weight loss is recommended in obese patients with AF, particularly those who are being evaluated to undergo AF ablation.	I	B
Strict control of risk factors and avoidance of triggers are recommended as part of a rhythm control strategy.	I	B
Recommendations for long-term antiarrhythmic drugs		
Flecainide or propafenone are recommended for long-term rhythm control in AF patients with normal LV function and without structural heart disease, including significant LVH and myocardial ischaemia.	I	A
Dronedarone is recommended for long-term rhythm control in AF patients with: • Normal or mildly impaired (but stable) LV function, or • HFpEF, ischaemic, or VHD.	I	A
Amiodarone is recommended for long-term rhythm control in all AF patients, including those with HFrEF. However, owing to its extracardiac toxicity, other AADs should be considered first whenever possible.	I	A
In AF patients treated with sotalol, close monitoring of QT interval, serum potassium levels, CrCl, and other proarrhythmia risk factors is recommended.	I	B
AAD therapy is not recommended in patients with permanent AF under rate control and in patients with advanced conduction disturbances unless antibradycardia pacing is provided.	III	C
Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with AF		
Identification and management of risk factors and concomitant diseases is recommended as an integral part of treatment in AF patients.	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.	I	B
Opportunistic screening for AF is recommended in hypertensive patients.	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	B
Recommendations for sports activity in patients with AF		
It is recommended to counsel professional athletes that long-lasting intense sports participation may promote AF, while moderate physical activity is recommended to prevent AF.	I	B
Recommendations for postoperative AF		
Perioperative amiodarone or beta blocker therapy is recommended for the prevention of postoperative AF after cardiac surgery.	I	A
Beta-blockers should not be used routinely for the prevention of postoperative AF in patients undergoing non-cardiac surgery.	III	B

Continued

Recommendations pertaining to sex-related differences in AF		
It is recommended that women and men with AF are equally offered diagnostic assessment and therapies to prevent stroke and other AF-related complications.	I	A

AAD = antiarrhythmic drug; ACS = acute coronary syndrome; AF = atrial fibrillation; AFL = atrial flutter; AHRE = atrial high-rate episodes; BP = blood pressure; CCS = chronic coronary syndrome; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); CIED = cardiac implantable electronic device; CrCl = creatinine clearance; ECG = electrocardiogram; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; i.v. = intravenous; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRO = patient-reported outcome; PVI = pulmonary vein isolation; QoL = quality of life; TIA = transient ischaemic attack; TOE = transoesophageal echocardiography; TTR = time in therapeutic range; UFH = unfractionated heparin; VHD = Valvular heart disease; VKA = vitamin K antagonist.

21 Supplementary data

Supplementary Data with additional Supplementary Figures, Tables, and text complementing the full text are available on the *European Heart Journal* website and via the ESC website at www.escardio.org/guidelines.

22 Appendix

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23 References

1. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot N, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace* 2018;**20**:157–208.
2. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers HH, Hanke T. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012;**126**:806–814.
3. Gorenek B, Boriani G, Dan GA, Fauchier L, Fenelon G, Huang H, Kudaiberdieva G, Lip GYH, Mahajan R, Potpara T, Ramirez JD, Vos MA, Marin F, ESC Scientific Document Group. European Heart Rhythm Association (EHRA) position paper on arrhythmia management and device therapies in endocrine disorders, endorsed by Asia Pacific Heart Rhythm Society (APHRS) and Latin American Heart Rhythm Society (LAHRS). *Europace* 2018;**20**:895–896.
4. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. *Nat Rev Cardiol* 2017;**14**:701–714.
5. Perino AC, Fan J, Askari M, Heidenreich PA, Keung E, Raitt MH, Piccini JP, Ziegler PD, Turakhia MP. Practice variation in anticoagulation prescription and outcomes after device-detected atrial fibrillation. *Circulation* 2019;**139**:2502–2512.
6. Steinberg JS, O'Connell H, Li S, Ziegler PD. Thirty-second gold standard definition of atrial fibrillation and its relationship with subsequent arrhythmia patterns: analysis of a large prospective device database. *Circ Arrhythm Electrophysiol* 2018;**11**:e006274.
7. Camm AJ, Simantirakis E, Goette A, Lip GY, Vardas P, Calvert M, Chlouverakis G, Diener HC, Kirchhof P. Atrial high-rate episodes and stroke prevention. *Europace* 2017;**19**:169–179.
8. Pollak WM, Simmons JD, Interian A, Jr., Atapattu SA, Castellanos A, Myerburg RJ, Mitrani RD. Clinical utility of intraatrial pacemaker stored electrograms to diagnose atrial fibrillation and flutter. *Pacing Clin Electrophysiol* 2001;**24**:424–429.
9. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, Brandes A, Crystal E, Costantini O, Sandhu RK, Parkash R, Connolly SJ, Hohnloser SH, Healey JS; ASSERT Steering Committee and Investigators. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;**9**:1241–1246.
10. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. *Circulation* 2019;**139**:e56–e528.
11. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–847.
12. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. *Am J Cardiol* 2013;**112**:1142–1147.
13. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;**34**:2746–2751.
14. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation* 2013;**128**:2470–2477.
15. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res* 2017;**120**:1501–1517.
16. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009;**158**:111–117.
17. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, Chen SA. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF Cohort Study. *Chest* 2018;**153**:453–466.
18. Guo Y, Tian Y, Wang H, Si Q, Wang Y, Lip GYH. Prevalence, incidence, and lifetime risk of atrial fibrillation in China: new insights into the global burden of atrial fibrillation. *Chest* 2015;**147**:109–119.
19. Di Carlo A, Bellino L, Consoli D, Mori F, Zaninelli A, Baldereschi M, Baldereschi M, Cattarinussi A, D'Alfonso MG, Gradia C, Sgherzi B, Pracucci G, Piccardi B, Polizzi B, Inzitari D, National Research Program: Progetto FAI. La Fibrillazione Atriale in Italia. Prevalence of atrial fibrillation in the Italian elderly population and projections from 2020 to 2060 for Italy and the European Union: the FAI Project. *Europace* 2019;**21**:1468–1475.
20. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol* 2018;**11**:e006350.
21. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW, Lane DA, La Manna G, Morton J, Mitjans AM, Vos MA, Turakhia MP, Lip GY. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making – a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2015;**17**:1169–1196.

22. Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabetes Complications* 2018;**32**:501–511.
23. Cadby G, McArdle N, Briffa T, Hillman DR, Simpson L, Knuiman M, Hung J. Severity of OSA is an independent predictor of incident atrial fibrillation hospitalization in a large sleep-clinic cohort. *Chest* 2015;**148**:945–952.
24. Hobbelt AH, Siland JE, Geelhoed B, Van Der Harst P, Hillege HL, Van Gelder IC, Rienstra M. Clinical, biomarker, and genetic predictors of specific types of atrial fibrillation in a community-based cohort: data of the PREVEND study. *Europace* 2017;**19**:226–232.
25. Nalliah CJ, Sanders P, Kalman JM. The impact of diet and lifestyle on atrial fibrillation. *Curr Cardiol Rep* 2018;**20**:137.
26. Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, Oto A, Potpara TS, Steffel J, Marin F, de Oliveira Figueiredo MJ, de Simone G, Tzou WS, Chiang CE, Williams B, Reviewers, Dan GA, Gorenek B, Fauchier L, Savelieva I, Hatala R, van Gelder I, Brguljan-Hitij J, Erdine S, Lovic D, Kim YH, Salinas-Arce J, Field M. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;**19**:891–911.
27. Gallagher C, Hendriks JML, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P. Alcohol and incident atrial fibrillation – a systematic review and meta-analysis. *Int J Cardiol* 2017;**246**:46–52.
28. Ricci C, Gervasi F, Gaeta M, Smuts CM, Schutte AE, Leitzmann MF. Physical activity volume in relation to risk of atrial fibrillation. A non-linear meta-regression analysis. *Eur J Prev Cardiol* 2018;**25**:857–866.
29. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam Study. *Eur Heart J* 2006;**27**:949–953.
30. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;**110**:1042-1046.
31. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jorgensen T, Soderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB, BiomarCaRE Consortium. Sex differences and similarities in atrial fibrillation epidemiology, risk factors, and mortality in community cohorts: results from the BiomarCaRE Consortium (*Biomarker for Cardiovascular Risk Assessment in Europe*). *Circulation* 2017;**136**:1588–1597.
32. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;**361**:k1453.
33. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, Perel P, Morley K, Banerjee A, Hemingway H. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost* 2017;**117**:837–850.
34. Feghaly J, Zakka P, London B, MacRae CA, Refaat MM. Genetics of atrial fibrillation. *J Am Heart Assoc* 2018;**7**:e009884.
35. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156–1159.
36. Alonso A, Jensen PN, Lopez FL, Chen LY, Psaty BM, Folsom AR, Heckbert SR. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study. *PLoS One* 2014;**9**:e109662.
37. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011;**123**:2946–2953.
38. Andersen K, Farahmand B, Ahlbom A, Held C, Ljunghall S, Michaelsson K, Sundstrom J. Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study. *Eur Heart J* 2013;**34**:3624–3631.
39. Asad Z, Abbas M, Javed I, Korantzopoulos P, Stavrakis S. Obesity is associated with incident atrial fibrillation independent of gender: a meta-analysis. *J Cardiovasc Electrophysiol* 2018;**29**:725–732.
40. Aune D, Sen A, Schlesinger S, Norat T, Janszky I, Romundstad P, Tonstad S, Riboli E, Vatten LJ. Body mass index, abdominal fatness, fat mass and the risk of atrial fibrillation: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2017;**32**:181–192.
41. Bansal N, Zelnick LR, Alonso A, Benjamin EJ, de Boer IH, Deo R, Katz R, Kestenbaum B, Mathew J, Robinson-Cohen C, Sarnak MJ, Shlipak MG, Sotoodehnia N, Young B, Heckbert SR. eGFR and albuminuria in relation to risk of incident atrial fibrillation: a meta-analysis of the Jackson Heart Study, the Multi-Ethnic Study of Atherosclerosis, and the Cardiovascular Health Study. *Clin J Am Soc Nephrol* 2017;**12**:1386–1398.
42. Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, den Elzen WPJ, Peeters RP, Luben R, Volzke H, Dorr M, Walsh JP, Bremner A, Iacoviello M, Macfarlane P, Heeringa J, Stott DJ, Westendorp RGJ, Khaw KT, Magnani JW, Aujesky D, Rodondi N, Thyroid Studies Collaboration. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation* 2017;**136**:2100–2116.
43. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;**271**:840–844.
44. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ, Jacobs V, Mallender C, Muhlestein JB, Osborn JS, Weiss JP, Day JD. Long-term natural history of adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol* 2015;**8**:1465–1471.
45. Chang SH, Kuo CF, Chou IJ, See LC, Yu KH, Luo SF, Huang LH, Zhang W, Doherty M, Wen MS, Kuo CT, Yeh YH. Association of a family history of atrial fibrillation with incidence and outcomes of atrial fibrillation: a population-based family cohort study. *JAMA Cardiol* 2017;**2**:863–870.
46. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, Pan W, Polak JF, Witteman JC, Kronmal RA, Folsom AR, Nazarian S, Stricker BH, Heckbert SR, Alonso A. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. *J Am Heart Assoc* 2016;**5**.
47. Cheng M, Hu Z, Lu X, Huang J, Gu D. Caffeine intake and atrial fibrillation incidence: dose response meta-analysis of prospective cohort studies. *Can J Cardiol* 2014;**30**:448–454.
48. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;**301**:2571–2577.
49. Conen D, Chiuve SE, Everett BM, Zhang SM, Buring JE, Albert CM. Caffeine consumption and incident atrial fibrillation in women. *Am J Clin Nutr* 2010;**92**:509–514.
50. Desai R, Patel U, Singh S, Bhuva R, Fong HK, Nunna P, Zalavadia D, Dave H, Savani S, Doshi R. The burden and impact of arrhythmia in chronic obstructive pulmonary disease: insights from the National Inpatient Sample. *Int J Cardiol* 2019;**281**:49–55.
51. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. *Circulation* 2004;**109**:1267–1271.
52. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004;**291**:2851–2855.
53. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol* 1994;**74**:236–241.
54. Giacomantonio NB, Bredin SS, Foulds HJ, Warburton DE. A systematic review of the health benefits of exercise rehabilitation in persons living with atrial fibrillation. *Can J Cardiol* 2013;**29**:483–491.
55. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options – a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8–27.
56. Ko D, Benson MD, Ngo D, Yang Q, Larson MG, Wang TJ, Trinquart L, McManus DD, Lubitz SA, Ellinor PT, Vasan RS, Gerszten RE, Benjamin EJ, Lin H. Proteomics profiling and risk of new-onset atrial fibrillation: Framingham Heart Study. *J Am Heart Assoc* 2019;**8**:e010976.
57. Kwok CS, Anderson SG, Myint PK, Mamas MA, Loke YK. Physical activity and incidence of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2014;**177**:467–476.
58. Lip GYH, Collet JP, de Caterina R, Fauchier L, Lane DA, Larsen TB, Marin F, Morais J, Narasimhan C, Olshansky B, Pierard L, Potpara T, Sarrafzadegan N,

Sliwa K, Varela G, Vilahur G, Weiss T, Boriani G, Rocca B. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: executive summary of a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, Endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Thromb Haemost* 2017;**117**:2215–2236.
59. Loomba RS, Buelow MW, Aggarwal S, Arora RR, Kovach J, Ginde S. Arrhythmias in adults with congenital heart disease: what are risk factors for specific arrhythmias?*Pacing Clin Electrophysiol* 2017;**40**:353–361.
60. Lubitz SA, Yin X, Fontes JD, Magnani JW, Rienstra M, Pai M, Villalon ML, Vasan RS, Pencina MJ, Levy D, Larson MG, Ellinor PT, Benjamin EJ. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA* 2010;**304**:2263–2269.
61. May AM, Blackwell T, Stone PH, Stone KL, Cawthon PM, Sauer WH, Varosy PD, Redline S, Mehra R, Sleep MrOS (Outcomes of Sleep Disorders in Older Men) Study Group. Central sleep-disordered breathing predicts incident atrial fibrillation in older men. *Am J Respir Crit Care Med* 2016;**193**:783–791.
62. Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease – double trouble. *Adv Med Sci* 2018;**63**:30–35.
63. Monrad M, Sajadieh A, Christensen JS, Ketzel M, Raaschou-Nielsen O, Tjonneland A, Overvad K, Loft S, Sorensen M. Long-term exposure to traffic-related air pollution and risk of incident atrial fibrillation: a cohort study. *Environ Health Perspect* 2017;**125**:422–427.
64. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, Nazarian S, Soliman EZ. Coronary artery calcium progression and atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2015;**8**:pii: e003786.
65. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA, Al-Mallah MH. Cardiorespiratory fitness and risk of incident atrial fibrillation: results from the Henry Ford Exercise Testing (FIT) Project. *Circulation* 2015;**131**:1827–1834.
66. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–492.
67. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50-Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–162.
68. Shen J, Johnson VM, Sullivan LM, Jacques PF, Magnani JW, Lubitz SA, Pandey S, Levy D, Vasan RS, Quatromoni PA, Junyent M, Ordovas JM, Benjamin EJ. Dietary factors and incident atrial fibrillation: the Framingham Heart Study. *Am J Clin Nutr* 2011;**93**:261–266.
69. Svensson T, Kitlinski M, Engstrom G, Melander O. Psychological stress and risk of incident atrial fibrillation in men and women with known atrial fibrillation genetic risk scores. *Sci Rep* 2017;**7**:42613.
70. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, Benjamin EJ, Redline S. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc* 2017;**6**:pii.
71. Walkey AJ, Greiner MA, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, Curtis LH, Benjamin EJ. Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors. *Am Heart J* 2013;**165**:949–955.e3.
72. Zoller B, Ohlsson H, Sundquist J, Sundquist K. High familial risk of atrial fibrillation/atrial flutter in multiplex families: a nationwide family study in Sweden. *J Am Heart Assoc* 2012;**2**:e003384.
73. Lip GYH, Skjoth F, Nielsen PB, Larsen TB. Evaluation of the C2HEST risk score as a possible opportunistic screening tool for incident atrial fibrillation in a healthy population (from a nationwide Danish cohort study). *Am J Cardiol* 2020;**125**:48–54.
74. Yiin GSC, Li L, Bejot Y, Rothwell PM. Time trends in atrial fibrillation-associated stroke and premorbid anticoagulation. *Stroke* 2018:STROKEAHA118022249.
75. Akao M, Chun YH, Wada H, Esato M, Hashimoto T, Abe M, Hasegawa K, Tsuji H, Furuke K; Fushimi AFRegistry Investigators. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. *J Cardiol* 2013;**61**:260–266.
76. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M. Causes of death in Japanese patients with atrial fibrillation: the Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:35–42.
77. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995–2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061–1067.
78. Andrew NE, Thrift AG, Cadilhac DA. The prevalence, impact and economic implications of atrial fibrillation in stroke: what progress has been made?*Neuroepidemiology* 2013;**40**:227–239.
79. Bakhai A, Darius H, De Caterina R, Smart A, Le Heuzey JY, Schilling RJ, Zamorano JL, Shah M, Bramlage P, Kirchhof P. Characteristics and outcomes of atrial fibrillation patients with or without specific symptoms: results from the PREFER in AF registry. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:299–305.
80. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–952.
81. Blum S, Muff C, Aeschbacher S, Ammann P, Erne P, Moschovitis G, Di Valentino M, Shah D, Schlapfer J, Fischer A, Merkel T, Kuhne M, Sticherling C, Osswald S, Conen D. Prospective assessment of sex-related differences in symptom status and health perception among patients with atrial fibrillation. *J Am Heart Assoc* 2017;**6**:e005401.
82. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Sinagra G, Petrescu L, Tavazzi L, Maggioni AP, Lip GY. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med* 2015;**128**:509–518.e2.
83. Ceornodolea AD, Bal R, Severens JL. Epidemiology and management of atrial fibrillation and stroke: review of data from four European countries. *Stroke Res Treat* 2017;**2017**:8593207.
84. Chao TF, Lip GY, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Chen TJ, Chiang CE, Chen SA. Validation of a modified CHA2DS2-VASc score for stroke risk stratification in Asian patients with atrial fibrillation: a nationwide cohort study. *Stroke* 2016;**47**:2462–2469.
85. Chao T-F, Liu C-J, Wang K-L, Lin Y-J, Chang S-L, Lo L-W, Hu Y-F, Tuan T-C, Chen T-J, Lip GY. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation?*J Am Coll Cardiol* 2015;**65**:635–642.
86. Dagres N, Chao T-F, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ, Bunch TJ, Chen LY, Chen S-A, Darrieux F, de Paola A, Fauchier L, Goette A, Kalman J, Kalra L, Kim Y-H, Lane DA, Lip GYH, Lubitz SA, Márquez MF, Potpara T, Pozzer DL, Ruskin JN, Savelieva I, Teo WS, Tse H-F, Verma A, Zhang S, Chung MK, Bautista-Vargas W-F, Chiang C-E, Cuesta A, Dan G-A, Frankel DS, Guo Y, Hatala R, Lee YS, Murakawa Y, Pellegrini CN, Pinho C, Milan DJ, Morin DP, Nadalin E, Ntaios G, Prabhu MA, Proietti M, Rivard L, Valentino M, Shantsila A. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice?*EP Europace* 2018;**20**:1399–1421.
87. Esato M, Chun YH, An Y, Ogawa H, Wada H, Hasegawa K, Tsuji H, Abe M, Lip GYH, Akao M. Clinical impact of asymptomatic presentation status in patients with paroxysmal and sustained atrial fibrillation: the Fushimi AF Registry. *Chest* 2017;**152**:1266–1275.
88. Freeman JV, Simon DN, Go AS, Spertus J, Fonarow GC, Gersh BJ, Hylek EM, Kowey PR, Mahaffey KW, Thomas LE, Chang P, Peterson ED, Piccini JP; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Investigators. Association between atrial fibrillation symptoms, quality of life, and patient outcomes: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Circ Cardiovasc Qual Outcomes* 2015;**8**:393–402.
89. Frost L, Engholm G, Johnsen S, Moller H, Henneberg EW, Husted S. Incident thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries after discharge from the hospital with a diagnosis of atrial fibrillation. *Arch Intern Med* 2001;**161**:272–276.
90. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, Bergamasco L, Boffano C, Valentini MC, Cesarani F, Scaglione M. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;**62**:1990–1997.
91. Garcia-Fernandez A, Roldan V, Rivera-Caravaca JM, Lip GYH, Marin F. Applicability of the modified CHA2DS2-VASc score for stroke risk stratification in Caucasian atrial fibrillation patients. *Eur J Intern Med* 2017;**38**:e21–e22.
92. Gleason KT, Nazarian S, Dennison Himmelfarb CR. Atrial fibrillation symptoms and sex, race, and psychological distress: a literature review. *J Cardiovasc Nurs* 2018;**33**:137–143.
93. Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2016;**68**:2508–2521.
94. Graves KG, May HT, Jacobs V, Bair TL, Stevens SM, Woller SC, Crandall BG, Cutler MJ, Day JD, Mallender C, Osborn JS, Peter Weiss J, Jared Bunch T. Atrial fibrillation incrementally increases dementia risk across all CHADS2 and

CHA2DS2VASc strata in patients receiving long-term warfarin. *Am Heart J* 2017;**188**:93–98.
95. John RM, Michaud GF, Stevenson WG. Atrial fibrillation hospitalization, mortality, and therapy. *Eur Heart J* 2018;**39**:3958–3960.
96. Kalantarian S, Ruskin JN. Atrial fibrillation and cognitive decline: phenomenon or epiphenomenon?*Cardiol Clin* 2016;**34**:279–285.
97. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013;**158**:338–46.
98. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes* 2011;**4**:313–320.
99. Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W, Wegscheider K, Meinertz T, ATRIUM Study Group. Management of patients with atrial fibrillation by primary-care physicians in Germany: 1-year results of the ATRIUM registry. *Clin Cardiol* 2014;**37**:277–284.
100. Kochhauser S, Joza J, Essebag V, Proietti R, Koehler J, Tsang B, Wulffhart Z, Pantano A, Khaykin Y, Ziegler PD, Verma A. The impact of duration of atrial fibrillation recurrences on measures of health-related quality of life and symptoms. *Pacing Clin Electrophysiol* 2016;**39**:166–72.
101. Konig S, Ueberham L, Schuler E, Wiedemann M, Reithmann C, Seyfarth M, Sause A, Tebbenjohanns J, Schade A, Shin DI, Staudt A, Zacharzowsky U, Andrie R, Wetzel U, Neuser H, Wunderlich C, Kuhlen R, Tijssen JGP, Hindricks G, Bollmann A. In-hospital mortality of patients with atrial arrhythmias: insights from the German-wide Helios hospital network of 161 502 patients and 34 025 arrhythmia-related procedures. *Eur Heart J* 2018;**39**:3947–3957.
102. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. *J Am Coll Cardiol* 2016;**68**:2217–2228.
103. Kupper N, van den Broek K, Haagh E, van der Voort P, Widdershoven J, Denollet J. Type D personality affects health-related quality of life in patients with lone atrial fibrillation by increasing symptoms related to sympathetic activation. *J Psychosom Res* 2018;**115**:44–52.
104. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011;**76**:914–922.
105. Levy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation* 1999;**99**:3028–3035.
106. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996;**27**:1760–1764.
107. Lip GY, Laroche C, Boriani G, Cimaglia P, Dan GA, Santini M, Kalarus Z, Rasmussen LH, Popescu MI, Tica O, Hellum CF, Mortensen B, Tavazzi L, Maggioni AP. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot Survey on Atrial Fibrillation. *Europace* 2015;**17**:24–31.
108. McCabe PJ, Rhudy LM, DeVon HA. Patients' experiences from symptom onset to initial treatment for atrial fibrillation. *J Clin Nurs* 2015;**24**:786–796.
109. McCabe PJ, Schumacher K, Barnason SA. Living with atrial fibrillation: a qualitative study. *J Cardiovasc Nurs* 2011;**26**:336–344.
110. Meyre P, Blum S, Berger S, Aeschbacher S, Schoepfer H, Briel M, Osswald S, Conen D. Risk of hospital admissions in patients with atrial fibrillation: a systematic review and meta-analysis. *Can J Cardiol* 2019;**35**:1332–1343.
111. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ; European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 2005;**26**:2422–2434.
112. Overvad TF, Nielsen PB, Lip GY. Treatment thresholds for stroke prevention in atrial fibrillation: observations on the CHA2DS2-VASc score. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:37–41.
113. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 1994;**89**:224–227.
114. Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. *Lancet* 2016;**388**:829–840.
115. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The epidemiology of atrial fibrillation and stroke. *Cardiol Clin* 2016;**34**:255–268.
116. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, Breithardt G, Singer DE, Hankey GJ, Hacke W, Becker RC, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KA, Califf RM; ROCKET AF Steering Committee Investigators. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc* 2016;**5**:e002197.
117. Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol* 2013;**168**:4744–4749.
118. Randolph TC, Simon DN, Thomas L, Allen LA, Fonarow GC, Gersh BJ, Kowey PR, Reiffel JA, Naccarelli GV, Chan PS, Spertus JA, Peterson ED, Piccini JP; ORBIT AF Investigators. Patient factors associated with quality of life in atrial fibrillation. *Am Heart J* 2016;**182**:135–143.
119. Rienstra M, Lubitz SA, Mahida S, Magnani JW, Fontes JD, Sinner MF, Van Gelder IC, Ellinor PT, Benjamin EJ. Symptoms and functional status of patients with atrial fibrillation: state-of-the-art and future research opportunities. *Circulation* 2012;**125**:2933–2943.
120. Rienstra M, Vermond RA, Crijns HJ, Tijssen JG, Van Gelder IC; RACE Investigators. Asymptomatic persistent atrial fibrillation and outcome: results of the RACE study. *Heart Rhythm* 2014;**11**:939–945.
121. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. *Can J Cardiol* 2017;**33**:1556–1564.
122. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Dello Russo A, Tondo C, Natale A. Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012;**9**:1761–1768.
123. Schnabel RB, Michal M, Wilde S, Wiltink J, Wild PS, Sinning CR, Lubos E, Ojeda FM, Zeller T, Munzel T, Blankenberg S, Beutel ME. Depression in atrial fibrillation in the general population. *PLoS One* 2013;**8**:e79109.
124. Schnabel RB, Pecen L, Ojeda FM, Lucerna M, Rzayeva N, Blankenberg S, Darius H, Kotecha D, Caterina R, Kirchhof P. Gender differences in clinical presentation and 1-year outcomes in atrial fibrillation. *Heart* 2017;**103**:1024–1030.
125. Senoo K, Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, Oikawa Y, Yajima J, Koike A, Nagashima K, Kirigaya H, Sawada H, Aizawa T, Yamashita T. Distribution of first-detected atrial fibrillation patients without structural heart diseases in symptom classifications. *Circ J* 2012;**76**:1020–1023.
126. Serpytis R, Navickaite A, Serpytiene E, Barysiene J, Marinskis G, Jatuzis D, Petrulioniene Z, Laucevicius A, Serpytis P. Impact of atrial fibrillation on cognitive function, psychological distress, quality of life, and impulsiveness. *Am J Med* 2018;**131**:703.e1-703e5.
127. Siontis KC, Gersh BJ, Killian JM, Noseworthy PA, McCabe P, Weston SA, Roger VL, Chamberlain AM. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: characteristics and prognostic implications. *Heart Rhythm* 2016;**13**:1418–1424.
128. Steg PG, Alam S, Chiang CE, Gamra H, Goethals M, Inoue H, Krapf L, Lewalter T, Merioua I, Murin J, Naditch-Brule L, Ponikowski P, Rosenqvist M, Silva-Cardoso J, Zharinov O, Brette S, Neill JO; RealiseAF investigators. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. *Heart* 2012;**98**:195–201.
129. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED, Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2014;**167**:735–742.e2.
130. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–364.
131. Streur M, Ratcliffe SJ, Ball J, Stewart S, Riegel B. Symptom clusters in adults with chronic atrial fibrillation. *J Cardiovasc Nurs* 2017;**32**:296–303.
132. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;**132**:1259–1264.
133. Ugowe FE, Jackson LRn. Atrial fibrillation and mortality risk: seeing the big picture. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:6–7.
134. Vermond RA, Crijns HJ, Tijssen JG, Alings AM, Van den Berg MP, Hillege HL, Van Veldhuisen DJ, Van Gelder IC, Rienstra M; RACE II investigators. Symptom severity is associated with cardiovascular outcome in patients with permanent atrial fibrillation in the RACE II study. *Europace* 2014;**16**:1417–1425.
135. Walters TE, Wick K, Tan G, Mearns M, Joseph SA, Morton JB, Sanders P, Bryant C, Kistler PM, Kalman JM. Psychological distress and suicidal ideation in patients with atrial fibrillation: prevalence and response to management strategy. *J Am Heart Assoc* 2018;**7**:e005502.
136. Walters TE, Wick K, Tan G, Mearns M, Joseph SA, Morton JB, Sanders P, Bryant C, Kistler PM, Kalman JM. Symptom severity and quality of life in patients with atrial fibrillation: psychological function outweighs clinical predictors. *Int J Cardiol* 2019;**279**:84–89.
137. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049–1056.

138. Wijesurendra RS, Casadei B. Atrial fibrillation: effects beyond the atrium?*Cardiovasc Res* 2015;**105**:238–247.
139. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: a systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol* 2015;**191**:172–177.
140. Ziff OJ, Carter PR, McGowan J, Uppal H, Chandran S, Russell S, Bainey KR, Potluri R. The interplay between atrial fibrillation and heart failure on long-term mortality and length of stay: insights from the United Kingdom ACALM registry. *Int J Cardiol* 2018;**252**:117–121.
141. Sepehri Shamloo A, Dagres N, Mussigbrodt A, Stauber A, Kircher S, Richter S, Dinov B, Bertagnolli L, Husser-Bollmann D, Bollmann A, Hindricks G, Arya A. Atrial fibrillation and cognitive impairment: new insights and future directions. *Heart Lung Circ* 2020;**29**:69–85.
142. Conen D, Rodondi N, Muller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, Novak J, Schlapfer J, Di Valentino M, Aeschbacher S, Blum S, Meyre P, Sticherling C, Bonati LH, Ehret G, Moutzouri E, Fischer U, Monsch AU, Stippich C, Wuerfel J, Sinnecker T, Coslovsky M, Schwenkglenks M, Kuhne M, Osswald S, Swiss AFSI. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol* 2019;**73**:989–999.
143. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
144. Boriani G, Diemberger I, Ziacchi M, Valzania C, Gardini B, Cimaglia P, Martignani C, Biffi M. AF burden is important – fact or fiction?*Int J Clin Pract* 2014;**68**:444–452.
145. Boriani G, Pettorelli D. Atrial fibrillation burden and atrial fibrillation type: clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation. *Vascul Pharmacol* 2016;**83**:26–35.
146. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. *J Am Coll Cardiol* 2014;**63**:2840–2848.
147. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: does it exist?*J Am Coll Cardiol* 2014;**63**:1715–1723.
148. Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB, Marin F, Morais J, Narasimhan C, Olshansky B, Pierard L, Potpara T, Sarrafzadegan N, Sliwa K, Varela G, Vilahur G, Weiss T, Boriani G, Rocca B, ESC Scientific Document Group. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;**19**:1757–1758.
149. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation. *Circulation* 2019;;**140**:e125–e151.
150. NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani H, Hendriks J, Hespe C, Hung J, Kalman JM, Sanders P, Worthington J, Yan TD, Zwar N. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the diagnosis and management of atrial fibrillation 2018. *Heart Lung Circ* 2018;**27**:1209–1266.
151. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, Boriani G, Van Gelder IC, Heidbuchel H, Hindricks G, Camm AJ. The 4S-AF scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): A novel approach to in-depth characterization (rather than Classification) of atrial fibrillation. *Thromb Haemost* 2020; doi: 10.1055/s-0040-1716408.
152. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, Noseworthy PA, Perez MV, Turakhia MP,American Heart Association Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, and Stroke Council. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation* 2018;**137**:e623–e644.
153. Ziegler PD, Koehler JL, Mehra R. Comparison of continuous versus intermittent monitoring of atrial arrhythmias. *Heart Rhythm* 2006;**3**:1445–1452.
154. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan GA, Kalarus Z, Diemberger I, Tavazzi L, Maggioni AP, Lip GYH; EORP-AF Long-Term General Registry Investigators Steering Committee (National Coordinators). Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) long-term general registry. *Europace* 2018;**20**:747–757.
155. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC; ORBIT-AF Investigators and Patients. Predictors and prognostic implications of incident heart failure in patients with prevalent atrial fibrillation. *JACC Heart Fail* 2017;**5**:44–52.
156. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**:1591–1602.
157. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;**34**:2464–2471.
158. Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri MF, Antman EM, Braunwald E; ENGAGE AF-TIMI 48 Investigators. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 Trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). *Circ Arrhythm Electrophysiol* 2017;**10**:e004267.
159. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP; ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. *Eur Heart J* 2015;**36**:288–296.
160. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183–187.
161. Takabayashi K, Hamatani Y, Yamashita Y, Takagi D, Unoki T, Ishii M, Iguchi M, Masunaga N, Ogawa H, Esato M, Chun YH, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GY, Akao M. Incidence of stroke or systemic embolism in paroxysmal versus sustained atrial fibrillation: the Fushimi Atrial Fibrillation Registry. *Stroke* 2015;**46**:3354–3361.
162. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ; Euro Heart Survey Investigators. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?*Eur Heart J* 2008;**29**:915–922.
163. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, Harrison TN, Liu TI, Solomon MD. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: the KP-RHYTHM Study. *JAMA Cardiol* 2018;**3**:601–608.
164. Ecker V, Knoery C, Rushworth G, Rudd I, Ortner A, Begley D, Leslie SJ. A review of factors associated with maintenance of sinus rhythm after elective electrical cardioversion for atrial fibrillation. *Clin Cardiol* 2018;**41**:862–870.
165. Nyong J, Amit G, Adler AJ, Owolabi OO, Perel P, Prieto-Merino D, Lambiase P, Casas JP, Morillo CA. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. *Cochrane Database Syst Rev* 2016;**11**:CD012088.
166. Piccini JP, Passman R, Turakhia M, Connolly AT, Nabutovsky Y, Varma N. Atrial fibrillation burden, progression, and the risk of death: a case-crossover analysis in patients with cardiac implantable electronic devices. *Europace* 2019;**21**:404–413.
167. Deng H, Bai Y, Shantsila A, Fauchier L, Potpara TS, Lip GYH. Clinical scores for outcomes of rhythm control or arrhythmia progression in patients with atrial fibrillation: a systematic review. *Clin Res Cardiol* 2017;**106**:813–823.
168. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
169. Potpara TS, Stankovic GR, Beleslin BD, Polovina MM, Marinkovic JM, Ostojic MC, Lip GYH. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation Study. *Chest* 2012;**141**:339–347.
170. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–1490.

171. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, Conroy JM, Al-Khatib SM, Hess PL, Kirchhof P, De Bono J, Lip GY, Banerjee A, Ruskin J, Blendea D, Camm AJ. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J* 2014;**35**:1448–1456.
172. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin LA, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP, SCREEN CollaboratorsAF-. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation* 2017;**135**:1851–1867.
173. Mairesse GH, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, Banerjee A, Gorenek B, Brachmann J, Varma N, Glotz de Lima G, Kalman J, Claes N, Lobban T, Lane D, Lip GYH, Boriani G, ESC Scientific Document Group. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE). *Europace* 2017;**19**:1589–1623.
174. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, Dorian P, Green MS, Humphries KH, Klein GJ, Sheldon R, Talajic M, Kerr CR. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Heart Rhythm* 2017;**14**:801–807.
175. Vidal-Perez R, Otero-Ravina F, Lado-Lopez M, Turrado-Turrado V, Rodriguez-Moldes E, Gomez-Vazquez JL, de Frutos-de Marcos C, de Blas-Abad P, Besada-Gesto R, Gonzalez-Juanatey JR; BARBANZA Investigators. The change in the atrial fibrillation type as a prognosis marker in a community study: long-term data from AFBAR (Atrial Fibrillation in the BARbanza) study. *Int J Cardiol* 2013;**168**:2146–2152.
176. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;**55**:725–731.
177. Hobbelt AH, Spronk HM, Crijns H, Ten Cate H, Rienstra M, Van Gelder IC. Prethrombotic state in young very low-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2017;**69**:1990–1992.
178. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M, Almeida AL, Choi EY, Wu C, Alonso A, Heckbert SR, Bluemke DA, Lima JA. Cardiac magnetic resonance-measured left atrial volume and function and incident atrial fibrillation: results from MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 2016;**9**:e004299.
179. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW, Healey JS; ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–2099.
180. Guichard JB, Nattel S. Atrial Cardiomyopathy: A useful notion in cardiac disease management or a passing fad?*J Am Coll Cardiol* 2017;**70**:756–765.
181. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol* 2015;**65**:2239–2251.
182. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;**388**:806–817.
183. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost* 2014;**112**:276–286.
184. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. *Bol Oficina Sanit Panam* 1968;**65**:281–393.
185. Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, Okoli G, Sterne JA, Feder G, Eaton D, Hingorani A, Fawsitt C, Lobban T, Bryden P, Richards A, Sofat R. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2017;**21**:1–236.
186. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, Carter C, Baca-Motes K, Felicione E, Sarich T, Topol EJ. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA* 2018;**320**:146–155.
187. Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, Brandes A, Bustamante A, Casadei B, Crijns H, Doehner W, Engstrom G, Fauchier L, Friberg L, Gladstone DJ, Glotzer TV, Goto S, Hankey GJ, Harbison JA, Hobbs FDR, Johnson LSB, Kamel H, Kirchhof P, Korompoki E, Krieger DW, Lip GYH, Lochen ML, Mairesse GH, Montaner J, Neubeck L, Ntaios G, Piccini JP, Potpara TS, Quinn TJ, Reiffel JA, Ribeiro ALP, Rienstra M, Rosenqvist M, Sakis T, Sinner MF, Svendsen JH, Van Gelder IC, Wachter R, Wijeratne T, Yan B. Searching for atrial fibrillation poststroke: a white paper of the AF-SCREEN International Collaboration. *Circulation* 2019;**140**:1834–1850.
188. Yan BP, Lai WHS, Chan CKY, Chan SC, Chan LH, Lam KM, Lau HW, Ng CM, Tai LY, Yip KW, To OTL, Freedman B, Poh YC, Poh MZ. Contact-free screening of atrial fibrillation by a smartphone using facial pulsatile photoplethysmographic signals. *J Am Heart Assoc* 2018;**7**.
189. Orchard J, Lowres N, Freedman SB, Ladak L, Lee W, Zwar N, Peiris D, Kamaladasa Y, Li J, Neubeck L. Screening for atrial fibrillation during influenza vaccinations by primary care nurses using a smartphone electrocardiograph (iECG): a feasibility study. *Eur J Prev Cardiol* 2016;**23**:13–20.
190. Lampert R. Screening for atrial fibrillation using smartphone-based technology and layperson volunteers: high-tech meets community participatory research for the best of both worlds. *Heart Rhythm* 2018;**15**:1312–1313.
191. Lahdenoja O, Hurnanen T, Iftikhar Z, Nieminen S, Knuutila T, Saraste A, Kiviniemi T, Vasankari T, Airaksinen J, Pankaala M, Koivisto T. Atrial fibrillation detection via accelerometer and gyroscope of a smartphone. *IEEE J Biomed Health Inform* 2018;**22**:108–118.
192. Freedman B. Screening for atrial fibrillation using a smartphone: is there an app for that?*J Am Heart Assoc* 2016;**5**.
193. Chan NY, Choy CC. Screening for atrial fibrillation in 13 122 Hong Kong citizens with smartphone electrocardiogram. *Heart* 2017;**103**:24–31.
194. Chan PH, Wong CK, Poh YC, Pun L, Leung WW, Wong YF, Wong MM, Poh MZ, Chu DW, Siu CW. Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. *J Am Heart Assoc* 2016;**5**.
195. Brasier N, Raichle CJ, Dorr M, Becke A, Nohturfft V, Weber S, Bulacher F, Salomon L, Noah T, Birkemeyer R, Eckstein J. Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO). *Europace* 2019;**21**:41–47.
196. Tison GH, Sanchez JM, Ballinger B, Singh A, Olgin JE, Pletcher MJ, Vittinghoff E, Lee ES, Fan SM, Gladstone RA, Mikell C, Sohoni N, Hsieh J, Marcus GM. Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol* 2018;**3**:409–416.
197. Li KHC, White FA, Tipoe T, Liu T, Wong MC, Jesuthasan A, Baranchuk A, Tse G, Yan BP. The current state of mobile phone apps for monitoring heart rate, heart rate variability, and atrial fibrillation: narrative review. *JMIR Mhealth Uhealth* 2019;**7**:e11606.
198. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K, Lindsay BD, Wazni OM, Tarakji KG. Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:2381–2388.
199. Wasserlauf J, You C, Patel R, Valys A, Albert D, Passman R. Smartwatch performance for the detection and quantification of atrial fibrillation. *Circ Arrhythm Electrophysiol* 2019;**12**:e006834.
200. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, Kapa S, Friedman PA. Anartificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–867.
201. Turakhia MP, Desai M, Hedlin H, Rajmane A, Talati N, Ferris T, Desai S, Nag D, Patel M, Kowey P, Rumsfeld JS, Russo AM, Hills MT, Granger CB, Mahaffey KW, Perez MV. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the Apple Heart Study. *Am Heart J* 2019;**207**:66–75.
202. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y, Yan L, Xing Y, Shi H, Li S, Liu Y, Liu F, Feng M, Chen Y, Lip GYH; MAFA II Investigators. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:2365–2375.
203. Harris K, Edwards D, Mant J. How can we best detect atrial fibrillation?*J R Coll Physicians Edinb* 2012;**42 Suppl 18**:5–22.
204. Wiesel J, Wiesel D, Suri R, Messineo FC. The use of a modified sphygmomanometer to detect atrial fibrillation in outpatients. *Pacing Clin Electrophysiol* 2004;**27**:639–643.
205. Wiesel J, Fitzig L, Herschman Y, Messineo FC. Detection of atrial fibrillation using a modified microlife blood pressure monitor. *Am J Hypertens* 2009;**22**:848–852.
206. Stergiou GS, Karpettas N, Protogerou A, Nasothimiou EG, Kyriakidis M. Diagnostic accuracy of a home blood pressure monitor to detect atrial fibrillation. *J Hum Hypertens* 2009;**23**:654–658.
207. Willits I, Keltie K, Craig J, Sims A. WatchBP Home A for opportunistically detecting atrial fibrillation during diagnosis and monitoring of hypertension: a*NICE Medical Technology Guidance. Appl Health Econ Health Policy* 2014;**12**:255–265.
208. Desteghe L, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Performance of

handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. *Europace* 2017;**19**:29–39.
209. Kaasenbrood F, Hollander M, Rutten FH, Gerhards LJ, Hoes AW, Tieleman RG. Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination. *Europace* 2016;**18**:1514–1520.
210. Wiesel J, Abraham S, Messineo FC. Screening for asymptomatic atrial fibrillation while monitoring the blood pressure at home: trial of regular versus irregular pulse for prevention of stroke (TRIPPS 2.0). *Am J Cardiol* 2013;**111**:1598–1601.
211. Jacobs MS, Kaasenbrood F, Postma MJ, van Hulst M, Tieleman RG. Cost-effectiveness of screening for atrial fibrillation in primary care with a handheld, single-lead electrocardiogram device in the Netherlands. *Europace* 2018;**20**:12–18.
212. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167–1176.
213. William AD, Kanbour M, Callahan T, Bhargava M, Varma N, Rickard J, Saliba W, Wolski K, Hussein A, Lindsay BD, Wazni OM, Tarakji KG. Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: the iREAD Study. *Heart Rhythm* 2018;**15**:1561–1565.
214. Nemati S, Ghassemi MM, Ambai V, Isakadze N, Levantsevych O, Shah A, Clifford GD. Monitoring and detecting atrial fibrillation using wearable technology. *Conf Proc IEEE Eng Med Biol Soc* 2016;**2016**:3394–3397.
215. Petryszyn P, Niewinski P, Staniak A, Piotrowski P, Well A, Well M, Jeskowiak I, Lip G, Ponikowski P. Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis. *PLoS One* 2019;**14**:e0213198.
216. Orchard J, Lowres N, Neubeck L, Freedman B. Atrial fibrillation: is there enough evidence to recommend opportunistic or systematic screening?*Int J Epidemiol* 2018;**47**:1361.
217. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP Study. *Circulation* 2015;**131**:2176–2184.
218. Halcox JPJ, Wareham K, Cardew A, Gilmore M, Barry JP, Phillips C, Gravenor MB. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF Study. *Circulation* 2017;**136**:1784–1794.
219. Turakhia MP, Shafrin J, Bognar K, Goldman DP, Mendys PM, Abdulsattar Y, Wiederkehr D, Trocio J. Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. *Am J Cardiol* 2015;**116**:733–739.
220. Fay MR, Fitzmaurice DA, Freedman B. Screening of older patients for atrial fibrillation in general practice: current evidence and its implications for future practice. *Eur J Gen Pract* 2017;**23**:246–253.
221. Boriani G, Valzania C, Biffi M, Diemberger I, Ziacchi M, Martignani C. Asymptomatic lone atrial fibrillation – how can we detect the arrhythmia?*Curr Pharm Des* 2015;**21**:659–666.
222. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M, Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;**9**:iii-iv, ix-x, 1–74.
223. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, Frykman-Kull V, Levin LA. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace* 2015;**17**:1023–1029.
224. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost* 2013;**110**:213–222.
225. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation* 2013;**127**:930–937.
226. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M, Gasparini M, Lewalter T, Camm JA, Singer DE. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J* 2014;**35**:508–516.
227. Lowres N, Krass I, Neubeck L, Redfern J, McLachlan AJ, Bennett AA, Freedman SB. Atrial fibrillation screening in pharmacies using an iPhone ECG: a qualitative review of implementation. *Int J Clin Pharm* 2015;**37**:1111–1120.
228. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P, Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;**16**:965–972.
229. De With RR, Rienstra M, Smit MD, Weijs B, Zwartkruis VW, Hobbelt AH, Alings M, Tijssen JGP, Brugemann J, Geelhoed B, Hillege HL, Tukkie R, Hemels ME, Tieleman RG, Ranchor AV, Van Veldhuisen DJ, Crijns H, Van Gelder IC. Targeted therapy of underlying conditions improves quality of life in patients with persistent atrial fibrillation: results of the RACE 3 study. *Europace* 2019;**21**:563–571.
230. Schnabel RB, Pecen L, Rzayeva N, Lucerna M, Purmah Y, Ojeda FM, De Caterina R, Kirchhof P. Symptom burden of atrial fibrillation and its relation to interventions and outcome in Europe. *J Am Heart Assoc* 2018;**7**.
231. Björkenheim A, Brandes A, Magnuson A, Chemnitz A, Svedberg L, Edvardsson N, Poçi D. Assessment of atrial fibrillation – specific symptoms before and 2 years after atrial fibrillation ablation: do patients and physicians differ in their perception of symptom relief?*JACC: Clinical Electrophysiology* 2017;**3**:1168–1176.
232. Sandhu RK, Smigorowsky M, Lockwood E, Savu A, Kaul P, McAlister FA. Impact of electrical cardioversion on quality of life for the treatment of atrial fibrillation. *Can J Cardiol* 2017;**33**:450–455.
233. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD; Sotalol Amiodarone Atrial Fibrillation Efficacy Trial Investigators. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;**352**:1861–1872.
234. Gilbert KA, Hogarth AJ, MacDonald W, Lewis NT, Tan LB, Tayebjee MH. Restoration of sinus rhythm results in early and late improvements in the functional reserve of the heart following direct current cardioversion of persistent AF: FRESH-AF. *Int J Cardiol* 2015;**199**:121–125.
235. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, Hocini M, Extramiana F, Sacher F, Bordachar P, Klein G, Weerasooriya R, Clementy J, Haissaguerre M. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**:2498–2505.
236. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F, Jr., Bates ER, Lehmann MH, Vicedomini G, Augello G, Agricola E, Sala S, Santinelli V, Morady F. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934–941.
237. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI, Brugada J; SARA investigators. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**:501–507.
238. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, De Sanctis V, Pappalardo A, Laurenzi F, Avella A, Casella M, Dello Russo A, Romeo F, Pelargonio G, Tondo C. Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *J Cardiovasc Electrophysiol* 2009;**20**:22–28.
239. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; ThermoCool AF Trial Investigators. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**:333–340.
240. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634–2640.
241. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A; RAAFT Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700.
242. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**:1587–1595.
243. Pokorney SD, Kim S, Thomas L, Fonarow GC, Kowey PR, Gersh BJ, Mahaffey KW, Peterson ED, Piccini JP; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Investigators. Cardioversion and subsequent quality of life and natural history of atrial fibrillation. *Am Heart J* 2017;**185**:59–66.
244. Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Khaykin Y, Guerra PG, Nair G, Torrecilla EG, Verma A. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol* 2013;**29**:1211–1217.
245. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, Van Veldhuisen DJ, Crijns H, Van Gelder IC; RACE Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–2996.

246. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G, Rubulis A, Malmborg H, Raatikainen P, Lonnerholm S, Hoglund N, Mortsell D. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA* 2019;**321**:1059–1068.
247. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019.
248. Gaita F, Scaglione M, Battaglia A, Matta M, Gallo C, Galata M, Caponi D, Di Donna P, Anselmino M. Very long-term outcome following transcatheter ablation of atrial fibrillation. Are results maintained after 10 years of follow-up?*Europace* 2018;**20**:443–450.
249. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, Lederlin M, Mondillo S, Edvardsen T, Sitges M, Grapsa J, Garbi M, Senior R, Gimelli A, Potpara TS, Van Gelder IC, Gorenek B, Mabo P, Lancellotti P, Kuck KH, Popescu BA, Hindricks G, Habib G, Cardim NM, Cosyns B, Delgado V, Haugaa KH, Muraru D, Nieman K, Boriani G, Cohen A. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:355–383.
250. Delgado V, Di Biase L, Leung M, Romero J, Tops LF, Casadei B, Marrouche N, Bax JJ. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. *J Am Coll Cardiol* 2017;**70**:3157–3172.
251. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, Blauer JJ, Rao SN, DiBella EV, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. *Circulation* 2009;**119**:1758–1767.
252. Cameli M, Lisi M, Righini FM, Massoni A, Natali BM, Focardi M, Tacchini D, Geyer A, Curci V, Di Tommaso C, Lisi G, Maccherini M, Chiavarelli M, Massetti M, Tanganelli P, Mondillo S. Usefulness of atrial deformation analysis to predict left atrial fibrosis and endocardial thickness in patients undergoing mitral valve operations for severe mitral regurgitation secondary to mitral valve prolapse. *Am J Cardiol* 2013;**111**:595–601.
253. Nakamori S, Nezafat M, Ngo LH, Manning WJ, Nezafat R. Left atrial epicardial fat volume is associated with atrial fibrillation: a prospective cardiovascular magnetic resonance 3D Dixon Study. *J Am Heart Assoc* 2018;**7**.
254. Murphy A, Banerjee A, Breithardt G, Camm AJ, Commerford P, Freedman B, Gonzalez-Hermosillo JA, Halperin JL, Lau CP, Perel P, Xavier D, Wood D, Jouven X, Morillo CA. The World Heart Federation roadmap for nonvalvular atrial fibrillation. *Glob Heart* 2017;**12**:273–284.
255. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *Eur Heart J* 2020;**41**:12–85.
256. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment?*BMJ* 1999;**319**:780–782.
257. Lane DA, Aguinaga L, Blomstrom-Lundqvist C, Boriani G, Dan GA, Hills MT, Hylek EM, LaHaye SA, Lip GY, Lobban T, Mandrola J, McCabe PJ, Pedersen SS, Pisters R, Stewart S, Wood K, Potpara TS, Gorenek B, Conti JB, Keegan R, Power S, Hendriks J, Ritter P, Calkins H, Violi F, Hurwitz J. Cardiac tachyarrhythmias and patient values and preferences for their management: the European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2015;**17**:1747–1769.
258. Bergtun S, Oterhals K, Fridlund B. Patients' experiences 1-6 months after atrial fibrillation ablation: an holistic perspective. *J Adv Nurs* 2019;**75**:150–160.
259. Borg Xuereb C, Shaw RL, Lane DA. Patients' and physicians' experiences of atrial fibrillation consultations and anticoagulation decision-making: a multi-perspective IPA design. *Psychol Health* 2016;**31**:436–455.
260. Loewen PS, Ji AT, Kapanen A, McClean A. Patient values and preferences for antithrombotic therapy in atrial fibrillation. A narrative systematic review. *Thromb Haemost* 2017;**117**:1007–1022.
261. Seaburg L, Hess EP, Coylewright M, Ting HH, McLeod CJ, Montori VM. Shared decision making in atrial fibrillation: where we are and where we should be going. *Circulation* 2014;**129**:704–710.
262. Bajorek BV, Ogle SJ, Duguid MJ, Shenfield GM, Krass I. Management of warfarin in atrial fibrillation: views of health professionals, older patients and their carers. *Med J Aust* 2007;**186**:175–180.
263. Hess EP, Knoedler MA, Shah ND, Kline JA, Breslin M, Branda ME, Pencille LJ, Asplin BR, Nestler DM, Sadosty AT, Stiell IG, Ting HH, Montori VM. The chest pain choice decision aid: a randomized trial. *Circ Cardiovasc Qual Outcomes* 2012;**5**:251–259.
264. Lane DA, Meyerhoff J, Rohner U, Lip GYH. Atrial fibrillation patient preferences for oral anticoagulation and stroke knowledge: results of a conjoint analysis. *Clin Cardiol* 2018;**41**:855–861.
265. Lindberg T, Sanmartin Berglund J, Elmstahl S, Bohman DM. Older individuals' need for knowledge and follow-up about their chronic atrial fibrillation, lifelong medical treatment and medical controls. *Scand J Caring Sci* 2017;**31**:1022–1030.
266. Palacio AM, Kirolos I, Tamariz L. Patient values and preferences when choosing anticoagulants. *Patient Prefer Adherence* 2015;**9**:133–138.
267. Lane DA, Lip GY. Patient's values and preferences for stroke prevention in atrial fibrillation: balancing stroke and bleeding risk with oral anticoagulation. *Thromb Haemost* 2014;**111**:381–383.
268. MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, McLeod S, Bhatnagar N, Guyatt GH. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e1S–e23S.
269. Desteghe L, Engelhard L, Raymaekers Z, Kluts K, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Knowledge gaps in patients with atrial fibrillation revealed by a new validated knowledge questionnaire. *Int J Cardiol* 2016;**223**:906–914.
270. Frankel DS, Parker SE, Rosenfeld LE, Gorelick PB. HRS/NSA 2014 Survey of atrial fibrillation and stroke: gaps in knowledge and perspective, opportunities for improvement. *J Stroke Cerebrovasc Dis* 2015;**24**:1691–700.
271. Lane DA, Ponsford J, Shelley A, Sirpal A, Lip GY. Patient knowledge and perceptions of atrial fibrillation and anticoagulant therapy: effects of an educational intervention programme. The West Birmingham Atrial Fibrillation Project. *Int J Cardiol* 2006;**110**:354–358.
272. McCabe PJ, Schad S, Hampton A, Holland DE. Knowledge and self-management behaviors of patients with recently detected atrial fibrillation. *Heart Lung* 2008;**37**:79–90.
273. Ihara M, Washida K. Linking atrial fibrillation with Alzheimer's disease: epidemiological, pathological, and mechanistic evidence. *J Alzheimers Dis* 2018;**62**:61–72.
274. Lip GYH, Lane DA, Sarwar S. Streamlining primary and secondary care management pathways for stroke prevention in atrial fibrillation. *Eur Heart J* 2017;**38**:2980–2982.
275. Guo Y, Lane DA, Wang L, Chen Y, Lip GYH; mAF-App II Trial investigators. Mobile Health (mHealth) technology for improved screening, patient involvement and optimising integrated care in atrial fibrillation: the mAFA (mAF-App) II randomised trial. *Int J Clin Pract* 2019:e13352.
276. Franchi C, Antoniazzi S, Ardoino I, Proietti M, Marcucci M, Santalucia P, Monzani V, Mannucci PM, Nobili A, Collaborators S-A. Simulation-based education for physicians to increase oral anticoagulants in hospitalized elderly patients with atrial fibrillation. *Am J Med* 2019;**132**:e634–e647.
277. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, He W, Xian Y, Ciobanu AO, Kamath DY, Fox KA, Rao MP, Pokorney SD, Berwanger O, Tajer C, de Barros ESPGM, Roettig ML, Huo Y, Granger CB; IMPACT-AF Investigators. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;**390**:1737–1746.
278. Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. *Thromb Haemost* 2017;**117**:209–218.
279. Parimbelli E, Sacchi L, Budasu R, Napolitano C, Peleg M, Quaglini S. The role of nurses in e-health: the MobiGuide project experience. *Stud Health Technol Inform* 2016;**225**:153–157.
280. Guo Y, Chen Y, Lane DA, Liu L, Wang Y, Lip GYH. Mobile health technology for atrial fibrillation management integrating decision support, education, and patient involvement: mAF App trial. *Am J Med* 2017;**130**:1388–1396.e6.
281. Kotecha D, Chua WWL, Fabritz L, Hendriks J, Casadei B, Schotten U, Vardas P, Heidbuchel H, Dean V, Kirchhof P, European Society of Cardiology (ESC) Atrial Fibrillation Guidelines Taskforce, the CATCH ME consortium, and the European Heart Rhythm Association (EHRA). European Society of Cardiology smartphone and tablet applications for patients with atrial fibrillation and their health care providers. *Europace* 2018;**20**:225–233.
282. Lee J-A, Evangelista LS, Moore AA, Juth V, Guo Y, Gago-Masague S, Lem CG, Nguyen M, Khatibi P, Baje M, Amin AN. Feasibility study of a mobile health intervention for older adults on oral anticoagulation therapy. *Gerontol Geriatr Med* 2016;**2**. doi:10.1177/2333721416672970. Published 2016 Oct 7.
283. Stephan LS, Dytz Almeida E, Guimaraes RB, Ley AG, Mathias RG, Assis MV, Leiria TL. Processes and recommendations for creating mHealth apps for low-income populations. *JMIR Mhealth Uhealth* 2017;**5**:e41.
284. Clarkesmith DE, Pattison HM, Khaing PH, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. *Cochrane Database Syst Rev* 2017;**4**:CD008600.

285. Man-Son-Hing M, Laupacis A, O'Connor AM, Biggs J, Drake E, Yetisir E, Hart RG. A patient decision aid regarding antithrombotic therapy for stroke prevention in atrial fibrillation: a randomized controlled trial. *JAMA* 1999;**282**:737–743.
286. McAlister FA, Man-Son-Hing M, Straus SE, Ghali WA, Anderson D, Majumdar SR, Gibson P, Cox JL, Fradette M; Decision Aid in Atrial Fibrillation Investigators. Impact of a patient decision aid on care among patients with nonvalvular atrial fibrillation: a cluster randomized trial. *CMAJ* 2005;**173**:496–501.
287. Thomson RG, Eccles MP, Steen IN, Greenaway J, Stobbart L, Murtagh MJ, May CR. A patient decision aid to support shared decision-making on antithrombotic treatment of patients with atrial fibrillation: randomised controlled trial. *Qual Saf Health Care* 2007;**16**:216–223.
288. Eckman MH, Costea A, Attari M, Munjal J, Wise RE, Knochelmann C, Flaherty ML, Baker P, Ireton R, Harnett BM, Leonard AC, Steen D, Rose A, Kues J. Shared decision-making tool for thromboprophylaxis in atrial fibrillation – a feasibility study. *Am Heart J* 2018;**199**:13–21.
289. Eckman MH, Lip GY, Wise RE, Speer B, Sullivan M, Walker N, Kissela B, Flaherty ML, Kleindorfer D, Baker P, Ireton R, Hoskins D, Harnett BM, Aguilar C, Leonard AC, Arduser L, Steen D, Costea A, Kues J. Impact of an atrial fibrillation decision support tool on thromboprophylaxis for atrial fibrillation. *Am Heart J* 2016;**176**:17–27.
290. Karlsson LO, Nilsson S, Bang M, Nilsson L, Charitakis E, Janzon M. A clinical decision support tool for improving adherence to guidelines on anticoagulant therapy in patients with atrial fibrillation at risk of stroke: a cluster-randomized trial in a Swedish primary care setting (the CDS-AF study). *PLoS Med* 2018;**15**:e1002528.
291. Vinereanu D, Lopes RD, Mulder H, Gersh BJ, Hanna M, de Barros ESPGM, Atar D, Wallentin L, Granger CB, Alexander JH; ARISTOTLE Investigators. Echocardiographic risk factors for stroke and outcomes in patients with atrial fibrillation anticoagulated with apixaban or warfarin. *Stroke* 2017;**48**:3266–3273.
292. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y, Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* 2012;**33**:2692–2699.
293. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Chan YK, Esterman A, Thompson DR, Scuffham PA, Carrington MJ. Standard versus atrial fibrillation-specific management strategy (SAFETY) to reduce recurrent admission and prolong survival: pragmatic, multicentre, randomised controlled trial. *Lancet* 2015;**385**:775–784.
294. Carter L, Gardner M, Magee K, Fearon A, Morgulis I, Doucette S, Sapp JL, Gray C, Abdelwahab A, Parkash R. An integrated management approach to atrial fibrillation. *J Am Heart Assoc* 2016;**5**.
295. Wijtvliet E, Tieleman RG, van Gelder IC, Pluymaekers NAHA, Rienstra M, Folkeringa RJ, Bronzwaer P, Elvan A, Elders J, Tukkie R, Luermans JGLM, Van Asselt ADIT, Van Kuijk SMJ, Tijssen JG, Crijns HJGM; RACE Investigators. Nurse-led vs. usual-care for atrial fibrillation. *Eur Heart J* 2020;**41**:634–641.
296. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart* 2017;**103**:1947–1953.
297. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;**6**:42.
298. Lip GYH, Lane DA, Potpara TS. Innovative strategies to improve adherence to non-vitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation. *Eur Heart J* 2018;**39**:1404–1406.
299. Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, Arbelo E, Banerjee A, Bollmann A, Caffrey-Armstrong B, Cehic DA, Corbalan R, Collins M, Dandamudi G, Dorairaj P, Fay M, Van Gelder IC, Goto S, Granger CB, Gyorgy B, Healey JS, Hendriks JM, Hills MT, Hobbs FDR, Huisman MV, Koplan KE, Lane DA, Lewis WR, Lobban T, Steinberg BA, McLeod CJ, Moseley S, Timmis A, Yutao G, Camm AJ. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *Eur Heart J* 2020;**41**:1132–1140.
300. Dobler CC, Harb N, Maguire CA, Armour CL, Coleman C, Murad MH. Treatment burden should be included in clinical practice guidelines. *BMJ* 2018;**363**:k4065.
301. Eton DT, Ramalho de Oliveira D, Egginton JS, Ridgeway JL, Odell L, May CR, Montori VM. Building a measurement framework of burden of treatment in complex patients with chronic conditions: a qualitative study. *Patient Relat Outcome Meas* 2012;**3**:39–49.
302. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med* 2012;**10**:68.
303. Vijan S, Hayward RA, Ronis DL, Hofer TP. Brief report: the burden of diabetes therapy: implications for the design of effective patient-centered treatment regimens. *J Gen Intern Med* 2005;**20**:479–482.
304. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001;**26**:331–342.
305. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, Magid DJ. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;**166**:1836–1841.
306. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;**297**:177–186.
307. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ* 2009;**339**:b2803.
308. Wilcox AR, Dragnev MC, Darcey CJ, Siegel CA. A new tool to measure the burden of Crohn's disease and its treatment: do patient and physician perceptions match?*Inflamm Bowel Dis* 2010;**16**:645–650.
309. Bohlen K, Scoville E, Shippee ND, May CR, Montori VM. Overwhelmed patients: a videographic analysis of how patients with type 2 diabetes and clinicians articulate and address treatment burden during clinical encounters. *Diabetes Care* 2012;**35**:47–49.
310. Buffel du Vaure C, Ravaud P, Baron G, Barnes C, Gilberg S, Boutron I. Potential workload in applying clinical practice guidelines for patients with chronic conditions and multimorbidity: a systematic analysis. *BMJ Open* 2016;**6**:e010119.
311. Potpara TS, Mihajlovic M, Zec N, Marinkovic M, Kovacevic V, Simic J, Kocijancic A, Vajagic L, Jotic A, Mujovic N, Stankovic G. Self-reported treatment burden in patients with atrial fibrillation: quantification, major determinants and implications for integrated holistic management of the arrhythmia. *Europace* 2020; doi:10.1093/europace/euaa210.
312. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med* 2014;**12**:109.
313. Steinberg BA, Dorian P, Anstrom KJ, Hess R, Mark DB, Noseworthy PA, Spertus JA, Piccini JP. Patient-reported outcomes in atrial fibrillation research: results of a Clinicaltrials.gov analysis. *JACC Clin Electrophysiol* 2019;**5**:599–605.
314. Calvert M, Kyte D, Price G, Valderas JM, Hjollund NH. Maximising the impact of patient reported outcome assessment for patients and society. *BMJ* 2019;**364**:k5267.
315. Rotenstein LS, Huckman RS, Wagle NW. Making patients and doctors happier – the potential of patient-reported outcomes. *N Engl J Med* 2017;**377**:1309–1312.
316. Van Der Wees PJ, Nijhuis-Van Der Sanden MW, Ayanian JZ, Black N, Westert GP, Schneider EC. Integrating the use of patient-reported outcomes for both clinical practice and performance measurement: views of experts from 3 countries. *Milbank Q* 2014;**92**:754–775.
317. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak H-N, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N. Quality indicators for the care and outcomes of adults with atrial fibrillation. Task Force for the development of quality indicators in Atrial Fibrillation of the European Heart Rhythm Association (EHRA) and of the European Society of Cardiology (ESC): Developed in collaboration with the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS) and the Latin-American Heart Rhythm Society (LAHRS). *Europace* 2020;doi:10.1093/europace/euaa253.
318. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–628.
319. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) Pathway. *Am J Med* 2018;**131**:1359–1366.e6.
320. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, Joung B, Lip GYH. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost* 2019;**19**:1695–1703.
321. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: the ABC (Atrial fibrillation Better Care) pathway in the ATHERO-AF study cohort. *Mayo Clin Proc* 2019;**94**:1261–1267
322. Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GY. ABC (Atrial fibrillation Better Care) pathway and healthcare costs in atrial fibrillation: the ATHERO-AF study. *Am J Med* 2019;**132**:856–861.

323. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, Wen J, Xing Y, Wu F, Xia Y, Liu T, Wu F, Liang Z, Liu F, Zhao Y, Li R, Li X, Zhang L, Guo J, Burnside G, Chen Y, Lip GYH; mAF-App II Trial Investigators. Mobile health technology to improve care for patients with atrial fibrillation. *J Am Coll Cardiol* 2020;**75**:1523–1534.
324. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;**76**:2289–2304.
325. Szymanski FM, Lip GY, Filipiak KJ, Platek AE, Hrynkiewicz-Szymanska A, Opolski G. Stroke risk factors beyond the CHA(2)DS(2)-VASc score: can we improve our identification of 'high stroke risk' patients with atrial fibrillation?*Am J Cardiol* 2015;**116**:1781–1788.
326. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med* 1998;**158**:1316–1320.
327. Ntaios G, Lip GY, Lambrou D, Papavasileiou V, Manios E, Milionis H, Spengos K, Makaritsis K, Vemmos K. Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation. *Neurology* 2015;**84**:1213–1219.
328. Esteve-Pastor MA, Roldan V, Rivera-Caravaca JM, Ramirez-Macias I, Lip GYH, Marin F. The use of biomarkers in clinical management guidelines: a critical appraisal. *Thromb Haemost* 2019;**119**:1901–1919.
329. Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of biomarkers for risk stratification in patients with atrial fibrillation. *Clin Chem* 2017;**63**:152–164.
330. Yaghi S, Kamel H. Stratifying stroke risk in atrial fibrillation: beyond clinical risk scores. *Stroke* 2017;**48**:2665–2670.
331. Ioannou A, Papageorgiou N, Falconer D, Rehal O, Sewart E, Zacharia E, Toutouzas K, Vlachopoulos C, Siasos G, Tsioufis C, Tousoulis D. Biomarkers associated with stroke risk in atrial fibrillation. *Curr Med Chem* 2019;**26**:803–823.
332. Sepehri Shamloo A, Bollmann A, Dagres N, Hindricks G, Arya A. Natriuretic peptides: biomarkers for atrial fibrillation management. *Clin Res Cardiol* 2020;**109**:957–966.
333. Decker JJ, Norby FL, Rooney MR, Soliman EZ, Lutsey PL, Pankow JS, Alonso A, Chen LY. Metabolic syndrome and risk of ischemic stroke in atrial fibrillation: ARIC Study. *Stroke* 2019;**50**:3045–3050.
334. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;**137**:263–272.
335. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;**14**:295–301.
336. Jung H, Sung JH, Yang PS, Jang E, Yu HT, Kim TH, Pak HN, Lee MH, Joung B, Lip GYH. Stroke risk stratification for atrial fibrillation patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2018;**72**:2409–2411.
337. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. *Chest* 2019;**155**:354–363.
338. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, Yu HT, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Ideal blood pressure in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**72**:1233–1245.
339. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged >/=75 years with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Stroke* 2015;**46**:143–50.
340. Overvad TF, Skjoth F, Lip GY, Lane DA, Albertsen IE, Rasmussen LH, Larsen TB. Duration of diabetes mellitus and risk of thromboembolism and bleeding in atrial fibrillation: nationwide cohort study. *Stroke* 2015;**46**:2168–74.
341. Lip GYH, Clementy N, Pierre B, Boyer M, Fauchier L. The impact of associated diabetic retinopathy on stroke and severe bleeding risk in diabetic patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2015;**147**:1103–1110.
342. Fangel MV, Nielsen PB, Larsen TB, Christensen B, Overvad TF, Lip GYH, Goldhaber SZ, Jensen MB. Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: a Danish nationwide cohort study. *Int J Cardiol* 2018;**268**:137–142.
343. Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Chen TJ, Lip GY, Chen SA. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation* 2016;**133**:1540–1547.
344. Bronnum Nielsen P, Larsen TB, Gorst-Rasmussen A, Skjoth F, Rasmussen LH, Lip GYH. Intracranial hemorrhage and subsequent ischemic stroke in patients with atrial fibrillation: a nationwide cohort study. *Chest* 2015;**147**:1651–1658.
345. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study. *Circulation* 2015;**132**:517–525.
346. Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, Chen PC, Lin JL. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation – a nation-wide database analysis. *Atherosclerosis* 2011;**217**:292–295.
347. Anandasundaram B, Lane DA, Apostolakis S, Lip GY. The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. *J Thromb Haemost* 2013;**11**:975–987.
348. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;**33**:1500–1510.
349. Steensig K, Olesen KKW, Thim T, Nielsen JC, Jensen SE, Jensen LO, Kristensen SD, Botker HE, Lip GYH, Maeng M. Should the presence or extent of coronary artery disease be quantified in the CHA2DS2-VASc score in atrial fibrillation? A report from the Western Denmark Heart Registry. *Thromb Haemost* 2018;**118**:2162–2170.
350. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol* 1998;**31**:1622–1626.
351. Kim TH, Yang PS, Yu HT, Jang E, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. Age threshold for ischemic stroke risk in atrial fibrillation. *Stroke* 2018;**49**:1872–1879.
352. Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chung FP, Liao JN, Chen TJ, Chiang CE, Lip GY, Chen SA. Age threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. *J Am Coll Cardiol* 2015;**66**:1339–1347.
353. Nielsen PB, Skjoth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc?*Circulation* 2018;**137**:832–840.
354. Killu AM, Granger CB, Gersh BJ. Risk stratification for stroke in atrial fibrillation: a critique. *Eur Heart J* 2019;**40**:1294–1302.
355. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH, Marin F. Long-term stroke risk prediction in patients with atrial fibrillation: comparison of the ABC-Stroke and CHA2DS2-VASc scores. *J Am Heart Assoc* 2017;**6**: pii: JAHA.117.006490. doi: 10.1161/JAHA.117.006490.
356. Alkhouli M, Friedman PA. Ischemic stroke risk in patients with nonvalvular atrial fibrillation: JACC review topic of the week. *J Am Coll Cardiol* 2019;**74**:3050–3065.
357. Wu VC, Wu M, Aboyans V, Chang SH, Chen SW, Chen MC, Wang CL, Hsieh IC, Chu PH, Lin YS. Female sex as a risk factor for ischaemic stroke varies with age in patients with atrial fibrillation. *Heart* 2020;**106**:534–540.
358. Tomasdottir M, Friberg L, Hijazi Z, Lindback J, Oldgren J. Risk of ischemic stroke and utility of CHA2 DS2 -VASc score in women and men with atrial fibrillation. *Clin Cardiol* 2019;**42**:1003–1009.
359. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ* 2012;**344**:e3522.
360. Overvad TF, Potpara TS, Nielsen PB. Stroke risk stratification: CHA2DS2-VA or CHA2DS2-VASc?*Heart Lung Circ* 2019;**28**:e14–e15.
361. Nielsen PB, Overvad TF. Female sex as a risk modifier for stroke risk in atrial fibrillation: using CHA2DS2-VASc versus CHA2DS2-VA for stroke risk stratification in atrial fibrillation: a note of caution. *Thromb Haemost* 2020. doi: 10.1055/s-0040-1710014. Epub ahead of print.
362. Marzona I, Proietti M, Farcomeni A, Romiti GF, Romanazzi I, Raparelli V, Basili S, Lip GYH, Nobili A, Roncaglioni MC. Sex differences in stroke and major adverse clinical events in patients with atrial fibrillation: a systematic review and meta-analysis of 993,600 patients. *Int J Cardiol* 2018;**269**:182–191.
363. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2015;**36**:297–306.
364. Poli M, Philip P, Taillard J, Debruxelles S, Renou P, Orgogozo JM, Rouanet F, Sibon I. Atrial fibrillation is a major cause of stroke in apneic patients: a prospective study. *Sleep Med* 2017;**30**:251–254.
365. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, Fox KAA, Gao H, Goldhaber SZ, Goto S, Haas S, Kayani G, Pieper K, Turpie AGG, van Eickels M, Verheugt FWA, Kakkar AK; GARFIELD-AF Investigators. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: rationale for comprehensive management of atrial fibrillation. *PLoS One* 2018;**13**:e0191592.
366. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. *Am J Med* 2013;**126**:640.e9-17.

367. Lip GY, Lane D, Van Walraven C, Hart RG. Additive role of plasma von Willebrand factor levels to clinical factors for risk stratification of patients with atrial fibrillation. *Stroke* 2006;**37**:2294–2300.
368. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Kayani G, Oto A, Mantovani LG, Misselwitz F, Piccini JP, Turpie AGG, Verheugt FWA, Kakkar AK; GARFIELD-AF Investigators. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open* 2017;**7**:e017157.
369. Zhu W, Fu L, Ding Y, Huang L, Xu Z, Hu J, Hong K. Meta-analysis of ATRIA versus CHA2DS2-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation. *Int J Cardiol* 2017;**227**:436–442.
370. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
371. Graves KG, May HT, Knowlton KU, Muhlestein JB, Jacobs V, Lappe DL, Anderson JL, Horne BD, Bunch TJ. Improving CHA2DS2-VASc stratification of non-fatal stroke and mortality risk using the Intermountain Mortality Risk Score among patients with atrial fibrillation. *Open Heart* 2018;**5**:e000907.
372. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L; ARISTOTLE and STABILITY Investigators. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90.
373. Hijazi Z, Lindahl B, Oldgren J, Andersson U, Lindback J, Granger CB, Alexander JH, Gersh BJ, Hanna M, Harjola VP, Hylek EM, Lopes RD, Siegbahn A, Wallentin L. Repeated measurements of cardiac biomarkers in atrial fibrillation and validation of the ABC stroke score over time. *J Am Heart Assoc* 2017;**6**.
374. Oldgren J, Hijazi Z, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Granger CB, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Wallentin L; RE-LY and ARISTOTLE Investigators. Performance and validation of a novel biomarker-based stroke risk score for atrial fibrillation. *Circulation* 2016;**134**:1697–1707.
375. Berg DD, Ruff CT, Jarolim P, Giugliano RP, Nordio F, Lanz HJ, Mercuri MF, Antman EM, Braunwald E, Morrow DA. Performance of the ABC scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in ENGAGE AF-TIMI 48. *Circulation* 2019;**139**:760–771.
376. Rivera-Caravaca JM, Marin F, Vilchez JA, Galvez J, Esteve-Pastor MA, Vicente V, Lip GYH, Roldan V. Refining stroke and bleeding prediction in atrial fibrillation by adding consecutive biomarkers to clinical risk scores. *Stroke* 2019;**50**:1372–1379.
377. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdes M, Marin F, Lip GY. Long-term bleeding risk prediction in 'real world'patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. *Thromb Haemost* 2017;**117**:1848–1858.
378. Shin SY, Han SJ, Kim JS, Im SI, Shim J, Ahn J, Lee EM, Park YM, Kim JH, Lip GYH, Lim HE. Identification of markers associated with development of stroke in 'clinically low-risk' atrial fibrillation patients. *J Am Heart Assoc* 2019;**8**:e012697.
379. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: insights into the optimal assessment of age and incident comorbidities. *Eur Heart J* 2019;**40**:1504–1514.
380. Nielsen PB, Larsen TB, Skjoth F, Overvad TF, Lip GY. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. *Sci Rep* 2016;**6**:27410.
381. Fauchier L, Clementy N, Bisson A, Ivanes F, Angoulvant D, Babuty D, Lip GY. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated?*Stroke* 2016;**47**:1831–1836.
382. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:122–132.
383. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH, Joung B. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a nationwide cohort study. *Thromb Haemost* 2018;**118**:1296–1304.
384. Chao TF, Chiang CE, Chen TJ, Lip GYH, Chen SA. Reassessment of risk for stroke during follow-up of patients with atrial fibrillation. *Ann Intern Med* 2019;**170**:663–664.
385. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of 'truly low' thromboembolic risk in patients initially diagnosed with 'lone' atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Circ Arrhythm Electrophysiol* 2012;**5**:319–326.
386. Weijs B, Dudink E, de Vos CB, Limantoro I, Tieleman RG, Pisters R, Cheriex EC, Luermans J, Crijns H. Idiopathic atrial fibrillation patients rapidly outgrow their low thromboembolic risk: a 10-year follow-up study. *Neth Heart J* 2019;**27**:487–497.
387. Chao TF, Liao JN, Tuan TC, Lin YJ, Chang SL, Lo LW, Hu YF, Chung FP, Chen TJ, Lip GYH, Chen SA. Incident co-morbidities in patients with atrial fibrillation initially with a CHA2DS2-VASc score of 0 (males) or 1 (females): implications for reassessment of stroke risk in initially 'low-risk' patients. *Thromb Haemost* 2019;**119**:1162–1170.
388. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM, Sanders GD. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost* 2018;**118**:2171–2187.
389. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and Delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost* 2018;**118**:768–777.
390. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;**159**:677–685.
391. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713–719.
392. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol* 2011;**58**:395–401.
393. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015;**36**:3258–3264.
394. Rohla M, Weiss TW, Pecen L, Patti G, Siller-Matula JM, Schnabel RB, Schilling R, Kotecha D, Lucerna M, Huber K, De Caterina R, Kirchhof P. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention oF thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF). *BMJ Open* 2019;**9**:e022478.
395. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–1100.
396. Mori N, Sotomi Y, Hirata A, Hirayama A, Sakata Y, Higuchi Y. External validation of the ORBIT bleeding score and the HAS-BLED score in nonvalvular atrial fibrillation patients using direct oral anticoagulants (Asian data from the DIRECT registry). *Am J Cardiol* 2019;**124**:1044–1048.
397. Yao X, Gersh BJ, Sangaralingham LR, Kent DM, Shah ND, Abraham NS, Noseworthy PA. Comparison of the CHA2DS2-VASc, CHADS2, HAS-BLED, ORBIT, and ATRIA risk scores in predicting non-vitamin K antagonist oral anticoagulants-associated bleeding in patients with atrial fibrillation. *Am J Cardiol* 2017;**120**:1549–1556.
398. Rutherford OW, Jonasson C, Ghanima W, Holst R, Halvorsen S. New score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs. *Open Heart* 2018;**5**:e000931.
399. Thomas MR, Lip GY. Novel risk markers and risk assessments for cardiovascular disease. *Circ Res* 2017;**120**:133–149.
400. Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications. *Cardiovasc Res* 2019;**115**:31–45.
401. Ban N, Siegfried CJ, Lin JB, Shui YB, Sein J, Pita-Thomas W, Sene A, Santeford A, Gordon M, Lamb R, Dong Z, Kelly SC, Cavalli V, Yoshino J, Apte RS. GDF15 is elevated in mice following retinal ganglion cell death and in glaucoma patients. *JCI Insight* 2017;**2**:pii: 91455. doi: 10.1172/jci.insight.91455.
402. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L; ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016;**387**:2302–2311.
403. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdes M, Marin F, Lip GYH. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemost* 2017;**117**:1848–1858.
404. Caldeira D, Costa J, Fernandes RM, Pinto FJ, Ferreira JJ. Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES in patients with atrial fibrillation: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2014;**40**:277–284.

405. Zhu W, He W, Guo L, Wang X, Hong K. The HAS-BLED score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: a systematic review and meta-analysis. *Clin Cardiol* 2015;**38**:555–561.
406. Chang G, Xie Q, Ma L, Hu K, Zhang Z, Mu G, Cui Y. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: a network meta-analysis. *J Thromb Haemost* 2020;**18**:791–801.
407. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;**14**:1711–1714.
408. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. *Int J Cardiol* 2018;**254**:157–161.
409. Guo Y, Zhu H, Chen Y, Lip GYH. Comparing bleeding risk assessment focused on modifiable risk factors only versus validated bleeding risk scores in atrial fibrillation. *Am J Med* 2018;**131**:185–192.
410. Esteve-Pastor MA, Rivera-Caravaca JM, Shantsila A, Roldan V, Lip GYH, Marin F. Assessing bleeding risk in atrial fibrillation patients: comparing a bleeding risk score based only on modifiable bleeding risk factors against the HAS-BLED score. The AMADEUS trial. *Thromb Haemost* 2017;**117**:2261–2266.
411. Guo Y, Lane DA, Chen Y, Lip GYH; mAF-App II Trial investigators. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAFA-II randomized trial. *Am J Med* 2020:pii: S0002-9343(20)30274-6.
412. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
413. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC working group on thrombosis – Task Force on anticoagulants in heart disease. *Thromb Haemost* 2013;**110**:1087–1107.
414. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C, Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circ Cardiovasc Qual Outcomes* 2008;**1**:84–91.
415. Sjalander S, Sjogren V, Renlund H, Norrving B, Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res* 2018;**167**:113–118.
416. Amin A, Deitelzweig S, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, Graham J. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. *J Thromb Thrombolysis* 2014;**38**:150–159.
417. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest* 2013;**144**:1555–1563.
418. Proietti M, Lip GY. Simple decision-making between a vitamin K antagonist and a non-vitamin K antagonist oral anticoagulant: using the SAMe-TT2R2 score. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:150–152.
419. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
420. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
421. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
422. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
423. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
424. Wang KL, Lip GY, Lin SJ, Chiang CE. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. *Stroke* 2015;**46**:2555–2561.
425. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817.
426. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost* 2016;**116**:754–763.
427. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Lu S, Bartels DB, Lip GYH; GLORIA-AF Investigators. Two-year follow-up of patients treated with dabigatran for stroke prevention in atrial fibrillation: Global Registry on Long-Term Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry. *Am Heart J* 2018;**198**:55–63.
428. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145–1153.
429. Martinez CAA, Lanas F, Radaideh G, Kharabsheh SM, Lambelet M, Viaud MAL, Ziadeh NS, Turpie AGG; XANTUS Investigators. XANTUS-EL: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. *Egypt Heart J* 2018;**70**:307–313.
430. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Lip GYH. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in 'real-world' clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost* 2017;**117**:1072–1082.
431. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. *J Am Coll Cardiol* 2018;**72**:838–853.
432. Ingrasciotta Y, Crisafulli S, Pizzimenti V, Marciano I, Mancuso A, Ando G, Corrao S, Capranzano P, Trifiro G. Pharmacokinetics of new oral anticoagulants: implications for use in routine care. *Expert Opin Drug Metab Toxicol* 2018;**14**:1057–1069.
433. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Lip GYH, Chen SA. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 2018;**138**:37–47.
434. Stanton BE, Barasch NS, Tellor KB. Comparison of the safety and effectiveness of apixaban versus warfarin in patients with severe renal impairment. *Pharmacotherapy* 2017;**37**:412–419.
435. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X, Noseworthy PA, Shah ND, Saran R, Nallamothu BK. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation* 2018;**138**:1519–1529.
436. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP; ORBIT-AF Investigators and Patients. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II registry. *J Am Coll Cardiol* 2016;**68**:2597–2604.
437. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 2017;**69**:2779–2790.
438. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;**367**:1903–1912.
439. ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–2078.
440. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace* 2014;**16**:631–638.
441. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators, Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;**370**:493–503.
442. Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011;**8**:602–606.

443. Verheugt FWA, Gao H, Al Mahmeed W, Ambrosio G, Angchaisuksiri P, Atar D, Bassand JP, Camm AJ, Cools F, Eikelboom J, Kayani G, Lim TW, Misselwitz F, Pieper KS, van Eickels M, Kakkar AK; GARFIELD-AF Investigators. Characteristics of patients with atrial fibrillation prescribed antiplatelet monotherapy compared with those on anticoagulants: insights from the GARFIELD-AF registry. *Eur Heart J* 2018;**39**:464–473.
444. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–542.
445. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) trial. *Circulation* 2013;**127**:720–729.
446. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
447. Holmes DR, Jr., Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, Valderrabano M, Reddy VY. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. *J Am Coll Cardiol* 2015;**65**:2614–2623.
448. Reddy VY, Mobius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551–2556.
449. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW, on behalf of the EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016;**37**:2465–2474.
450. Boersma LV, Ince H, Kische S, Pokushalov E, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Foley D, Sievert H, Mazzone P, De Potter T, Vireca E, Stein K, Bergmann MW, for the EWOLUTION Investigators. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017;**14**:1302–1308.
451. Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, Hoosien M, Shah N, Singh V, Grover P, Savani GT, Panaich SS, Rathod A, Patel N, Arora S, Bhalara V, Coffey JO, O'Neill W, Makkar R, Grines CL, Schreiber T, Di Biase L, Natale A, Viles-Gonzalez JF. Utilization and adverse outcomes of percutaneous left atrial appendage closure for stroke prevention in atrial fibrillation in the United States: influence of hospital volume. *Circ Arrhythm Electrophysiol* 2015;**8**:42–48.
452. Pison L, Potpara TS, Chen J, Larsen TB, Bongiorni MG, Blomstrom-Lundqvist C; Scientific Initiative Committee EHRA. Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. *Europace* 2015;**17**:642–646.
453. Price MJ, Gibson DN, Yakubov SJ, Schultz JC, Di Biase L, Natale A, Burkhardt JD, Pershad A, Byrne TJ, Gidney B, Aragon JR, Goldstein J, Moulton K, Patel T, Knight B, Lin AC, Valderrabano M. Early safety and efficacy of percutaneous left atrial appendage suture ligation: results from the US transcatheter LAA ligation consortium. *J Am Coll Cardiol* 2014;**64**:565–572.
454. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S, Fatemi M, Franceschi F, Guedeney P, Jacon P, Paziaud O, Venier S, Deharo JC, Gras D, Klug D, Mansourati J, Montalescot G, Piot O, Defaye P. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:1528–1536.
455. Lakkireddy D, Afzal MR, Lee RJ, Nagaraj H, Tschopp D, Gidney B, Ellis C, Altman E, Lee B, Kar S, Bhadwar N, Sanchez M, Gadiyaram V, Evonich R, Rasekh A, Cheng J, Cuoco F, Chandhok S, Gunda S, Reddy M, Atkins D, Bommana S, Cuculich P, Gibson D, Nath J, Ferrell R, Matthew E, Wilber D. Short and long-term outcomes of percutaneous left atrial appendage suture ligation: results from a US multicenter evaluation. *Heart Rhythm* 2016;**13**:1030–1036.
456. van Laar C, Verberkmoes NJ, van Es HW, Lewalter T, Dunnington G, Stark S, Longoria J, Hofman FH, Pierce CM, Kotecha D, van Putte BP. Thoracoscopic left atrial appendage clipping: a multicenter cohort analysis. *JACC Clin Electrophysiol* 2018;**4**:893–901.
457. Healey JS, Crystal E, Lamy A, Teoh K, Semelhago L, Hohnloser SH, Cybulsky I, Abouzahr L, Sawchuck C, Carroll S, Morillo C, Kleine P, Chu V, Lonn E, Connolly SJ. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005;**150**:288–293.
458. Whitlock RP, Vincent J, Blackall MH, Hirsh J, Fremes S, Novick R, Devereaux PJ, Teoh K, Lamy A, Connolly SJ, Yusuf S, Carrier M, Healey JS. Left Atrial Appendage Occlusion Study II (LAAOS II). *Can J Cardiol* 2013;**29**:1443–1447.
459. Tsai YC, Phan K, Munkholm-Larsen S, Tian DH, La Meir M, Yan TD. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis. *Eur J Cardiothorac Surg* 2015;**47**:847–854.
460. Aryana A, Singh SK, Singh SM, O'Neill PG, Bowers MR, Allen SL, Lewandowski SL, Vierra EC, d'Avila A. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm* 2015;**12**:1431–1437.
461. Gillinov AM, Gelijns AC, Parides MK, DeRose JJ Jr, Moskowitz AJ, Voisine P, Ailawadi G, Bouchard D, Smith PK, Mack MJ, Acker MA, Mullen JC, Rose EA, Chang HL, Puskas JD, Couderc JP, Gardner TJ, Varghese R, Horvath KA, Bolling SF, Michler RE, Geller NL, Ascheim DD, Miller MA, Bagiella E, Moquete EG, Williams P, Taddei-Peters WC, O'Gara PT, Blackstone EH, Argenziano M; CTSN Investigators. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med* 2015;**372**:1399–1409.
462. Whitlock R, Healey J, Vincent J, Brady K, Teoh K, Royse A, Shah P, Guo Y, Alings M, Folkeringa RJ, Paparella D, Colli A, Meyer SR, Legare JF, Lamontagne F, Reents W, Boning A, Connolly S. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg* 2014;**3**:45–54.
463. Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2017;**356**:j510.
464. Larsen TB, Skjoth F, Nielsen PB, Kjaeldgaard JN, Lip GY. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016;**353**:i3189.
465. Tilz RR, Potpara T, Chen J, Dobreanu D, Larsen TB, Haugaa KH, Dagres N. Left atrial appendage occluder implantation in Europe: indications and anticoagulation post-implantation. Results of the European Heart Rhythm Association Survey. *Europace* 2017;**19**:1737–1742.
466. Ogawa H, An Y, Ikeda S, Aono Y, Doi K, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M; Fushimi AF Registry Investigators. Progression from paroxysmal to sustained atrial fibrillation is associated with increased adverse events. *Stroke* 2018;**49**:2301–2308.
467. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, Hendriks JML, Kalman JM, Lau DH, Sanders P. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J* 2018;**39**:1407–1415.
468. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt AH, Rienstra M, Connolly SJ. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;**38**:1339–1344.
469. Boriani G, Glotzer TV, Ziegler PD, De Melis M, Mangoni di SSL, Sepsi M, Landolina M, Lunati M, Lewalter T, Camm AJ. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. *Heart Rhythm* 2018;**15**:376–383.
470. Pastori D, Lip GYH, Farcomeni A, Del Sole F, Sciacqua A, Perticone F, Marcucci R, Grifoni E, Pignatelli P, Violi F, ATHERO-AF study group. Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. *Int J Cardiol* 2018;**264**:58–63.
471. Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Lip GYH, Chen SA. Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention?*J Am Heart Assoc* 2017;**6**.
472. Lee SR, Lee HJ, Choi EK, Han KD, Jung JH, Cha MJ, Oh S, Lip GYH. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. *J Am Coll Cardiol* 2019;**73**:3295–3308.
473. Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2015;**351**:h5876.
474. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;**4**:14–21.
475. Proietti M, Lip GY. Major outcomes in atrial fibrillation patients with one risk factor: impact of time in therapeutic range observations from the SPORTIF trials. *Am J Med* 2016;**129**:1110–1116.

476. Lip GY, Nielsen PB. Should patients with atrial fibrillation and 1 stroke risk factor (CHA2DS2-VASc Score 1 in Men, 2 in Women) be anticoagulated? Yes: even 1 stroke risk factor confers a real risk of stroke. *Circulation* 2016;**133**:1498–1503; discussion 1503.
477. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. *JAMA* 2015;**313**:1950–1962.
478. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, Parkhomenko A, Lopez-Sendon JL, Lopes RD, Siegbahn A, Granger CB, Wallentin L. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time: insights from the ARISTOTLE randomized clinical trial. *JAMA Cardiol* 2016;**1**:451–460.
479. Bohm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, Yusuf S, Diener HC, Hijazi Z, Wallentin L. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. *J Am Coll Cardiol* 2015;**65**:2481–2493.
480. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. *PLoS One* 2013;**8**:e74037.
481. Teiger E, Thambo JB, Defaye P, Hermida JS, Abbey S, Klug D, Juliard JM, Pasquie JL, Rioufol G, Lepillier A, Elbaz M, Horvilleur J, Brenot P, Pierre B, Le Corvoisier P. Percutaneous left atrial appendage closure is a reasonable option for patients with atrial fibrillation at high risk for cerebrovascular events. *Circ Cardiovasc Interv* 2018;**11**:e005841.
482. Saw J, Fahmy P, Azzalini L, Marquis JF, Hibbert B, Morillo C, Carrizo A, Ibrahim R. Early Canadian multicenter experience with WATCHMAN for percutaneous left atrial appendage closure. *J Cardiovasc Electrophysiol* 2017;**28**:396–401.
483. Martin Gutierrez E, Castano M, Gualis J, Martinez-Comendador JM, Maiorano P, Castillo L, Laguna G. Beneficial effect of left atrial appendage closure during cardiac surgery: a meta-analysis of 280 585 patients. *Eur J Cardiothorac Surg* 2020;**57**:252–262.
484. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ, Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med* 2014;**160**:760–773.
485. Tamariz LJ, Bass EB. Pharmacological rate control of atrial fibrillation. *Cardiol Clin* 2004;**22**:35–45.
486. Nikolaidou T, Channer KS. Chronic atrial fibrillation: a systematic review of medical heart rate control management. *Postgrad Med J* 2009;**85**:303–312.
487. Groenveld HF, Crijns HJ, Van den Berg MP, Van Sonderen E, Alings AM, Tijssen JG, Hillege HL, Tuininga YS, Van Veldhuisen DJ, Ranchor AV, Van Gelder IC; RACE II Investigators. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) study. *J Am Coll Cardiol* 2011;**58**:1795–1803.
488. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–1373.
489. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, Crijns HJ; RACE and AFFIRM Investigators. Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935–942.
490. Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B. Rate control in atrial fibrillation. *Lancet* 2016;**388**:818–828.
491. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–2243.
492. Ulimoen SR, Enger S, Carlson J, Platonov PG, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Comparison of four single-drug regimens on ventricular rate and arrhythmia-related symptoms in patients with permanent atrial fibrillation. *Am J Cardiol* 2013;**111**:225–230.
493. Ulimoen SR, Enger S, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A. Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J* 2014;**35**:517–524.
494. Figulla HR, Gietzen F, Zeymer U, Raiber M, Hegselmann J, Soballa R, Hilgers R. Diltiazem improves cardiac function and exercise capacity in patients with idiopathic dilated cardiomyopathy. Results of the Diltiazem in Dilated Cardiomyopathy trial. *Circulation* 1996;**94**:346–352.
495. Hallberg P, Lindback J, Lindahl B, Stenestrand U, Melhus H, group R-H. Digoxin and mortality in atrial fibrillation: a prospective cohort study. *Eur J Clin Pharmacol* 2007;**63**:959–971.
496. Turakhia MP, Santangeli P, Winkelmayer WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes TH, Frayne SM, Phibbs CS, Yang F, Hoang DD, Ho PM, Heidenreich PA. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol* 2014;**64**:660–668.
497. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients taking digoxin – analysis from the AFFIRM study. *Eur Heart J* 2013;**34**:1481–1488.
498. Andrey JL, Romero S, Garcia-Egido A, Escobar MA, Corzo R, Garcia-Dominguez G, Lechuga V, Gomez F. Mortality and morbidity of heart failure treated with digoxin. A propensity-matched study. *Int J Clin Pract* 2011;**65**:1250–1258.
499. Flory JH, Ky B, Haynes K, S MB, Munson J, Rowan, C, Strom BL, Hennessy S. Observational cohort study of the safety of digoxin use in women with heart failure. *BMJ Open* 2012;**2**:e000888.
500. Gheorghiade M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013;**34**:1489–1497.
501. Aguirre Davila L, Weber K, Bavendiek U, Bauersachs J, Wittes J, Yusuf S, Koch A. Digoxin-mortality: randomized vs. observational comparison in the DIG trial. *Eur Heart J* 2019;**40**:3336–3341.
502. Ziff OJ, Lane DA, Samra M, Griffith M, Kirchhof P, Lip GY, Steeds RP, Townend J, Kotecha D. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;**351**:h4451.
503. Bavendiek U, Berliner D, Davila LA, Schwab J, Maier L, Philipp SA, Rieth A, Westenfeld R, Piorkowski C, Weber K, Hanselmann A, Oldhafer M, Schallhorn S, von der Leyen H, Schroder C, Veltmann C, Stork S, Bohm M, Koch A, Bauersachs J; DIGIT-HF Investigators and Committees. Rationale and design of the DIGIT-HF trial (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure): a randomized, double-blind, placebo-controlled study. *Eur J Heart Fail* 2019;**21**:676–684.
504. Clemo HF, Wood MA, Gilligan DM, Ellenbogen KA. Intravenous amiodarone for acute heart rate control in the critically ill patient with atrial tachyarrhythmias. *Am J Cardiol* 1998;**81**:594–598.
505. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Korv J, Lal A, Putaala J, Werring DJ. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: a European Stroke Organisation guideline. *Eur Stroke J* 2019;**4**:198–223.
506. Gosselink AT, Crijns HJ, Van Gelder IC, Hillige H, Wiesfeld AC, Lie KI. Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. *JAMA* 1992;**267**:3289–3293.
507. Scheuermeyer FX, Grafstein E, Stenstrom R, Christenson J, Heslop C, Heilbron B, McGrath L, Innes G. Safety and efficiency of calcium channel blockers versus beta-blockers for rate control in patients with atrial fibrillation and no acute underlying medical illness. *Acad Emerg Med* 2013;**20**:222–230.
508. Schreck DM, Rivera AR, Tricarico VJ. Emergency management of atrial fibrillation and flutter: intravenous diltiazem versus intravenous digoxin. *Ann Emerg Med* 1997;**29**:135–140.
509. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, Robinson K, Yu D, Bass EB. The evidence regarding the drugs used for ventricular rate control. *J Fam Pract* 2000;**49**:47–59.
510. Siu CW, Lau CP, Lee WL, Lam KF, Tse HF. Intravenous diltiazem is superior to intravenous amiodarone or digoxin for achieving ventricular rate control in patients with acute uncomplicated atrial fibrillation. *Crit Care Med* 2009;**37**:2174–2179; quiz 2180.
511. Tisdale JE, Padhi ID, Goldberg AD, Silverman NA, Webb CR, Higgins RS, Paone G, Frank DM, Borzak S. A randomized, double-blind comparison of intravenous diltiazem and digoxin for atrial fibrillation after coronary artery bypass surgery. *Am Heart J* 1998;**135**:739–747.
512. Darby AE, Dimarco JP. Management of atrial fibrillation in patients with structural heart disease. *Circulation* 2012;**125**:945–957.
513. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do?*Eur Heart J* 2015;**36**:3250–3257.
514. Delle Karth G, Geppert A, Neunteufl T, Priglinger U, Haumer M, Gschwandtner M, Siostrzonek P, Heinz G. Amiodarone versus diltiazem for rate control in critically ill patients with atrial tachyarrhythmias. *Crit Care Med* 2001;**29**:1149–1153.
515. Hou ZY, Chang MS, Chen CY, Tu MS, Lin SL, Chiang HT, Woosley RL. Acute treatment of recent-onset atrial fibrillation and flutter with a tailored dosing regimen of intravenous amiodarone. A randomized, digoxin-controlled study. *Eur Heart J* 1995;**16**:521–528.

516. Lim KT, Davis MJ, Powell A, Arnolda L, Moulden K, Bulsara M, Weerasooriya R. Ablate and pace strategy for atrial fibrillation: long-term outcome of AIRCRAFT trial. *Europace* 2007;**9**:498–505.
517. Queiroga A, Marshall HJ, Clune M, Gammage MD. Ablate and pace revisited: long term survival and predictors of permanent atrial fibrillation. *Heart* 2003;**89**:1035–1038.
518. Geelen P, Brugada J, Andries E, Brugada P. Ventricular fibrillation and sudden death after radiofrequency catheter ablation of the atrioventricular junction. *Pacing Clin Electrophysiol* 1997;**20**:343–348.
519. Wang RX, Lee HC, Hodge DO, Cha YM, Friedman PA, Rea RF, Munger TM, Jahangir A, Srivathsan K, Shen WK. Effect of pacing method on risk of sudden death after atrioventricular node ablation and pacemaker implantation in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:696–701.
520. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. *Circ Arrhythm Electrophysiol* 2012;**5**:68–76.
521. Bradley DJ, Shen WK. Overview of management of atrial fibrillation in symptomatic elderly patients: pharmacologic therapy versus AV node ablation. *Clin Pharmacol Ther* 2007;**81**:284–287.
522. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1043–1051.
523. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation* 2000;**101**:1138–1144.
524. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.
525. Chatterjee NA, Upadhyay GA, Ellenbogen KA, Hayes DL, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis of biventricular vs. right ventricular pacing mode. *Eur J Heart Fail* 2012;**14**:661–667.
526. Huang W, Su L, Wu S. Pacing treatment of atrial fibrillation patients with heart failure: His bundle pacing combined with atrioventricular node ablation. *Card Electrophysiol Clin* 2018;**10**:519–535.
527. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, Quartieri F, Calo L, Ungar A, Mont L; APAF-CRT Investigators. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018;**39**:3999–4008.
528. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc* 2017;**6**.
529. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol* 1999;**33**:304–310.
530. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure?*J Am Coll Cardiol* 2003;**42**:1944–1951.
531. Lewis RV, Irvine N, McDevitt DG. Relationships between heart rate, exercise tolerance and cardiac output in atrial fibrillation: the effects of treatment with digoxin, verapamil and diltiazem. *Eur Heart J* 1988;**9**:777–781.
532. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Van den Berg MP, Van Gelder IC. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. *Heart Rhythm* 2014;**11**:1543–1550.
533. Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola SH, Elkayam U. Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. *Circulation* 1986;**73**:316–324.
534. David D, Segni ED, Klein HO, Kaplinsky E. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effect of an added beta adrenergic blocking agent. *Am J Cardiol* 1979;**44**:1378–1382.
535. Weerasooriya R, Davis M, Powell A, Szili-Torok T, Shah C, Whalley D, Kanagaratnam L, Heddle W, Leitch J, Perks A, Ferguson L, Bulsara M. The Australian Intervention Randomized Control of Rate in Atrial Fibrillation Trial (AIRCRAFT). *J Am Coll Cardiol* 2003;**41**:1697–1702.
536. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and His bundle pacing. *Europace* 2017;**19**:iv10–iv16.
537. Shiga T, Yoshioka K, Watanabe E, Omori H, Yagi M, Okumura Y, Matsumoto N, Kusano K, Oshiro C, Ikeda T, Takahashi N, Komatsu T, Suzuki A, Suzuki T, Sato Y, Yamashita T; AF-QOL study investigators. Paroxysmal atrial fibrillation recurrences and quality of life in symptomatic patients: a crossover study of flecainide and pilsicainide. *J Arrhythm* 2017;**33**:310–317.
538. Capucci A, Piangerelli L, Ricciotti J, Gabrielli D, Guerra F. Flecainide-metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation. *Europace* 2016;**18**:1698–1704.
539. Shi LZ, Heng R, Liu SM, Leng FY. Effect of catheter ablation versus antiarrhythmic drugs on atrial fibrillation: a meta-analysis of randomized controlled trials. *Exp Ther Med* 2015;**10**:816–822.
540. Siontis KC, Ioannidis JPA, Katritsis GD, Noseworthy PA, Packer DL, Hummel JD, Jais P, Krittayaphong R, Mont L, Morillo CA, Nielsen JC, Oral H, Pappone C, Santinelli V, Weerasooriya R, Wilber DJ, Gersh BJ, Josephson ME, Katritsis DG. Radiofrequency ablation versus antiarrhythmic drug therapy for atrial fibrillation: meta-analysis of quality of life, morbidity, and mortality. *JACC Clin Electrophysiol* 2016;**2**:170–180.
541. Kim YG, Shim J, Choi JI, Kim YH. Radiofrequency catheter ablation improves the quality of life measured with a short form-36 questionnaire in atrial fibrillation patients: a systematic review and meta-analysis. *PLoS One* 2016;**11**:e0163755.
542. Bayes de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayes-Genis A, Guindo J, Vinolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol* 2012;**45**:445–451.
543. Jadidi A, Muller-Edenborn B, Chen J, Keyl C, Weber R, Allgeier J, Moreno-Weidmann Z, Trenk D, Neumann FJ, Lehrmann H, Arentz T. The duration of the amplified sinus-p-wave identifies presence of left atrial low voltage substrate and predicts outcome after pulmonary vein isolation in patients with persistent atrial fibrillation. *JACC Clin Electrophysiol* 2018;**4**:531–543.
544. Dudink E, Erkuner O, Berg J, Nieuwlaat R, de Vos CB, Weijs B, Capucci A, Camm AJ, Breithardt G, Le Heuzey JY, Luermans J, Crijns H. The influence of progression of atrial fibrillation on quality of life: a report from the Euro Heart Survey. *Europace* 2018;**20**:929–934.
545. Zhang YY, Qiu C, Davis PJ, Jhaveri M, Prystowsky EN, Kowey P, Weintraub WS. Predictors of progression of recently diagnosed atrial fibrillation in REgistry on Cardiac Rhythm DisORDers Assessing the Control of Atrial Fibrillation (RecordAF) – United States cohort. *Am J Cardiol* 2013;**112**:79–84.
546. Bunch TJ, May HT, Bair TL, Johnson DL, Weiss JP, Crandall BG, Osborn JS, Anderson JL, Muhlestein JB, Lappe DL, Day JD. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Heart Rhythm* 2013;**10**:1257–1262.
547. Andrade JG, Champagne J, Deyell MW, Essebag V, Lauck S, Morillo C, Sapp J, Skanes A, Theoret-Patrick P, Wells GA, Verma A; EARLY-AF Study Investigators. A randomized clinical trial of early invasive intervention for atrial fibrillation (EARLY-AF) – methods and rationale. *Am Heart J* 2018;**206**:94–104.
548. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Morton JB, Sanders P, Kalman JM. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. *Heart Rhythm* 2012;**9**:473–480.
549. Aliot E, Brandes A, Eckardt L, Elvan A, Gulizia M, Heidbuchel H, Kautzner J, Mont L, Morgan J, Ng A, Szumowski L, Themistoclakis S, Van Gelder IC, Willems S, Kirchhof P. The EAST study: redefining the role of rhythmcontrol therapy in atrial fibrillation: EAST, the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Eur Heart J* 2015;**36**:255–256.
550. Michelena HI, Powell BD, Brady PA, Friedman PA, Ezekowitz MD. Gender in atrial fibrillation: ten years later. *Gend Med* 2010;**7**:206–217.
551. Sethi NJ, Feinberg J, Nielsen EE, Safi S, Gluud C, Jakobsen JC. The effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter: a systematic review with meta-analysis and trial sequential analysis. *PLoS One* 2017;**12**:e0186856.
552. Ha AC, Breithardt G, Camm AJ, Crijns HJ, Fitzmaurice GM, Kowey PR, Le Heuzey JY, Naditch-Brule L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C,

Weintraub WS, Dorian P. Health-related quality of life in patients with atrial fibrillation treated with rhythm control versus rate control: insights from a prospective international registry (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF). *Circ Cardiovasc Qual Outcomes* 2014;**7**:896–904.
553. Bulkova V, Fiala M, Havranek S, Simek J, Sknouril L, Januska J, Spinar J, Wichterle D. Improvement in quality of life after catheter ablation for paroxysmal versus long-standing persistent atrial fibrillation: a prospective study with 3-year follow-up. *J Am Heart Assoc* 2014;**3**.
554. Kirchhof P, Monnig G, Wasmer K, Heinecke A, Breithardt G, Eckardt L, Bocker D. A trial of self-adhesive patch electrodes and hand-held paddle electrodes for external cardioversion of atrial fibrillation (MOBIPAPA). *Eur Heart J* 2005;**26**:1292–1297.
555. Kirchhof P, Eckardt L, Loh P, Weber K, Fischer RJ, Seidl KH, Bocker D, Breithardt G, Haverkamp W, Borggrefe M. Anterior-posterior versus anterior-lateral electrode positions for external cardioversion of atrial fibrillation: a randomised trial. *Lancet* 2002;**360**:1275–1279.
556. Um KJ, McIntyre WF, Healey JS, Mendoza PA, Koziarz A, Amit G, Chu VA, Whitlock RP, Belley-Cote EP. Pre- and post-treatment with amiodarone for elective electrical cardioversion of atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;**21**:856–863.
557. Schmidt AS, Lauridsen KG, Torp P, Bach LF, Rickers H, Lofgren B. Maximum-fixed energy shocks for cardioverting atrial fibrillation. *Eur Heart J* 2020;**41**:626–631.
558. Pluymaekers N, Dudink E, Luermans J, Meeder JG, Lenderink T, Widdershoven J, Bucx JJJ, Rienstra M, Kamp O, Van Opstal JM, Alings M, Oomen A, Kirchhof CJ, Van Dijk VF, Ramanna H, Liem A, Dekker LR, Essers BAB, Tijssen JGP, Van Gelder IC, Crijns H; RACE ACWAS Investigators. Early or delayed cardioversion in recent-onset atrial fibrillation. *N Engl J Med* 2019;**380**:1499–1508.
559. Baranchuk A, Yeung C. Advanced interatrial block predicts atrial fibrillation recurrence across different populations: learning Bayes syndrome. *Int J Cardiol* 2018;**272**:221–222.
560. Toufan M, Kazemi B, Molazadeh N. The significance of the left atrial volume index in prediction of atrial fibrillation recurrence after electrical cardioversion. *J Cardiovasc Thorac Res* 2017;**9**:54–59.
561. Voskoboinik A, Kalman E, Plunkett G, Knott J, Moskovitch J, Sanders P, Kistler PM, Kalman JM. A comparison of early versus delayed elective electrical cardioversion for recurrent episodes of persistent atrial fibrillation: a multi-center study. *Int J Cardiol* 2019;**284**:33–37.
562. Furniss SS, Sneyd JR. Safe sedation in modern cardiological practice. *Heart* 2015;**101**:1526–1530.
563. Mittal S, Ayati S, Stein KM, Schwartzman D, Cavlovich D, Tchou PJ, Markowitz SM, Slotwiner DJ, Scheiner MA, Lerman BB. Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. *Circulation* 2000;**101**:1282–1287.
564. Inacio JF, da Rosa Mdos S, Shah J, Rosario J, Vissoci JR, Manica AL, Rodrigues CG. Monophasic and biphasic shock for transthoracic conversion of atrial fibrillation: systematic review and network meta-analysis. *Resuscitation* 2016;**100**:66–75.
565. Kirkland S, Stiell I, AlShawabkeh T, Campbell S, Dickinson G, Rowe BH. The efficacy of pad placement for electrical cardioversion of atrial fibrillation/flutter: a systematic review. *Acad Emerg Med* 2014;**21**:717–726.
566. Boriani G, Diemberger I, Biffi M, Martignani C, Branzi A. Pharmacological cardioversion of atrial fibrillation: current management and treatment options. *Drugs* 2004;**64**:2741–2762.
567. Danias PG, Caulfield TA, Weigner MJ, Silverman DI, Manning WJ. Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol* 1998;**31**:588–592.
568. Dan GA, Martinez-Rubio A, Agewall S, Boriani G, Borggrefe M, Gaita F, van Gelder I, Gorenek B, Kaski JC, Kjeldsen K, Lip GYH, Merkely B, Okumura K, Piccini JP, Potpara T, Poulsen BK, Saba M, Savelieva I, Tamargo JL, Wolpert C, ESC Scientific Document Group. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). *Europace* 2018;**20**:731–732.
569. Markey GC, Salter N, Ryan J. Intravenous flecainide for emergency department management of acute atrial fibrillation. *J Emerg Med* 2018;**54**:320–327.
570. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Kirkorian G, Touboul P. Amiodarone versus placebo and class Ic drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. *J Am Coll Cardiol* 2003;**41**:255–262.
571. Capucci A, Lenzi T, Boriani G, Trisolino G, Binetti N, Cavazza M, Fontana G, Magnani B. Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. *Am J Cardiol* 1992;**70**:69–72.
572. Donovan KD, Dobb GJ, Coombs LJ, Lee KY, Weekes JN, Murdock CJ, Clarke GM. Efficacy of flecainide for the reversion of acute onset atrial fibrillation. *Am J Cardiol* 1992;**70**:50A-54A; discussion 54A-55A.
573. Reisinger J, Gatterer E, Lang W, Vanicek T, Eisserer G, Bachleitner T, Niemeth C, Aicher F, Grander W, Heinze G, Kuhn P, Siostrzonek P. Flecainide versus ibutilide for immediate cardioversion of atrial fibrillation of recent onset. *Eur Heart J* 2004;**25**:1318–1324.
574. Khan IA. Oral loading single dose flecainide for pharmacological cardioversion of recent-onset atrial fibrillation. *Int J Cardiol* 2003;**87**:121–128.
575. Galve E, Rius T, Ballester R, Artaza MA, Arnau JM, Garcia-Dorado D, Soler-Soler J. Intravenous amiodarone in treatment of recent-onset atrial fibrillation: results of a randomized, controlled study. *J Am Coll Cardiol* 1996;**27**:1079–1082.
576. Vardas PE, Kochiadakis GE, Igoumenidis NE, Tsatsakis AM, Simantirakis EN, Chlouverakis GI. Amiodarone as a first-choice drug for restoring sinus rhythm in patients with atrial fibrillation: a randomized, controlled study. *Chest* 2000;**117**:1538–1545.
577. Letelier LM, Udol K, Ena J, Weaver B, Guyatt GH. Effectiveness of amiodarone for conversion of atrial fibrillation to sinus rhythm: a meta-analysis. *Arch Intern Med* 2003;**163**:777–785.
578. Bash LD, Buono JL, Davies GM, Martin A, Fahrbach K, Phatak H, Avetisyan R, Mwamburi M. Systematic review and meta-analysis of the efficacy of cardioversion by vernakalant and comparators in patients with atrial fibrillation. *Cardiovasc Drugs Ther* 2012;**26**:167–179.
579. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G; AVRO Investigators. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:313–321.
580. Akel T, Lafferty J. Efficacy and safety of intravenous vernakalant for the rapid conversion of recent-onset atrial fibrillation: a meta-analysis. *Ann Noninvasive Electrocardiol* 2018;**23**:e12508.
581. Beatch GN, Mangal B. Safety and efficacy of vernakalant for the conversion of atrial fibrillation to sinus rhythm; a phase 3b randomized controlled trial. *BMC Cardiovasc Disord* 2016;**16**:113.
582. Roy D, Pratt CM, Torp-Pedersen C, Wyse DG, Toft E, Juul-Moller S, Nielsen T, Rasmussen SL, Stiell IG, Coutu B, Ip JH, Pritchett EL, Camm AJ; Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a phase 3, randomized, placebo-controlled trial. *Circulation* 2008;**117**:1518–1525.
583. Kowey PR, Dorian P, Mitchell LB, Pratt CM, Roy D, Schwartz PJ, Sadowski J, Sobczyk D, Bochenek A, Toft E; Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:652–659.
584. Pohjantahti-Maaroos H, Hyppola H, Lekkala M, Sinisalo E, Heikkola A, Hartikainen J. Intravenous vernakalant in comparison with intravenous flecainide in the cardioversion of recent-onset atrial fibrillation. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:114–120.
585. Vos MA, Golitsyn SR, Stangl K, Ruda MY, Van Wijk LV, Harry JD, Perry KT, Touboul P, Steinbeck G, Wellens HJ. Superiority of ibutilide (a new class III agent) over DL-sotalol in converting atrial flutter and atrial fibrillation. The Ibutilide/Sotalol Comparator Study Group. *Heart* 1998;**79**:568–575.
586. Alboni P, Botto GL, Baldi N, Luzi M, Russo V, Gianfranchi L, Marchi P, Calzolari M, Solano A, Baroffio R, Gaggioli G. Outpatient treatment of recent-onset atrial fibrillation with the 'pill-in-the-pocket' approach. *N Engl J Med* 2004;**351**:2384–2391.
587. Brembilla-Perrot B, Houriez P, Beurrier D, Claudon O, Terrier de la Chaise A, Louis P. Predictors of atrial flutter with 1:1 conduction in patients treated with class I antiarrhythmic drugs for atrial tachyarrhythmias. *Int J Cardiol* 2001;**80**:7–15.
588. Zhang N, Guo JH, Zhang H, Li XB, Zhang P, Xn Y. Comparison of intravenous ibutilide vs. propafenone for rapid termination of recent onset atrial fibrillation. *Int J Clin Pract* 2005;**59**:1395–1400.
589. Conde D, Costabel JP, Caro M, Ferro A, Lambardi F, Corrales Barboza A, Lavalle Cobo A, Trivi M. Flecainide versus vernakalant for conversion of recent-onset atrial fibrillation. *Int J Cardiol* 2013;**168**:2423–2425.
590. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM, Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol* 2000;**86**:950–953.
591. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans

affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;**98**:2574–2579.
592. Hofmann R, Steinwender C, Kammler J, Kypta A, Wimmer G, Leisch F. Intravenous amiodarone bolus for treatment of atrial fibrillation in patients with advanced congestive heart failure or cardiogenic shock. *Wien Klin Wochenschr* 2004;**116**:744–749.
593. Crijns HJ, Weijs B, Fairley AM, Lewalter T, Maggioni AP, Martin A, Ponikowski P, Rosenqvist M, Sanders P, Scanavacca M, Bash LD, Chazelle F, Bernhardt A, Gitt AK, Lip GY, Le Heuzey JY. Contemporary real life cardioversion of atrial fibrillation: results from the multinational RHYTHM-AF study. *Int J Cardiol* 2014;**172**:588–594.
594. Kirchhof P, Andresen D, Bosch R, Borggrefe M, Meinertz T, Parade U, Ravens U, Samol A, Steinbeck G, Treszl A, Wegscheider K, Breithardt G. Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation (Flec-SL): a prospective, randomised, open-label, blinded endpoint assessment trial. *Lancet* 2012;**380**:238–246.
595. Van Gelder IC, Tuinenburg AE, Schoonderwoerd BS, Tieleman RG, Crijns HJ. Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation. *Am J Cardiol* 1999;**84**:147R–151R.
596. Climent VE, Marin F, Mainar L, Gomez-Aldaravi R, Martinez JG, Chorro FJ, Roman P, Sogorb F. Effects of pretreatment with intravenous flecainide on efficacy of external cardioversion of persistent atrial fibrillation. *Pacing Clin Electrophysiol* 2004;**27**:368–372.
597. Mussigbrodt A, John S, Kosiuk J, Richter S, Hindricks G, Bollmann A. Vernakalant-facilitated electrical cardioversion: comparison of intravenous vernakalant and amiodarone for drug-enhanced electrical cardioversion of atrial fibrillation after failed electrical cardioversion. *Europace* 2016;**18**:51–56.
598. Singh SN, Tang XC, Reda D, Singh BN. Systematic electrocardioversion for atrial fibrillation and role of antiarrhythmic drugs: a substudy of the SAFE-T trial. *Heart Rhythm* 2009;**6**:152–155.
599. Oral H, Souza JJ, Michaud GF, Knight BP, Goyal R, Strickberger SA, Morady F. Facilitating transthoracic cardioversion of atrial fibrillation with ibutilide pretreatment. *N Engl J Med* 1999;**340**:1849–1854.
600. Khan IA. Single oral loading dose of propafenone for pharmacological cardioversion of recent-onset atrial fibrillation. *J Am Coll Cardiol* 2001;**37**:542–547.
601. Alboni P, Botto GL, Boriani G, Russo G, Pacchioni F, Iori M, Pasanisi G, Mancini M, Mariconti B, Capucci A. Intravenous administration of flecainide or propafenone in patients with recent-onset atrial fibrillation does not predict adverse effects during 'pill-in-the-pocket' treatment. *Heart* 2010;**96**:546–549.
602. Arbelo E, Brugada J, Hindricks G, Maggioni A, Tavazzi L, Vardas P, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse G, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines S; Atrial Fibrillation Ablation Pilot Study Investigators. ESC-EURObservational Research Programme: the Atrial Fibrillation Ablation Pilot Study, conducted by the European Heart Rhythm Association. *Europace* 2012;**14**:1094–1103.
603. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines SA; Atrial Fibrillation Ablation Pilot Study Investigators. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J* 2014;**35**:1466–1478.
604. Arbelo E, Brugada J, Blomstrom-Lundqvist C, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, Maggioni A, Tavazzi L, Dagres N, on the behalf of the ESC EHRA Atrial Fibrillation Ablation Long-term Registry Investigators. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J* 2017;**38**:1303–1316.
605. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, Kangkagate C. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *J Med Assoc Thai* 2003;**86 Suppl 1**:S8–16.
606. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J* 2006;**27**:216–221.
607. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol* 2006;**48**:2340–2347.
608. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta-analyses. *Circ Arrhythm Electrophysiol* 2009;**2**:349–361.
609. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**:1713–1723.
610. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004549.
611. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation* 2016;**133**:1637–1644.
612. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med* 2016;**374**:2235–2245.
613. Sohara H, Ohe T, Okumura K, Naito S, Hirao K, Shoda M, Kobayashi Y, Yamauchi Y, Yamaguchi Y, Kuwahara T, Hirayama H, YeongHwa C, Kusano K, Kaitani K, Banba K, Fujii S, Kumagai K, Yoshida H, Matsushita M, Satake S, Aonuma K. HotBalloon ablation of the pulmonary veins for paroxysmal AF: a multicenter randomized trial in Japan. *J Am Coll Cardiol* 2016;**68**:2747–2757.
614. Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace* 2015;**17**:370–378.
615. Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, Englund A, Hartikainen J, Mortensen LS, Hansen PS; MANTRA-PAF Investigators. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart* 2017;**103**:368–376.
616. Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, Dai J, Xu X, Mao W. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. *J Interv Card Electrophysiol* 2018;**52**:9–18.
617. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261–1274.
618. Noseworthy PA, Gersh BJ, Kent DM, Piccini JP, Packer DL, Shah ND, Yao X. Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J* 2019;**40**:1257–1264.
619. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Sparks PB, Morton JB, Kalman JM. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *J Cardiovasc Electrophysiol* 2012;**23**:232–238.
620. D'Ascenzo F, Corleto A, Biondi-Zoccai G, Anselmino M, Ferraris F, di Biase L, Natale A, Hunter RJ, Schilling RJ, Miyazaki S, Tada H, Aonuma K, Yenn-Jiang L, Tao H, Ma C, Packer D, Hammill S, Gaita F. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol* 2013;**167**:1984–1989.
621. Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, Vidal B, Arriagada G, Mendez F, Matiello M, Molina I, Brugada J. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007;**28**:836–841.
622. Nedios S, Kosiuk J, Koutalas E, Kornej J, Sommer P, Arya A, Richter S, Rolf S, Husser D, Hindricks G, Bollmann A. Comparison of left atrial dimensions in CT and echocardiography as predictors of long-term success after catheter ablation of atrial fibrillation. *J Interv Card Electrophysiol* 2015;**43**:237–244.
623. Njoku A, Kannabhiran M, Arora R, Reddy P, Gopinathannair R, Lakkireddy D, Dominic P. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace* 2018;**20**:33–42.
624. Costa FM, Ferreira AM, Oliveira S, Santos PG, Durazzo A, Carmo P, Santos KR, Cavaco D, Parreira L, Morgado F, Adragao P. Left atrial volume is more important than the type of atrial fibrillation in predicting the long-term success of catheter ablation. *Int J Cardiol* 2015;**184**:56–61.

625. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P, Brachmann J. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;**311**:498–506.
626. Kosich F, Schumacher K, Potpara T, Lip GY, Hindricks G, Kornej J. Clinical scores used for the prediction of negative events in patients undergoing catheter ablation for atrial fibrillation. *Clin Cardiol* 2019;**42**:320–329.
627. Kornej J, Hindricks G, Shoemaker MB, Husser D, Arya A, Sommer P, Rolf S, Saavedra P, Kanagasundram A, Patrick Whalen S, Montgomery J, Ellis CR, Darbar D, Bollmann A. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. *Clin Res Cardiol* 2015;**104**:871–876.
628. Kornej J, Hindricks G, Arya A, Sommer P, Husser D, Bollmann A. The APPLE score – a novel score for the prediction of rhythm outcomes after repeat catheter ablation of atrial fibrillation. *PLoS One* 2017;**12**:e0169933.
629. Kornej J, Schumacher K, Dinov B, Kosich F, Sommer P, Arya A, Husser D, Bollmann A, Lip GYH, Hindricks G. Prediction of electro-anatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. *Sci Rep* 2018;**8**:12686.
630. Kosiuk J, Dinov B, Kornej J, Acou WJ, Schonbauer R, Fiedler L, Buchta P, Myrda K, Gasior M, Polonski L, Kircher S, Arya A, Sommer P, Bollmann A, Hindricks G, Rolf S. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. *Heart Rhythm* 2015;**12**:2207–2212.
631. Mujovic N, Marinkovic M, Markovic N, Shantsila A, Lip GY, Potpara TS. Prediction of very late arrhythmia recurrence after radiofrequency catheter ablation of atrial fibrillation: the MB-LATER clinical score. *Sci Rep* 2017;**7**:40828.
632. Mesquita J, Ferreira AM, Cavaco D, Moscoso Costa F, Carmo P, Marques H, Morgado F, Mendes M, Adragao P. Development and validation of a risk score for predicting atrial fibrillation recurrence after a first catheter ablation procedure – ATLAS score. *Europace* 2018;**20**:f428–f435.
633. Winkle RA, Jarman JW, Mead RH, Engel G, Kong MH, Fleming W, Patrawala RA. Predicting atrial fibrillation ablation outcome: the CAAP-AF score. *Heart Rhythm* 2016;**13**:2119–2125.
634. Canpolat U, Aytemir K, Yorgun H, Sahiner L, Kaya EB, Oto A. A proposal for a new scoring system in the prediction of catheter ablation outcomes: promising results from the Turkish Cryoablation Registry. *Int J Cardiol* 2013;**169**:201–206.
635. Wojcik M, Berkowitsch A, Greiss H, Zaltsberg S, Pajitnev D, Deubner N, Hamm CW, Pitschner HF, Kuniss M, Neumann T. Repeated catheter ablation of atrial fibrillation: how to predict outcome?*Circ J* 2013;**77**:2271–2279.
636. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–2231.
637. Trines SA, Stabile G, Arbelo E, Dagres N, Brugada J, Kautzner J, Pokushalov E, Maggioni AP, Laroche C, Anselmino M, Beinart R, Traykov V, Blomstrom-Lundqvist C. Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *Pacing Clin Electrophysiol* 2019;**42**:1365–1373.
638. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, Twomey D, Ganesan AN, Rangnekar G, Roberts-Thomson KC, Lau DH, Sanders P. Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. *JACC Clin Electrophysiol* 2015;**1**:139–152.
639. Wokhlu A, Hodge DO, Monahan KH, Asirvatham SJ, Friedman PA, Munger TM, Cha YM, Shen WK, Brady PA, Bluhm CM, Haroldson JM, Hammill SC, Packer DL. Long-term outcome of atrial fibrillation ablation: impact and predictors of very late recurrence. *J Cardiovasc Electrophysiol* 2010;**21**:1071–1078.
640. Arya A, Hindricks G, Sommer P, Huo Y, Bollmann A, Gaspar T, Bode K, Husser D, Kottkamp H, Piorkowski C. Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. *Europace* 2010;**12**:173–180.
641. Santoro F, Di Biase L, Trivedi C, Burkhardt JD, Paoletti Perini A, Sanchez J, Horton R, Mohanty P, Mohanty S, Bai R, Santangeli P, Lakkireddy D, Reddy M, Elayi CS, Hongo R, Beheiry S, Hao S, Schweikert RA, Viles-Gonzalez J, Fassini G, Casella M, Dello Russo A, Tondo C, Natale A. Impact of uncontrolled hypertension on atrial fibrillation ablation outcome. *JACC Clin Electrophysiol* 2015;**1**:164–173.
642. Letsas KP, Weber R, Burkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. *Europace* 2009;**11**:158–163.
643. Jongnarangsin K, Chugh A, Good E, Mukerji S, Dey S, Crawford T, Sarrazin JF, Kuhne M, Chalfoun N, Wells D, Boonyapisit W, Pelosi F, Jr., Bogun F, Morady F, Oral H. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:668–672.
644. Patel D, Mohanty P, Di Biase L, Shaheen M, Lewis WR, Quan K, Cummings JE, Wang P, Al-Ahmad A, Venkatraman P, Nashawati E, Lakkireddy D, Schweikert R, Horton R, Sanchez J, Gallinghouse J, Hao S, Beheiry S, Cardinal DS, Zagrodzky J, Canby R, Bailey S, Burkhardt JD, Natale A. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: the impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010;**3**:445–451.
645. Matiello M, Nadal M, Tamborero D, Berruezo A, Montserrat J, Embid C, Rios J, Villacastin J, Brugada J, Mont L. Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients. *Europace* 2010;**12**:1084–1089.
646. Chilukuri K, Dalal D, Gadrey S, Marine JE, Macpherson E, Henrikson CA, Cheng A, Nazarian S, Sinha S, Spragg D, Berger R, Calkins H. A prospective study evaluating the role of obesity and obstructive sleep apnea for outcomes after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2010;**21**:521–525.
647. Ng CY, Liu T, Shehata M, Stevens S, Chugh SS, Wang X. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. *Am J Cardiol* 2011;**108**:47–51.
648. Naruse Y, Tada H, Satoh M, Yanagihara M, Tsuneoka H, Hirata Y, Ito Y, Kuroki K, Machino T, Yamasaki H, Igarashi M, Sekiguchi Y, Sato A, Aonuma K. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. *Heart Rhythm* 2013;**10**:331–337.
649. Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, Guo WH, Jiang CX, Ma CS. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: a meta-analysis of observational studies. *Europace* 2014;**16**:1309–1314.
650. Kawakami H, Nagai T, Fujii A, Uetani T, Nishimura K, Inoue K, Suzuki J, Oka Y, Okura T, Higaki J, Ogimoto A, Ikeda S. Apnea-hypopnea index as a predictor of atrial fibrillation recurrence following initial pulmonary vein isolation: usefulness of type-3 portable monitor for sleep-disordered breathing. *J Interv Card Electrophysiol* 2016;**47**:237–244.
651. Congrete S, Bintvihok M, Thongprayoon C, Bathini T, Boonpheng B, Sharma K, Chokesuwattanaskul R, Srivali N, Tanawuttiwat T, Cheungpasitporn W. Effect of obstructive sleep apnea and its treatment of atrial fibrillation recurrence after radiofrequency catheter ablation: a meta-analysis. *J Evid Based Med* 2018;**11**:145–151.
652. Deng F, Raza A, Guo J. Treating obstructive sleep apnea with continuous positive airway pressure reduces risk of recurrent atrial fibrillation after catheter ablation: a meta-analysis. *Sleep Med* 2018;**46**:5–11.
653. Wokhlu A, Monahan KH, Hodge DO, Asirvatham SJ, Friedman PA, Munger TM, Bradley DJ, Bluhm CM, Haroldson JM, Packer DL. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol* 2010;**55**:2308–2316.
654. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque JP, Kautzner J, Shah D, Michaud G, Wharton M, Harari D, Mahapatra S, Lambert H, Mansour M. Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation* 2015;**132**:907–915.
655. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275–1285.
656. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial. *Am Heart J* 2013;**166**:442–448.
657. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
658. Noseworthy PA, Van Houten HK, Gersh BJ, Packer DL, Friedman PA, Shah ND, Dunlay SM, Siontis KC, Piccini JP, Yao X. Generalizability of the CASTLE-AF trial: catheter ablation for patients with atrial fibrillation and heart failure in routine practice. *Heart Rhythm* 2020;**17**:1057–1065.
659. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, Tilz RR, Piorkowski C, Geller L, Kleemann T, Hindricks G. Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol* 2019;**12**:e007731.
660. Packer DL, Monahan KH, Al-KhalidiHR, Silverstein AP, Poole JP, Bahnson TD, Mark DB, Lee KL. Ablation of Atrial Fibrillation in Heart Failure Patients: Additional outcomes of the CABANATrial. *Heart Rhythm* 2019;16(suppl):S35.

661. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haissaguerre M, Natale A; PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778–1785.
662. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**:740–747.
663. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;**61**:1894–1903.
664. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31–38.
665. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O, Callahan T, Saliba W, Chung MK. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *JACC Clin Electrophysiol* 2015;**1**:200–209.
666. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol* 2017;**70**:1949–1961.
667. Elgendy AY, Mahmoud AN, Khan MS, Sheikh MR, Mojadidi MK, Omer M, Elgendy IY, Bavry AA, Ellenbogen KA, Miles WM, McKillop M. Meta-analysis comparing catheter-guided ablation versus conventional medical therapy for patients with atrial fibrillation and heart failure with reduced ejection fraction. *Am J Cardiol* 2018;**122**:806–813.
668. Briceno DF, Markman TM, Lupercio F, Romero J, Liang JJ, Villablanca PA, Birati EY, Garcia FC, Di Biase L, Natale A, Marchlinski FE, Santangeli P. Catheter ablation versus conventional treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *J Interv Card Electrophysiol* 2018;**53**:19–29.
669. Ma Y, Bai F, Qin F, Li Y, Tu T, Sun C, Zhou S, Liu Q. Catheter ablation for treatment of patients with atrial fibrillation and heart failure: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2018;**18**:165.
670. Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Bachuwa G, Hassan M, Bhatt DL. Catheter ablation of atrial fibrillation with heart failure: an updated meta-analysis of randomized trials. *Int J Cardiol* 2018;**269**:170–173.
671. Khan SU, Rahman H, Talluri S, Kaluski E. The clinical benefits and mortality reduction associated with catheter ablation in subjects with atrial fibrillation: a systematic review and meta-analysis. *JACC Clin Electrophysiol* 2018;**4**:626–635.
672. Martin CA, Lambiase PD. Pathophysiology, diagnosis and treatment of tachycardiomyopathy. *Heart* 2017;**103**:1543–1552.
673. Raymond-Paquin A, Nattel S, Wakili R, Tadros R. Mechanisms and clinical significance of arrhythmia-induced cardiomyopathy. *Can J Cardiol* 2018;**34**:1449–1460.
674. Brembilla-Perrot B, Ferreira JP, Manenti V, Sellal JM, Olivier A, Villemin T, Beurrier D, De Chillou C, Louis P, Brembilla A, Juilliere Y, Girerd N. Predictors and prognostic significance of tachycardiomyopathy: insights from a cohort of 1269 patients undergoing atrial flutter ablation. *Eur J Heart Fail* 2016;**18**:394–401.
675. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011;**17**:964–970.
676. Prabhu S, Costello BT, Taylor AJ, Gutman SJ, Voskoboinik A, McLellan AJA, Peck KY, Sugumar H, Iles L, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Lee G, Mariani J, Kaye DM, Ling LH, Kalman JM, Kistler PM. Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: a substudy of the CAMERA MRI trial. *JACC Clin Electrophysiol* 2018;**4**:999–1007.
677. Tamborero D, Mont L, Berruezo A, Matiello M, Benito B, Sitges M, Vidal B, de Caralt TM, Perea RJ, Vatasescu R, Brugada J. Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ Arrhythm Electrophysiol* 2009;**2**:35–40.
678. Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, Nakagawa H, Zhang B, Stagg RB, Boo LM, Marchlinski FE. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol* 2014;**64**:647–656.
679. McLellan AJ, Ling LH, Azzopardi S, Lee GA, Lee G, Kumar S, Wong MC, Walters TE, Lee JM, Looi KL, Halloran K, Stiles MK, Lever NA, Fynn SP, Heck PM, Sanders P, Morton JB, Kalman JM, Kistler PM. A minimal or maximal ablation strategy to achieve pulmonary vein isolation for paroxysmal atrial fibrillation: a prospective multi-centre randomized controlled trial (the Minimax study). *Eur Heart J* 2015;**36**:1812–1821.
680. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;**372**:1812–1822.
681. Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation: the prospective, randomized, controlled, noninferiority FreezeAF study. *Circulation* 2015;**132**:1311–1319.
682. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, Woollett I, Issa ZF, Natale A, Reddy VY; HeartLight Study Investigators. Pulmonary vein isolation using the visually guided laser balloon: a prospective, multicenter, and randomized comparison to standard radiofrequency ablation. *J Am Coll Cardiol* 2015;**66**:1350–1360.
683. Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T, Breithardt G, Willems S; Gap-AF–AFNET 1 Investigators. Impact of complete versus incomplete circumferential lines around the pulmonary veins during catheter ablation of paroxysmal atrial fibrillation: results from the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003337.
684. Nery PB, Belliveau D, Nair GM, Bernick J, Redpath CJ, Szczotka A, Sadek MM, Green MS, Wells G, Birnie DH. Relationship between pulmonary vein reconnection and atrial fibrillation recurrence: a systematic review and meta-analysis. *JACC Clin Electrophysiol* 2016;**2**:474–483.
685. Bassiouny M, Saliba W, Hussein A, Rickard J, Diab M, Aman W, Dresing T, Tt Callahan, Bhargava M, Martin DO, Shao M, Baranowski B, Tarakji K, Tchou PJ, Hakim A, Kanj M, Lindsay B, Wazni O. Randomized study of persistent atrial fibrillation ablation: ablate in sinus rhythm versus ablate complex-fractionated atrial electrograms in atrial fibrillation. *Circ Arrhythm Electrophysiol* 2016;**9**:e003596.
686. Hindricks G, Sepehri Shamloo A, Lenarczyk R, Kalarus Z, Arya A, Kircher S, Darma A, Dagres N. Catheter ablation of atrial fibrillation: current status, techniques, outcomes and challenges. *Kardiol Pol* 2018;**76**:1680–1686.
687. Nanthakumar K, Plumb VJ, Epstein AE, Veenhuyzen GD, Link D, Kay GN. Resumption of electrical conduction in previously isolated pulmonary veins: rationale for a different strategy?*Circulation* 2004;**109**:1226–1229.
688. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. *Circulation* 2005;**112**:627–635.
689. Ouyang F, Antz M, Ernst S, Hachiya H, Mavrakis H, Deger FT, Schaumann A, Chun J, Falk P, Hennig D, Liu X, Bansch D, Kuck KH. Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. *Circulation* 2005;**111**:127–135.
690. Cheema A, Dong J, Dalal D, Marine JE, Henrikson CA, Spragg D, Cheng A, Nazarian S, Bilchick K, Sinha S, Scherr D, Almasry I, Halperin H, Berger R, Calkins H. Incidence and time course of early recovery of pulmonary vein conduction after catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:387–391.
691. Pratola C, Baldo E, Notarstefano P, Toselli T, Ferrari R. Radiofrequency ablation of atrial fibrillation: is the persistence of all intraprocedural targets necessary for long-term maintenance of sinus rhythm?*Circulation* 2008;**117**:136–143.
692. Rajappan K, Kistler PM, Earley MJ, Thomas G, Izquierdo M, Sporton SC, Schilling RJ. Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: a prospective characterization of anatomical sites. *Pacing Clin Electrophysiol* 2008;**31**:1598–1605.
693. Bansch D, Bittkau J, Schneider R, Schneider C, Wendig I, Akin I, Nienaber CA. Circumferential pulmonary vein isolation: wait or stop early after initial successful pulmonary vein isolation?*Europace* 2013;**15**:183–188.

694. Nakamura K, Naito S, Kaseno K, Tsukada N, Sasaki T, Hayano M, Nishiuchi S, Fuke E, Miki Y, Sakamoto T, Nakamura K, Kumagai K, Kataoka A, Takaoka H, Kobayashi Y, Funabashi N, Oshima S. Optimal observation time after completion of circumferential pulmonary vein isolation for atrial fibrillation to prevent chronic pulmonary vein reconnections. *Int J Cardiol* 2013;**168**:5300–5310.
695. Neuzil P, Reddy VY, Kautzner J, Petru J, Wichterle D, Shah D, Lambert H, Yulzari A, Wissner E, Kuck KH. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study. *Circ Arrhythm Electrophysiol* 2013;**6**:327–333.
696. Jiang RH, Po SS, Tung R, Liu Q, Sheng X, Zhang ZW, Sun YX, Yu L, Zhang P, Fu GS, Jiang CY. Incidence of pulmonary vein conduction recovery in patients without clinical recurrence after ablation of paroxysmal atrial fibrillation: mechanistic implications. *Heart Rhythm* 2014;**11**:969–976.
697. Kim TH, Park J, Uhm JS, Joung B, Lee MH, Pak HN. Pulmonary vein reconnection predicts good clinical outcome after second catheter ablation for atrial fibrillation. *Europace* 2017;**19**:961–967.
698. Bordignon S, Furnkranz A, Perrotta L, Dugo D, Konstantinou A, Nowak B, Schulte-Hahn B, Schmidt B, Chun KR. High rate of durable pulmonary vein isolation after second-generation cryoballoon ablation: analysis of repeat procedures. *Europace* 2015;**17**:725–731.
699. Ullah W, McLean A, Tayebjee MH, Gupta D, Ginks MR, Haywood GA, O'Neill M, Lambiase PD, Earley MJ, Schilling RJ, Group UKMT. Randomized trial comparing pulmonary vein isolation using the SmartTouch catheter with or without real-time contact force data. *Heart Rhythm* 2016;**13**:1761–1767.
700. Phlips T, Taghji P, El Haddad M, Wolf M, Knecht S, Vandekerckhove Y, Tavernier R, Duytschaever M. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace* 2018;**20**:f419–f427.
701. Shah D, Haissaguerre M, Jais P, Hocini M. Nonpulmonary vein foci: do they exist?*Pacing Clin Electrophysiol* 2003;**26**:1631–1635.
702. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol* 2004;**43**:2044–2053.
703. Haissaguerre M, Sanders P, Hocini M, Takahashi Y, Rotter M, Sacher F, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P. Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J Cardiovasc Electrophysiol* 2005;**16**:1125–1137.
704. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y, Rostock T, Hsu LF, Bordachar P, Reuter S, Roudaut R, Clementy J, Jais P. Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol* 2005;**16**:1138–1147.
705. Jaïs P, O'Neill MD, Takahashi Y, Jönsson A, Hocini M, Sacher F, Sanders P, Kodali S, Rostock T, Rotter M, Clémenty J, Haïssaguerre M. Stepwise catheter ablation of chronic atrial fibrillation:importance of discrete anatomic sites for termination. *J Cardiovasc Electrophysiol* 2006;**17**:S28–S36.
706. Atienza F, Almendral J, Jalife J, Zlochiver S, Ploutz-Snyder R, Torrecilla EG, Arenal A, Kalifa J, Fernandez-Aviles F, Berenfeld O. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. *Heart Rhythm* 2009;**6**:33–40.
707. Stavrakis S, Nakagawa H, Po SS, Scherlag BJ, Lazzara R, Jackman WM. The role of the autonomic ganglia in atrial fibrillation. *JACC Clin Electrophysiol* 2015;**1**:1–13.
708. Di Biase L, Burkhardt JD, Mohanty P, Mohanty S, Sanchez JE, Trivedi C, Gunes M, Gokoglan Y, Gianni C, Horton RP, Themistoclakis S, Gallinghouse GJ, Bailey S, Zagrodzky JD, Hongo RH, Beheiry S, Santangeli P, Casella M, Dello Russo A, Al-Ahmad A, Hranitzky P, Lakkireddy D, Tondo C, Natale A. Left atrial appendage isolation in patients with longstanding persistent af undergoing catheter ablation: BELIEF trial. *J Am Coll Cardiol* 2016;**68**:1929–1940.
709. Gianni C, Mohanty S, Di Biase L, Metz T, Trivedi C, Gokoglan Y, Gunes MF, Bai R, Al-Ahmad A, Burkhardt JD, Gallinghouse GJ, Horton RP, Hranitzky PM, Sanchez JE, Halbfass P, Muller P, Schade A, Deneke T, Tomassoni GF, Natale A. Acute and early outcomes of focal impulse and rotor modulation (FIRM)-guided rotors-only ablation in patients with nonparoxysmal atrial fibrillation. *Heart Rhythm* 2016;**13**:830–835.
710. Santangeli P, Zado ES, Hutchinson MD, Riley MP, Lin D, Frankel DS, Supple GE, Garcia FC, Dixit S, Callans DJ, Marchlinski FE. Prevalence and distribution of focal triggers in persistent and long-standing persistent atrial fibrillation. *Heart Rhythm* 2016;**13**:374–382.
711. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol* 2013;**62**:2318–2325.
712. Arbelo E, Guiu E, Ramos P, Bisbal F, Borras R, Andreu D, Tolosana JM, Berruezo A, Brugada J, Mont L. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc* 2014;**3**:e000877.
713. Da Costa A, Levallois M, Romeyer-Bouchard C, Bisch L, Gate-Martinet A, Isaaz K. Remote-controlled magnetic pulmonary vein isolation combined with superior vena cava isolation for paroxysmal atrial fibrillation: a prospective randomized study. *Arch Cardiovasc Dis* 2015;**108**:163–171.
714. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol* 2015;**8**:1316–1324.
715. Vogler J, Willems S, Sultan A, Schreiber D, Luker J, Servatius H, Schaffer B, Moser J, Hoffmann BA, Steven D. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. *J Am Coll Cardiol* 2015;**66**:2743–2752.
716. Faustino M, Pizzi C, Agricola T, Xhyheri B, Costa GM, Flacco ME, Capasso L, Cicolini G, Di Girolamo E, Leonzio L, Manzoli L. Stepwise ablation approach versus pulmonary vein isolation in patients with paroxysmal atrial fibrillation: randomized controlled trial. *Heart Rhythm* 2015;**12**:1907–1915.
717. Scott PA, Silberbauer J, Murgatroyd FD. The impact of adjunctive complex fractionated atrial electrogram ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. *Europace* 2016;**18**:359–367.
718. Driessen AHG, Berger WR, Krul SPJ, van den Berg NWE, Neefs J, Piersma FR, Chan Pin Yin D, de Jong J, van Boven WP, de Groot JR. Ganglion plexus ablation in advanced atrial fibrillation: the AFACT study. *J Am Coll Cardiol* 2016;**68**:1155–1165.
719. Qin M, Liu X, Wu SH, Zhang XD. Atrial substrate modification in atrial fibrillation: targeting GP or CFAE? Evidence from meta-analysis of clinical trials. *PLoS One* 2016;**11**:e0164989.
720. Hu X, Jiang J, Ma Y, Tang A. Is there still a role for additional linear ablation in addition to pulmonary vein isolation in patients with paroxysmal atrial fibrillation? An updated meta-analysis of randomized controlled trials. *Int J Cardiol* 2016;**209**:266–274.
721. Wynn GJ, Panikker S, Morgan M, Hall M, Waktare J, Markides V, Hussain W, Salukhe T, Modi S, Jarman J, Jones DG, Snowdon R, Todd D, Wong T, Gupta D. Biatrial linear ablation in sustained nonpermanent AF: results of the substrate modification with ablation and antiarrhythmic drugs in nonpermanent atrial fibrillation (SMAN-PAF) trial. *Heart Rhythm* 2016;**13**:399–406.
722. Zhang Z, Letsas KP, Zhang N, Efremidis M, Xu G, Li G, Liu T. Linear ablation following pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. *Pacing Clin Electrophysiol* 2016;**39**:623–630.
723. Fink T, Schluter M, Heeger CH, Lemes C, Maurer T, Reissmann B, Riedl J, Rottner L, Santoro F, Schmidt B, Wohlmuth P, Mathew S, Sohns C, Ouyang F, Metzner A, Kuck KH. Stand-alone pulmonary vein isolation versus pulmonary vein isolation with additional substrate modification as index ablation procedures in patients with persistent and long-standing persistent atrial fibrillation: the randomized Alster-Lost-AF trial (Ablation at St. Georg Hospital for long-standing persistent atrial fibrillation). *Circ Arrhythm Electrophysiol* 2017;**10**.
724. Kim TH, Uhm JS, Kim JY, Joung B, Lee MH, Pak HN. Does additional electrogram-guided ablation after linear ablation reduce recurrence after catheter ablation for longstanding persistent atrial fibrillation? A prospective randomized study. *J Am Heart Assoc* 2017;**6**:e004811.
725. Kircher S, Arya A, Altmann D, Rolf S, Bollmann A, Sommer P, Dagres N, Richter S, Breithardt OA, Dinov B, Husser D, Eitel C, Gaspar T, Piorkowski C, Hindricks G. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation: a randomized study. *Europace* 2018;**20**:1766–1775.
726. Ammar-Busch S, Bourier F, Reents T, Semmler V, Telishevska M, Kathan S, Hofmann M, Hessling G, Deisenhofer I. Ablation of complex fractionated electrograms with or without ADditional LINEar Lesions for Persistent Atrial Fibrillation (the ADLINE trial). *J Cardiovasc Electrophysiol* 2017;**28**:636–641.
727. Blandino A, Bianchi F, Grossi S, Biondi-Zoccai G, Conte MR, Gaido L, Gaita F, Scaglione M, Rametta F. Left atrial substrate modification targeting low-voltage areas for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Pacing Clin Electrophysiol* 2017;**40**:199–212.
728. Yang B, Jiang C, Lin Y, Yang G, Chu H, Cai H, Lu F, Zhan X, Xu J, Wang X, Ching CK, Singh B, Kim YH, Chen M; STABLE-SR Investigators. STABLE-SR (Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm) for the treatment of nonparoxysmal atrial fibrillation: a prospective, multicenter randomized clinical trial. *Circ Arrhythm Electrophysiol* 2017;**10**:pii: e005405.
729. Yu HT, Shim J, Park J, Kim IS, Kim TH, Uhm JS, Joung B, Lee MH, Kim YH, Pak HN. Pulmonary vein isolation alone versus additional linear ablation in patients with persistent atrial fibrillation converted to paroxysmal type with

antiarrhythmic drug therapy: a multicenter, prospective, randomized study. *Circ Arrhythm Electrophysiol* 2017;**10**:pii: e004915.
730. Wang YL, Liu X, Zhang Y, Jiang WF, Zhou L, Qin M, Zhang DL, Zhang XD, Wu SH, Xu K. Optimal endpoint for catheter ablation of longstanding persistent atrial fibrillation: a randomized clinical trial. *Pacing Clin Electrophysiol* 2018;**41**:172–178.
731. Perez FJ, Schubert CM, Parvez B, Pathak V, Ellenbogen KA, Wood MA. Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: a meta-analysis. *Circ Arrhythm Electrophysiol* 2009;**2**:393–401.
732. Natale A, Newby KH, Pisano E, Leonelli F, Fanelli R, Potenza D, Beheiry S, Tomassoni G. Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. *J Am Coll Cardiol* 2000;**35**:1898–1904.
733. Wazni O, Marrouche NF, Martin DO, Gillinov AM, Saliba W, Saad E, Klein A, Bhargava M, Bash D, Schweikert R, Erciyes D, Abdul-Karim A, Brachman J, Gunther J, Pisano E, Potenza D, Fanelli R, Natale A. Randomized study comparing combined pulmonary vein-left atrial junction disconnection and cavotricuspid isthmus ablation versus pulmonary vein-left atrial junction disconnection alone in patients presenting with typical atrial flutter and atrial fibrillation. *Circulation* 2003;**108**:2479–2483.
734. Shah DC, Sunthorn H, Burri H, Gentil-Baron P. Evaluation of an individualized strategy of cavotricuspid isthmus ablation as an adjunct to atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2007;**18**:926–930.
735. Neumann T, Kuniss M, Conradi G, Janin S, Berkowitsch A, Wojcik M, Rixe J, Erkapic D, Zaltsberg S, Rolf A, Bachmann G, Dill T, Hamm CW, Pitschner HF. MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. *Europace* 2011;**13**:37–44.
736. Herrera Siklody C, Deneke T, Hocini M, Lehrmann H, Shin DI, Miyazaki S, Henschke S, Fluegel P, Schiebeling-Romer J, Bansmann PM, Bourdias T, Dousset V, Haissaguerre M, Arentz T. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. *J Am Coll Cardiol* 2011;**58**:681–688.
737. Herrera Siklody C, Arentz T, Minners J, Jesel L, Stratz C, Valina CM, Weber R, Kalusche D, Toti F, Morel O, Trenk D. Cellular damage, platelet activation, and inflammatory response after pulmonary vein isolation: a randomized study comparing radiofrequency ablation with cryoablation. *Heart Rhythm* 2012;**9**:189–196.
738. Pokushalov E, Romanov A, Artyomenko S, Baranova V, Losik D, Bairamova S, Karaskov A, Mittal S, Steinberg JS. Cryoballoon versus radiofrequency for pulmonary vein re-isolation after a failed initial ablation procedure in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;**24**:274–279.
739. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck KH, Kuniss M, Lewalter T, Spitzer S, Willems S, Senges J, Junger C, Hoffmann E. Cryoballoon versus RF ablation in paroxysmal atrial fibrillation: results from the German Ablation Registry. *J Cardiovasc Electrophysiol* 2014;**25**:1–7.
740. Perez-Castellano N, Fernandez-Cavazos R, Moreno J, Canadas V, Conde A, Gonzalez-Ferrer JJ, Macaya C, Perez-Villacastin J. The COR trial: a randomized study with continuous rhythm monitoring to compare the efficacy of cryoenergy and radiofrequency for pulmonary vein isolation. *Heart Rhythm* 2014;**11**:8–14.
741. Hunter RJ, Baker V, Finlay MC, Duncan ER, Lovell MJ, Tayebjee MH, Ullah W, Siddiqui MS, Mc LA, Richmond L, Kirkby C, Ginks MR, Dhinoja M, Sporton S, Earley MJ, Schilling RJ. Point-by-point radiofrequency ablation versus the cryoballoon or a novel combined approach: a randomized trial comparing 3 methods of pulmonary vein isolation for paroxysmal atrial fibrillation (the Cryo Versus RF trial). *J Cardiovasc Electrophysiol* 2015;**26**:1307–1314.
742. Squara F, Zhao A, Marijon E, Latcu DG, Providencia R, Di Giovanni G, Jauvert G, Jourda F, Chierchia GB, De Asmundis C, Ciconte G, Alonso C, Grimard C, Boveda S, Cauchemez B, Saoudi N, Brugada P, Albenque JP, Thomas O. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. *Europace* 2015;**17**:718–724.
743. Straube F, Dorwarth U, Ammar-Busch S, Peter T, Noelker G, Massa T, Kuniss M, Ewertsen NC, Chun KR, Tebbenjohanns J, Tilz R, Kuck KH, Ouarrak T, Senges J, Hoffmann E; Freeze Cohort Investigators. First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation. *Europace* 2016;**18**:368–375.
744. Schmidt M, Dorwarth U, Andresen D, Brachmann J, Kuck K, Kuniss M, Willems S, Deneke T, Tebbenjohanns J, Gerds-Li JH, Spitzer S, Senges J, Hochadel M, Hoffmann E. German ablation registry: cryoballoon vs. radiofrequency ablation in paroxysmal atrial fibrillation – one-year outcome data. *Heart Rhythm* 2016;**13**:836–844.
745. Boveda S, Providencia R, Defaye P, Pavin D, Cebron JP, Anselme F, Halimi F, Khoueiry Z, Combes N, Combes S, Jacob S, Albenque JP, Sousa P. Outcomes after cryoballoon or radiofrequency ablation for persistent atrial fibrillation: a multicentric propensity-score matched study. *J Interv Card Electrophysiol* 2016;**47**:133–142.
746. Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M, Elvan A, Lim HW, Kueffer FJ, Arentz T, Albenque JP, Tondo C, Kuhne M, Sticherling C, Brugada J; FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J* 2016;**37**:2858–2865.
747. Buist TJ, Adiyaman A, Smit JJJ, Ramdat Misier AR, Elvan A. Arrhythmia-free survival and pulmonary vein reconnection patterns after second-generation cryoballoon and contact-force radiofrequency pulmonary vein isolation. *Clin Res Cardiol* 2018;**107**:498–506.
748. Gunawardene MA, Hoffmann BA, Schaeffer B, Chung DU, Moser J, Akbulak RO, Jularic M, Eickholt C, Nuehrich J, Meyer C, Willems S. Influence of energy source on early atrial fibrillation recurrences: a comparison of cryoballoon vs. radiofrequency current energy ablation with the endpoint of unexcitability in pulmonary vein isolation. *Europace* 2018;**20**:43–49.
749. Mortsell D, Arbelo E, Dagres N, Brugada J, Laroche C, Trines SA, Malmborg H, Hoglund N, Tavazzi L, Pokushalov E, Stabile G, Blomstrom-Lundqvist C; ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry Investigators. Cryoballoon vs. radiofrequency ablation for atrial fibrillation: a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish catheter ablation registry. *Europace* 2019;**21**:581–589.
750. Akkaya E, Berkowitsch A, Zaltsberg S, Greiss H, Hamm CW, Sperzel J, Neumann T, Kuniss M. Ice or fire? Comparison of second-generation cryoballoon ablation and radiofrequency ablation in patients with symptomatic persistent atrial fibrillation and an enlarged left atrium. *J Cardiovasc Electrophysiol* 2018;**29**:375–384.
751. Murray MI, Arnold A, Younis M, Varghese S, Zeiher AM. Cryoballoon versus radiofrequency ablation for paroxysmal atrial fibrillation: a meta-analysis of randomized controlled trials. *Clin Res Cardiol* 2018;**107**:658–669.
752. Chen CF, Gao XF, Duan X, Chen B, Liu XH, Xu YZ. Comparison of catheter ablation for paroxysmal atrial fibrillation between cryoballoon and radiofrequency: a meta-analysis. *J Interv Card Electrophysiol* 2017;**48**:351–366.
753. Buiatti A, von Olshausen G, Barthel P, Schneider S, Luik A, Kaess B, Laugwitz KL, Hoppmann P. Cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: an updated meta-analysis of randomized and observational studies. *Europace* 2017;**19**:378–384.
754. Cardoso R, Mendirichaga R, Fernandes G, Healy C, Lambrakos LK, Viles-Gonzalez JF, Goldberger JJ, Mitrani RD. Cryoballoon versus radiofrequency catheter ablation in atrial fibrillation: a meta-analysis. *J Cardiovasc Electrophysiol* 2016;**27**:1151–1159.
755. Kabunga P, Phan K, Ha H, Sy RW. Meta-analysis of contemporary atrial fibrillation ablation strategies: irrigated radiofrequency versus duty-cycled phased radiofrequency versus cryoballoon ablation. *JACC Clin Electrophysiol* 2016;**2**:377–390.
756. Bollmann A, Ueberham L, Schuler E, Wiedemann M, Reithmann C, Sause A, Tebbenjohanns J, Schade A, Shin DI, Staudt A, Zacharzowsky U, Ulbrich M, Wetzel U, Neuser H, Bode K, Kuhlen R, Hindricks G. Cardiac tamponade in catheter ablation of atrial fibrillation: German-wide analysis of 21 141 procedures in the Helios atrial fibrillation ablation registry (SAFER). *Europace* 2018;**20**:1944–1951.
757. Ueberham L, Schuler E, Hindricks G, Kuhlen R, Bollmann A. SAFER. *Eur Heart J* 2018;**39**:2023–2024.
758. Hummel J, Michaud G, Hoyt R, DeLurgio D, Rasekh A, Kusumoto F, Giudici M, Dan D, Tschopp D, Calkins H, Boersma L; TTOP-AF Investigators. Phased RF ablation in persistent atrial fibrillation. *Heart Rhythm* 2014;**11**:202–209.
759. Boersma LV, van der Voort P, Debruyne P, Dekker L, Simmers T, Rossenbacker T, Balt J, Wijffels M, Degreef Y. Multielectrode pulmonary vein isolation versus single tip wide area catheter ablation for paroxysmal atrial fibrillation: a multinational multicenter randomized clinical trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003151.
760. Nagashima K, Okumura Y, Watanabe I, Nakahara S, Hori Y, Iso K, Watanabe R, Arai M, Wakamatsu Y, Kurokawa S, Mano H, Nakai T, Ohkubo K, Hirayama A. Hot balloon versus cryoballoon ablation for atrial fibrillation: lesion characteristics and middle-term outcomes. *Circ Arrhythm Electrophysiol* 2018;**11**:e005861.
761. Ucer E, Janeczko Y, Seegers J, Fredersdorf S, Friemel S, Poschenrieder F, Maier LS, Jungbauer CG. A RAndomized Trial to compare the acute reconnection after pulmonary vein ISolation with Laser-BalloON versus radiofrequency Ablation: RATISBONA trial. *J Cardiovasc Electrophysiol* 2018;**29**:733–739.
762. De Greef Y, Stroker E, Schwagten B, Kupics K, De Cocker J, Chierchia GB, de Asmundis C, Stockman D, Buysschaert I. Complications of pulmonary vein isolation in atrial fibrillation: predictors and comparison between four different ablation techniques: results from the Middelheim PVI-registry. *Europace* 2018;**20**:1279–1286.

763. Steinbeck G, Sinner MF, Lutz M, Muller-Nurasyid M, Kaab S, Reinecke H. Incidence of complications related to catheter ablation of atrial fibrillation and atrial flutter: a nationwide in-hospital analysis of administrative data for Germany in 2014. *Eur Heart J* 2018;**39**:4020–4029.
764. Fink T, Metzner A, Willems S, Eckardt L, Ince H, Brachmann J, Spitzer SG, Deneke T, Schmitt C, Hochadel M, Senges J, Rillig A. Procedural success, safety and patients satisfaction after second ablation of atrial fibrillation in the elderly: results from the German ablation registry. *Clin Res Cardiol* 2019;**108**:1354–1363.
765. Szegedi N, Szeplaki G, Herczeg S, Tahin T, Sallo Z, Nagy VK, Osztheimer I, Ozcan EE, Merkely B, Geller L. Repeat procedure is a new independent predictor of complications of atrial fibrillation ablation. *Europace* 2019;**21**:732–737.
766. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:32–38.
767. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C, Rosso R, Teh A, Halloran K, Kalman JM. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. *J Cardiovasc Electrophysiol* 2011;**22**:163–168.
768. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K, Grover P, Singh V, Vallurupalli S, Savani GT, Badheka A, Tuliani T, Dabhadkar K, Dibu G, Reddy YM, Sewani A, Kowalski M, Mitrani R, Paydak H, Viles-Gonzalez JF. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation* 2013;**128**:2104–2112.
769. Tripathi B, Arora S, Kumar V, Abdelrahman M, Lahewala S, Dave M, Shah M, Tan B, Savani S, Badheka A, Gopalan R, Shantha GPS, Viles-Gonzalez J, Deshmukh A. Temporal trends of in-hospital complications associated with catheter ablation of atrial fibrillation in the United States: an update from Nationwide Inpatient Sample database (2011–2014). *J Cardiovasc Electrophysiol* 2018;**29**:715–724.
770. Voskoboinik A, Sparks PB, Morton JB, Lee G, Joseph SA, Hawson JJ, Kistler PM, Kalman JM. Low rates of major complications for radiofrequency ablation of atrial fibrillation maintained over 14 years: a single centre experience of 2750 consecutive cases. *Heart Lung Circ* 2018;**27**:976–983.
771. Berger WR, Meulendijks ER, Limpens J, van den Berg NWE, Neefs J, Driessen AHG, Krul SPJ, van Boven WJP, de Groot JR. Persistent atrial fibrillation: a systematic review and meta-analysis of invasive strategies. *Int J Cardiol* 2019;**278**:137–143.
772. Shah AN, Mittal S, Sichrovsky TC, Cotiga D, Arshad A, Maleki K, Pierce WJ, Steinberg JS. Long-term outcome following successful pulmonary vein isolation: pattern and prediction of very late recurrence. *J Cardiovasc Electrophysiol* 2008;**19**:661–667.
773. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. *Am J Cardiol* 2009;**104**:366–372.
774. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Kokturk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation* 2010;**122**:2368–2377.
775. Bertaglia E, Tondo C, De Simone A, Zoppo F, Mantica M, Turco P, Iuliano A, Forleo G, La Rocca V, Stabile G. Does catheter ablation cure atrial fibrillation? Single-procedure outcome of drug-refractory atrial fibrillation ablation: a 6-year multicentre experience. *Europace* 2010;**12**:181–187.
776. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up?*J Am Coll Cardiol* 2011;**57**:160–166.
777. Medi C, Sparks PB, Morton JB, Kistler PM, Halloran K, Rosso R, Vohra JK, Kumar S, Kalman JM. Pulmonary vein antral isolation for paroxysmal atrial fibrillation: results from long-term follow-up. *J Cardiovasc Electrophysiol* 2011;**22**:137–141.
778. Schreiber D, Rostock T, Frohlich M, Sultan A, Servatius H, Hoffmann BA, Luker J, Berner I, Schaffer B, Wegscheider K, Lezius S, Willems S, Steven D. Five-year follow-up after catheter ablation of persistent atrial fibrillation using the stepwise approach and prognostic factors for success. *Circ Arrhythm Electrophysiol* 2015;**8**:308–317.
779. Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K, Komatsu Y, Roten L, Jadidi A, Linton N, Pedersen M, Daly M, O'Neill M, Knecht S, Weerasooriya R, Rostock T, Manninger M, Cochet H, Shah AJ, Yeim S, Denis A, Derval N, Hocini M, Sacher F, Haissaguerre M, Jais P. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol* 2015;**8**:18–24.
780. Bertaglia E, Senatore G, De Michieli L, De Simone A, Amellone C, Ferretto S, La Rocca V, Giuggia M, Corrado D, Zoppo F, Stabile G. Twelve-year follow-up of catheter ablation for atrial fibrillation: a prospective, multicenter, randomized study. *Heart Rhythm* 2017;**14**:486–492.
781. Skelly A, Hashimoto R, Al-Khatib S, et alet al*Catheter Ablation for Treatment of Atrial Fibrillation* [Internet]. Rockville, MD: Agency for Healthcare Research and Quality (US). Available from https://www.ncbi.nlm.nih.gov/books/NBK305763/ (accessed 20 April 2015).
782. Zheng YR, Chen ZY, Ye LF, Wang LH. Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials. *J Geriatr Cardiol* 2015;**12**:507–514.
783. Reynolds MR, Walczak J, White SA, Cohen DJ, Wilber DJ. Improvements in symptoms and quality of life in patients with paroxysmal atrial fibrillation treated with radiofrequency catheter ablation versus antiarrhythmic drugs. *Circ Cardiovasc Qual Outcomes* 2010;**3**:615–623.
784. Walfridsson H, Walfridsson U, Nielsen JC, Johannessen A, Raatikainen P, Janzon M, Levin LA, Aronsson M, Hindricks G, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation: results on health-related quality of life and symptom burden. The MANTRA-PAF trial. *Europace* 2015;**17**:215–221.
785. De Greef Y, Schwagten B, Chierchia GB, de Asmundis C, Stockman D, Buysschaert I. Diagnosis-to-ablation time as a predictor of success: early choice for pulmonary vein isolation and long-term outcome in atrial fibrillation: results from the Middelheim-PVI registry. *Europace* 2018;**20**:589–595.
786. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, Leong DP, Lau DH, Middeldorp ME, Roberts-Thomson KC, Wittert GA, Abhayaratna WP, Worthley SG, Sanders P. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol* 2011;**57**:1745–1751.
787. Kang JH, Lee DI, Kim S, Kim MN, Park YM, Ban JE, Choi JI, Lim HE, Park SW, Kim YH. Prediction of long-term outcomes of catheter ablation of persistent atrial fibrillation by parameters of preablation DC cardioversion. *J Cardiovasc Electrophysiol* 2012;**23**:1165–1170.
788. Mahajan R, Lau DH, Brooks AG, Shipp NJ, Manavis J, Wood JPM, Finnie JW, Samuel CS, Royce SG, Twomey DJ, Thanigaimani S, Kalman JM, Sanders P. Electrophysiological, electroanatomical, and structural remodeling of the atria as consequences of sustained obesity. *J Am Coll Cardiol* 2015;**66**:1–11.
789. Winkle RA, Mead RH, Engel G, Kong MH, Fleming W, Salcedo J, Patrawala RA. Impact of obesity on atrial fibrillation ablation: patient characteristics, long-term outcomes, and complications. *Heart Rhythm* 2017;**14**:819–827.
790. De Maat GE, Mulder B, Berretty WL, Al-Jazairi MIH, Tan YES, Wiesfeld ACP, Mariani MA, Van Gelder IC, Rienstra M, Blaauw Y. Obesity is associated with impaired long-term success of pulmonary vein isolation: a plea for risk factor management before ablation. *Open Heart* 2018;**5**:e000771.
791. Glover BM, Hong KL, Dagres N, Arbelo E, Laroche C, Riahi S, Bertini M, Mikhaylov EN, Galvin J, Kiliszek M, Pokushalov E, Kautzner J, Calvo N, Blomstrom-Lundqvist C, Brugada J; ESC-EHRA Atrial Fibrillation Ablation Long-Term Registry Investigators. Impact of body mass index on the outcome of catheter ablation of atrial fibrillation. *Heart* 2019;**105**:244–250.
792. Chang SL, Tuan TC, Tai CT, Lin YJ, Lo LW, Hu YF, Tsao HM, Chang CJ, Tsai WC, Chen SA. Comparison of outcome in catheter ablation of atrial fibrillation in patients with versus without the metabolic syndrome. *Am J Cardiol* 2009;**103**:67–72.
793. Tang RB, Dong JZ, Liu XP, Long DY, Yu RH, Kalifa J, Ma CS. Metabolic syndrome and risk of recurrence of atrial fibrillation after catheter ablation. *Circ J* 2009;**73**:438–443.
794. Mohanty S, Mohanty P, Di Biase L, Bai R, Pump A, Santangeli P, Burkhardt D, Gallinghouse JG, Horton R, Sanchez JE, Bailey S, Zagrodzky J, Natale A. Impact of metabolic syndrome on procedural outcomes in patients with atrial fibrillation undergoing catheter ablation. *J Am Coll Cardiol* 2012;**59**:1295–1301.
795. Mulder AA, Wijffels MC, Wever EF, Kelder JC, Boersma LV. Arrhythmia detection after atrial fibrillation ablation: value of incremental monitoring time. *Pacing Clin Electrophysiol* 2012;**35**:164–169.
796. Steven D, Rostock T, Lutomsky B, Klemm H, Servatius H, Drewitz I, Friedrichs K, Ventura R, Meinertz T, Willems S. What is the real atrial fibrillation burden after catheter ablation of atrial fibrillation? A prospective rhythm analysis in pacemaker patients with continuous atrial monitoring. *Eur Heart J* 2008;**29**:1037–1042.
797. Kaitani K, Inoue K, Kobori A, Nakazawa Y, Ozawa T, Kurotobi T, Morishima I, Miura F, Watanabe T, Masuda M, Naito M, Fujimoto H, Nishida T, Furukawa Y, Shirayama T, Tanaka M, Okajima K, Yao T, Egami Y, Satomi K, Noda T, Miyamoto K, Haruna T, Kawaji T, Yoshizawa T, Toyota T, Yahata M, Nakai K, Sugiyama H, Higashi Y, Ito M, Horie M, Kusano KF, Shimizu W, Kamakura S, Morimoto T, Kimura T, Shizuta S; EAST-AF Trial Investigators. Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation (EAST-AF) trial. *Eur Heart J* 2016;**37**:610–618.

798. Willems S, Khairy P, Andrade JG, Hoffmann BA, Levesque S, Verma A, Weerasooriya R, Novak P, Arentz T, Deisenhofer I, Rostock T, Steven D, Rivard L, Guerra PG, Dyrda K, Mondesert B, Dubuc M, Thibault B, Talajic M, Roy D, Nattel S, Macle L, ADVICE Trial Investigators. Redefining the blanking period after catheter ablation for paroxysmal atrial fibrillation: insights from the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e003909.
799. Klemm HU, Ventura R, Rostock T, Brandstrup B, Risius T, Meinertz T, Willems S. Correlation of symptoms to ECG diagnosis following atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2006;**17**:146–150.
800. Vasamreddy CR, Dalal D, Dong J, Cheng A, Spragg D, Lamiy SZ, Meininger G, Henrikson CA, Marine JE, Berger R, Calkins H. Symptomatic and asymptomatic atrial fibrillation in patients undergoing radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2006;**17**:134–139.
801. Oral H, Veerareddy S, Good E, Hall B, Cheung P, Tamirisa K, Han J, Fortino J, Chugh A, Bogun F, Pelosi F Jr, Morady F. Prevalence of asymptomatic recurrences of atrial fibrillation after successful radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2004;**15**:920–924.
802. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005;**112**:307–313.
803. Senatore G, Stabile G, Bertaglia E, Donnici G, De Simone A, Zoppo F, Turco P, Pascotto P, Fazzari M. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2005;**45**:873–876.
804. Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Russo AM, Hutchinson MD, Cooper J, Verdino R, Patel V, Joy PS, Gerstenfeld EP. Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study). *Circulation* 2009;**120**:1036–1040.
805. Duytschaever M, Demolder A, Phlips T, Sarkozy A, El Haddad M, Taghji P, Knecht S, Tavernier R, Vandekerckhove Y, De Potter T. PulmOnary vein isolation With vs. without continued antiarrhythmic Drug trEatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. *Eur Heart J* 2018;**39**:1429–1437.
806. Mardigyan V, Verma A, Birnie D, Guerra P, Redfearn D, Becker G, Champagne J, Sapp J, Gula L, Parkash R, Macle L, Crystal E, O'Hara G, Khaykin Y, Sturmer M, Veenhuyzen GD, Greiss I, Sarrazin JF, Mangat I, Novak P, Skanes A, Roux JF, Chauhan V, Hadjis T, Morillo CA, Essebag V. Anticoagulation management pre- and post atrial fibrillation ablation: a survey of Canadian centres. *Can J Cardiol* 2013;**29**:219–223.
807. Nakahara S, Hori Y, Kobayashi S, Sakai Y, Taguchi I, Takayanagi K, Nagashima K, Sonoda K, Kogawa R, Sasaki N, Watanabe I, Okumura Y. Epicardial adipose tissue-based defragmentation approach to persistent atrial fibrillation: its impact on complex fractionated electrograms and ablation outcome. *Heart Rhythm* 2014;**11**:1343–1351.
808. Chao TF, Hung CL, Tsao HM, Lin YJ, Yun CH, Lai YH, Chang SL, Lo LW, Hu YF, Tuan TC, Chang HY, Kuo JY, Yeh HI, Wu TJ, Hsieh MH, Yu WC, Chen SA. Epicardial adipose tissue thickness and ablation outcome of atrial fibrillation. *PLoS One* 2013;**8**:e74926.
809. Masuda M, Mizuno H, Enchi Y, Minamiguchi H, Konishi S, Ohtani T, Yamaguchi O, Okuyama Y, Nanto S, Sakata Y. Abundant epicardial adipose tissue surrounding the left atrium predicts early rather than late recurrence of atrial fibrillation after catheter ablation. *J Interv Card Electrophysiol* 2015;**44**:31–37.
810. Sepehri Shamloo A, Dagres N, Dinov B, Sommer P, Husser-Bollmann D, Bollmann A, Hindricks G, Arya A. Is epicardial fat tissue associated with atrial fibrillation recurrence after ablation? A systematic review and meta-analysis. *Int J Cardiol Heart Vasc* 2019;**22**:132–138.
811. Blanche C, Tran N, Rigamonti F, Burri H, Zimmermann M. Value of P-wave signal averaging to predict atrial fibrillation recurrences after pulmonary vein isolation. *Europace* 2013;**15**:198–204.
812. Bhargava M, Di Biase L, Mohanty P, Prasad S, Martin DO, Williams-Andrews M, Wazni OM, Burkhardt JD, Cummings JE, Khaykin Y, Verma A, Hao S, Beheiry S, Hongo R, Rossillo A, Raviele A, Bonso A, Themistoclakis S, Stewart K, Saliba WI, Schweikert RA, Natale A. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. *Heart Rhythm* 2009;**6**:1403–1412.
813. Winkle RA, Mead RH, Engel G, Patrawala RA. Long-term results of atrial fibrillation ablation: the importance of all initial ablation failures undergoing a repeat ablation. *Am Heart J* 2011;**162**:193–200.
814. Mohanty S, Mohanty P, DIB L, Bai R, Trivedi C, Santangeli P, Santoro F, Hongo R, Hao S, Beheiry S, Burkhardt D, Gallinghouse JG, Horton R, Sanchez JE, Bailey S, Hranitzky PM, Zagrodzky J, Natale A. Long-term outcome of catheter ablation in atrial fibrillation patients with coexistent metabolic syndrome and obstructive sleep apnea: impact of repeat procedures versus lifestyle changes. *J Cardiovasc Electrophysiol* 2014;**25**:930–938.
815. Ejima K, Shoda M, Arai K, Suzuki A, Yagishita D, Yagishita Y, Yashiro B, Sato T, Manaka T, Ashihara K, Hagiwara N. Impact of diastolic dysfunction on the outcome of catheter ablation in patients with atrial fibrillation. *Int J Cardiol* 2013;**164**:88–93.
816. Hocini M, Sanders P, Deisenhofer I, Jais P, Hsu LF, Scavee C, Weerasoriya R, Raybaud F, Macle L, Shah DC, Garrigue S, Le Metayer P, Clementy J, Haissaguerre M. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation* 2003;**108**:1172–1175.
817. Chen YW, Bai R, Lin T, Salim M, Sang CH, Long DY, Yu RH, Tang RB, Guo XY, Yan XL, Nie JG, Du X, Dong JZ, Ma CS. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardia-bradycardia syndrome?*Pacing Clin Electrophysiol* 2014;**37**:403–411.
818. Inada K, Yamane T, Tokutake K, Yokoyama K, Mishima T, Hioki M, Narui R, Ito K, Tanigawa S, Yamashita S, Tokuda M, Matsuo S, Shibayama K, Miyanaga S, Date T, Sugimoto K, Yoshimura M. The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. *Europace* 2014;**16**:208–213.
819. Cummings JE, Schweikert R, Saliba W, Hao S, Martin DO, Marrouche NF, Burkhardt JD, Kilicaslan F, Verma A, Beheiry S, Belden W, Natale A. Left atrial flutter following pulmonary vein antrum isolation with radiofrequency energy: linear lesions or repeat isolation. *J Cardiovasc Electrophysiol* 2005;**16**:293–297.
820. Schneider R, Lauschke J, Tischer T, Schneider C, Voss W, Moehlenkamp F, Glass A, Diedrich D, Bansch D. Pulmonary vein triggers play an important role in the initiation of atrial flutter: initial results from the prospective randomized Atrial Fibrillation Ablation in Atrial Flutter (Triple A) trial. *Heart Rhythm* 2015;**12**:865–871.
821. Patel NJ, Deshmukh A, Pau D, Goyal V, Patel SV, Patel N, Agnihotri K, Asirvatham S, Noseworthy P, Di Biase L, Natale A, Viles-Gonzalez JF. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: analysis of 89,638 procedures. *Heart Rhythm* 2016;**13**:1317–1325.
822. Cox JL, Schuessler RB, Boineau JP. The development of the maze procedure for the treatment of atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2000;**12**:2–14.
823. Melby SJ, Zierer A, Bailey MS, Cox JL, Lawton JS, Munfakh N, Crabtree TD, Moazami N, Huddleston CB, Moon MR, Damiano RJ Jr. A new era in the surgical treatment of atrial fibrillation: the impact of ablation technology and lesion set on procedural efficacy. *Ann Surg* 2006;**244**:583–592.
824. Badhwar V, Rankin JS, Damiano RJ, Jr., Gillinov AM, Bakaeen FG, Edgerton JR, Philpott JM, McCarthy PM, Bolling SF, Roberts HG, Thourani VH, Suri RM, Shemin RJ, Firestone S, Ad N. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the surgical treatment of atrial fibrillation. *Ann Thorac Surg* 2017;**103**:329–341.
825. Belley-Cote EP, Singal RK, McClure G, Devereaux K, Brady K, An K, Healey JS, Connolly SJ, Whitlock RP. Perspective and practice of surgical atrial fibrillation ablation: an international survey of cardiac surgeons. *Europace* 2019;**21**:445–450.
826. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. *J Thorac Cardiovasc Surg* 2006;**131**:1029–1035.
827. McClure GR, Belley-Cote EP, Jaffer IH, Dvirnik N, An KR, Fortin G, Spence J, Healey J, Singal RK, Whitlock RP. Surgical ablation of atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Europace* 2018;**20**:1442–1450.
828. Osmancik P, Budera P, Talavera D, Hlavicka J, Herman D, Holy J, Cervinka P, Smid J, Hanak P, Hatala R, Widimsky P. Five-year outcomes in cardiac surgery patients with atrial fibrillation undergoing concomitant surgical ablation versus no ablation. The long-term follow-up of the PRAGUE-12 study. *Heart Rhythm* 2019**16**:1334–1340.
829. Sharples L, Everett C, Singh J, Mills C, Spyt T, Abu-Omar Y, Fynn S, Thorpe B, Stoneman V, Goddard H, Fox-Rushby J, Nashef S. Amaze: a double-blind, multicentre randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of adding an ablation device-based maze procedure as an adjunct to routine cardiac surgery for patients with pre-existing atrial fibrillation. *Health Technol Assess* 2018;**22**:1–132.
830. Bagge L, Probst J, Jensen SM, Blomstrom P, Thelin S, Holmgren A, Blomstrom-Lundqvist C. Quality of life is not improved after mitral valve surgery combined with epicardial left atrial cryoablation as compared with mitral valve surgery alone: a substudy of the double blind randomized SWEDish Multicentre Atrial Fibrillation study (SWEDMAF). *Europace* 2018;**20**:f343–f350.
831. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, Brykczynski M, Skiba J, Zembala MO, Bartus K, Hirnle T, Dziembowska I, Deja M, Tobota Z, Maruszewski BJ. Surgical ablation for atrial fibrillation during isolated coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2019.

832. Suwalski P, Kowalewski M, Jasinski M, Staromlynski J, Zembala M, Widenka K, Brykczynski M, Skiba J, Zembala MO, Bartus K, Hirnle T, Dziembowska I, Tobota Z, Maruszewski BJ; KROK Investigators. Survival after surgical ablation for atrial fibrillation in mitral valve surgery: analysis from the Polish National Registry of Cardiac Surgery Procedures (KROK). *J Thorac Cardiovasc Surg* 2018; doi: 10.1016/j.jtcvs.2018.07.099.
833. Gillinov AM, Bakaeen F, McCarthy PM, Blackstone EH, Rajeswaran J, Pettersson G, Sabik JF 3rd, Najam F, Hill KM, Svensson LG, Cosgrove DM, Marrouche N, Natale A. Surgery for paroxysmal atrial fibrillation in the setting of mitral valve disease: a role for pulmonary vein isolation? *Ann Thorac Surg* 2006;**81**:19–26; discussion 27–28.
834. Basu S, Nagendran M, Maruthappu M. How effective is bipolar radiofrequency ablation for atrial fibrillation during concomitant cardiac surgery?*Interact Cardiovasc Thorac Surg* 2012;**15**:741–748.
835. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL, Pettersson BG, Sabik JF, 3rd, Smedira NG, Mihaljevic T, McCarthy PM, Shewchik J, Natale A. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg* 2006;**82**:502–513; discussion 513–514.
836. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Predictive factors of sustained sinus rhythm and recurrent atrial fibrillation after a radiofrequency modified maze procedure. *Eur J Cardiothorac Surg* 2008;**34**:771–775.
837. Lee SH, Kim JB, Cho WC, Chung CH, Jung SH, Choo SJ, Lee JW. The influence of age on atrial fibrillation recurrence after the maze procedure in patients with giant left atrium. *J Thorac Cardiovasc Surg* 2011;**141**:1015–1019.
838. Damiano RJ Jr, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Moon MR, Schuessler RB. The Cox maze IV procedure: predictors of late recurrence. *J Thorac Cardiovasc Surg* 2011;**141**:113–121.
839. Sunderland N, Maruthappu M, Nagendran M. What size of left atrium significantly impairs the success of maze surgery for atrial fibrillation?*Interact Cardiovasc Thorac Surg* 2011;**13**:332–338.
840. Bakker RC, Akin S, Rizopoulos D, Kik C, Takkenberg JJ, Bogers AJ. Results of clinical application of the modified maze procedure as concomitant surgery. *Interact Cardiovasc Thorac Surg* 2013;**16**:151–156.
841. Ad N, Holmes SD. Prediction of sinus rhythm in patients undergoing concomitant Cox maze procedure through a median sternotomy. *J Thorac Cardiovasc Surg* 2014;**148**:881–886.
842. Blomstrom-Lundqvist C, Johansson B, Berglin E, Nilsson L, Jensen SM, Thelin S, Holmgren A, Edvardsson N, Kallner G, Blomstrom P. A randomized double-blind study of epicardial left atrial cryoablation for permanent atrial fibrillation in patients undergoing mitral valve surgery: the SWEDish Multicentre Atrial Fibrillation study (SWEDMAF). *Eur Heart J* 2007;**28**:2902–2908.
843. Huffman MD, Karmali KN, Berendsen MA, Andrei AC, Kruse J, McCarthy PM, Malaisrie SC. Concomitant atrial fibrillation surgery for people undergoing cardiac surgery. *Cochrane Database Syst Rev* 2016:CD011814.
844. Budera P, Straka Z, Osmancik P, Vanek T, Jelinek S, Hlavicka J, Fojt R, Cervinka P, Hulman M, Smid M, Maly M, Widimsky P. Comparison of cardiac surgery with left atrial surgical ablation vs. cardiac surgery without atrial ablation in patients with coronary and/or valvular heart disease plus atrial fibrillation: final results of the PRAGUE-12 randomized multicentre study. *Eur Heart J* 2012;**33**:2644–2652.
845. Wang JG, Xin M, Han J, Li Y, Luo TG, Wang J, Meng F, Meng X. Ablation in selective patients with long-standing persistent atrial fibrillation: medium-term results of the Dallas lesion set. *Eur J Cardiothorac Surg* 2014;**46**:213–220.
846. Badhwar V, Rankin JS, Ad N, Grau-Sepulveda M, Damiano RJ, Gillinov AM, McCarthy PM, Thourani VH, Suri RM, Jacobs JP, Cox JL. Surgical ablation of atrial fibrillation in the United States: trends and propensity matched outcomes. *Ann Thorac Surg* 2017;**104**:493–500.
847. Joshibayev S, Bolatbekov B. Early and long-term outcomes and quality of life after concomitant mitral valve surgery, left atrial size reduction, and radiofrequency surgical ablation of atrial fibrillation. *Anatol J Cardiol* 2016;**16**:797–803.
848. Driessen AHG, Berger WR, Bierhuizen MFA, Piersma FR, van den Berg NWE, Neefs J, Krul SPJ, van Boven WP, de Groot JR. Quality of life improves after thoracoscopic surgical ablation of advanced atrial fibrillation: results of the Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery (AFACT) study. *J Thorac Cardiovasc Surg* 2018;**155**:972–980.
849. Castella M, Kotecha D, van Laar C, Wintgens L, Castillo Y, Kelder J, Aragon D, Nunez M, Sandoval E, Casellas A, Mont L, van Boven WJ, Boersma LVA, van Putte BP. Thoracoscopic vs. catheter ablation for atrial fibrillation: long-term follow-up of the FAST randomized trial. *Europace* 2019;**21**:746–753.
850. Osmancik P, Budera P, Talavera D, Herman D, Vesela J, Prochazkova R, Rizov V, Kacer P. Improvement in the quality of life of patients with persistent or long-standing persistent atrial fibrillation after hybrid ablation. *J Interv Card Electrophysiol* 2020;**57**:435–442.
851. Kim HJ, Kim JS, Kim TS. Epicardial thoracoscopic ablation versus endocardial catheter ablation for management of atrial fibrillation: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2016;**22**:729–737.
852. Gammie JS, Haddad M, Milford-Beland S, Welke KF, Ferguson TB Jr, O'Brien SM, Griffith BP, Peterson ED. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg* 2008;**85**:909–914.
853. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ, Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace* 2012;**14**:528–606.
854. van der Heijden CAJ, Vroomen M, Luermans JG, Vos R, Crijns H, Gelsomino S, La Meir M, Pison L, Maesen B. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2019;**56**:433–443.
855. Velagic V, DEA C, Mugnai G, Irfan G, Hunuk B, Stroker E, Hacioglu E, Umbrain V, Beckers S, Czapla J, Wellens F, Nijs J, Brugada P, M LAM, Chierchia GB. Repeat procedures after hybrid thoracoscopic ablation in the setting of long-standing persistent atrial fibrillation: electrophysiological findings and 2-year clinical outcome. *J Cardiovasc Electrophysiol* 2016;**27**:41–50.
856. Osmancik P, Budera P, Zdarska J, Herman D, Petr R, Straka Z. Electrophysiological findings after surgical thoracoscopic atrial fibrillation ablation. *Heart Rhythm* 2016;**13**:1246–1252.
857. Wang H, Han J, Wang Z, Yin Z, Liu Z, Jin Y, Han H. A prospective randomized trial of the cut-and-sew maze procedure in patients undergoing surgery for rheumatic mitral valve disease. *J Thorac Cardiovasc Surg* 2018;**155**: 608–617.
858. Lawrance CP, Henn MC, Miller JR, Sinn LA, Schuessler RB, Maniar HS, Damiano RJ Jr. A minimally invasive Cox maze IV procedure is as effective as sternotomy while decreasing major morbidity and hospital stay. *J Thorac Cardiovasc Surg* 2014;**148**:955–961.
859. Weimar T, Schena S, Bailey MS, Maniar HS, Schuessler RB, Cox JL, Damiano RJ Jr. The Cox-maze procedure for lone atrial fibrillation: a single-center experience over 2 decades. *Circ Arrhythm Electrophysiol* 2012;**5**:8–14.
860. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647–649.
861. Airaksinen KE, Gronberg T, Nuotio I, Nikkinen M, Ylitalo A, Biancari F, Hartikainen JE. Thromboembolic complications after cardioversion of acute atrial fibrillation: the FinCV (Finnish CardioVersion) study. *J Am Coll Cardiol* 2013;**62**:1187–1192.
862. Hansen ML, Jepsen RM, Olesen JB, Ruwald MH, Karasoy D, Gislason GH, Hansen J, Kober L, Husted S, Torp-Pedersen C. Thromboembolic risk in 16 274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. *Europace* 2015;**17**:18–23.
863. Lip GY. Cardioversion of atrial fibrillation. *Postgrad Med J* 1995;**71**:457–465.
864. Garg A, Khunger M, Seicean S, Chung MK, Tchou PJ. Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset. *JACC Clin Electrophysiol* 2016;**2**:487–494.
865. Tampieri A, Cipriano V, Mucci F, Rusconi AM, Lenzi T, Cenni P. Safety of cardioversion in atrial fibrillation lasting less than 48 h without post-procedural anticoagulation in patients at low cardioembolic risk. *Intern Emerg Med* 2018;**13**:87–93.
866. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, Davidoff R, Erbel R, Halperin JL, Orsinelli DA, Porter TR, Stoddard MF; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1411–1420.
867. Stellbrink C, Nixdorff U, Hofmann T, Lehmacher W, Daniel WG, Hanrath P, Geller C, Mugge A, Sehnert W, Schmidt-Lucke C, Schmidt-Lucke JA, Group ACES. Safety and efficacy of enoxaparin compared with unfractionated heparin and oral anticoagulants for prevention of thromboembolic complications in cardioversion of nonvalvular atrial fibrillation: the Anticoagulation in Cardioversion using Enoxaparin (ACE) trial. *Circulation* 2004;**109**:997–1003.
868. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, Talajic M, Scanavacca M, Vardas PE, Kirchhof P, Hemmrich M, Lanius V, Meng IL, Wildgoose P, van Eickels M, Hohnloser SH; X-VERT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J* 2014;**35**:3346–3355.
869. Ezekowitz MD, Pollack CV Jr, Halperin JL, England RD, VanPelt Nguyen S, Spahr J, Sudworth M, Cater NB, Breazna A, Oldgren J, Kirchhof P. Apixaban

compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. *Eur Heart J* 2018;**39**:2959–2971.
870. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY; ENSURE-AF investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;**388**:1995–2003.
871. Telles-Garcia N, Dahal K, Kocherla C, Lip GYH, Reddy P, Dominic P. Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2018;**268**:143–148.
872. Brunetti ND, Tarantino N, De Gennaro L, Correale M, Santoro F, Di Biase M. Direct oral anti-coagulants compared to vitamin-K antagonists in cardioversion of atrial fibrillation: an updated meta-analysis. *J Thromb Thrombolysis* 2018;**45**:550–556.
873. Kotecha D, Pollack CV Jr, De Caterina R, Renda G, Kirchhof P. Direct oral anticoagulants halve thromboembolic events after cardioversion of AF compared with warfarin. *J Am Coll Cardiol* 2018;**72**:1984–1986.
874. Itainen S, Lehto M, Vasankari T, Mustonen P, Kotamaki M, Numminen A, Lahtela H, Bah A, Hartikainen J, Hekkala AM, Airaksinen JKE. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients undergoing elective cardioversion. *Europace* 2018;**20**:565–568.
875. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, van Eickels M, Cohen A; X-TRA study and CLOT-AF Registry Investigators. Left atrial thrombus resolution in atrial fibrillation or flutter: results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF). *Am Heart J* 2016;**178**:126–134.
876. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;**109**:1973–1980.
877. Cardoso R, Knijnik L, Bhonsale A, Miller J, Nasi G, Rivera M, Blumer V, Calkins H. An updated meta-analysis of novel oral anticoagulants versus vitamin K antagonists for uninterrupted anticoagulation in atrial fibrillation catheter ablation. *Heart Rhythm* 2018;**15**:107–115.
878. Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, Biss B, Brouwer MA, Grimaldi M; RE-CIRCUIT Investigators. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. *N Engl J Med* 2017;**376**:1627–1636.
879. Cappato R, Marchlinski FE, Hohnloser SH, Naccarelli GV, Xiang J, Wilber DJ, Ma CS, Hess S, Wells DS, Juang G, Vijgen J, Hugl BJ, Balasubramaniam R, De Chillou C, Davies DW, Fields LE, Natale A; VENTURE-AF Investigators. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. *Eur Heart J* 2015;**36**:1805–1811.
880. Kirchhof P, Haeusler KG, Blank B, De Bono J, Callans D, Elvan A, Fetsch T, Van Gelder IC, Gentlesk P, Grimaldi M, Hansen J, Hindricks G, Al-Khalidi HR, Massaro T, Mont L, Nielsen JC, Nolker G, Piccini JP, De Potter T, Scherr D, Schotten U, Themistoclakis S, Todd D, Vijgen J, Di Biase L. Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. *Eur Heart J* 2018;**39**:2942–2955.
881. Hohnloser SH, Camm J, Cappato R, Diener HC, Heidbuchel H, Mont L, Morillo CA, Abozguia K, Grimaldi M, Rauer H, Reimitz PE, Smolnik R, Monninghoff C, Kautzner J. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. *Eur Heart J* 2019;**40**:3013–3021.
882. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–2429.
883. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2012:CD005049.
884. Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2019;**9**:CD005049.
885. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, Goette A, Lewalter T, Ravens U, Meinertz T, Breithardt G, Steinbeck G. The registry of the German Competence NETwork on Atrial Fibrillation: patient characteristics and initial management. *Europace* 2009;**11**:423–434.
886. Darkner S, Chen X, Hansen J, Pehrson S, Johannessen A, Nielsen JB, Svendsen JH. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J* 2014;**35**:3356–3364.
887. Leong-Sit P, Roux JF, Zado E, Callans DJ, Garcia F, Lin D, Marchlinski FE, Bala R, Dixit S, Riley M, Hutchinson MD, Cooper J, Russo AM, Verdino R, Gerstenfeld EP. Antiarrhythmics After Ablation of Atrial Fibrillation (5A Study): six-month follow-up study. *Circ Arrhythm Electrophysiol* 2011;**4**:11–14.
888. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–2060.
889. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–2169.
890. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2015;**3**:CD005049.
891. Kochiadakis GE, Igoumenidis NE, Marketou ME, Kaleboubas MD, Simantirakis EN, Vardas PE. Low dose amiodarone and sotalol in the treatment of recurrent, symptomatic atrial fibrillation: a comparative, placebo controlled study. *Heart* 2000;**84**:251–257.
892. Galperin J, Elizari MV, Chiale PA, Molina RT, Ledesma R, Scapin AO, Vazquez Blanco M; GEFCA Investigators-GEMA Group. Efficacy of amiodarone for the termination of chronic atrial fibrillation and maintenance of normal sinus rhythm: a prospective, multicenter, randomized, controlled, double blind trial. *J Cardiovasc Pharmacol Ther* 2001;**6**:341–350.
893. Channer KS, Birchall A, Steeds RP, Walters SJ, Yeo WW, West JN, Muthusamy R, Rhoden WE, Saeed BT, Batin P, Brooksby WP, Wilson I, Grant S. A randomized placebo-controlled trial of pre-treatment and short- or long-term maintenance therapy with amiodarone supporting DC cardioversion for persistent atrial fibrillation. *Eur Heart J* 2004;**25**:144–150.
894. Singh SN, Singh BN, Reda DJ, Fye CL, Ezekowitz MD, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD Jr, Antman EM, Falk RH, Lopez B, Tang XC. Comparison of sotalol versus amiodarone in maintaining stability of sinus rhythm in patients with atrial fibrillation (Sotalol-Amiodarone Fibrillation Efficacy Trial [Safe-T]). *Am J Cardiol* 2003;**92**:468–472.
895. Kochiadakis GE, Igoumenidis NE, Hamilos ME, Tzerakis PG, Klapsinos NC, Chlouverakis GI, Vardas PE. Sotalol versus propafenone for long-term maintenance of normal sinus rhythm in patients with recurrent symptomatic atrial fibrillation. *Am J Cardiol* 2004;**94**:1563–1566.
896. Gulizia M, Mangiameli S, Orazi S, Chiaranda G, Piccione G, Di Giovanni N, Colletti A, Pensabene O, Lisi F, Vasquez L, Grammatico A, Boriani G; PITAGORA Study Investigators. A randomized comparison of amiodarone and class IC antiarrhythmic drugs to treat atrial fibrillation in patients paced for sinus node disease: the Prevention Investigation and Treatment: A Group for Observation and Research on Atrial arrhythmias (PITAGORA) trial. *Am Heart J* 2008;**155**:100–107.e1.
897. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329–345.
898. Cadrin-Tourigny J, Wyse DG, Roy D, Blondeau L, Levesque S, Talajic M, Andrade JG, Dubuc M, Thibault B, Guerra PG, Macle L, Rivard L, Khairy P. Efficacy of amiodarone in patients with atrial fibrillation with and without left ventricular dysfunction: a pooled analysis of AFFIRM and AF-CHF trials. *J Cardiovasc Electrophysiol* 2014;**25**:1306–1313.
899. Massie BM, Fisher SG, Radford M, Deedwania PC, Singh BN, Fletcher RD, Singh SN. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. CHF-STAT Investigators. *Circulation* 1996;**93**:2128–2134.
900. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival trial of antiarrhythmic therapy in congestive heart failure. *N Engl J Med* 1995;**333**:77–82.
901. Zimetbaum P. Antiarrhythmic drug therapy for atrial fibrillation. *Circulation* 2012;**125**:381–389.
902. Kirchhof P, Franz MR, Bardai A, Wilde AM. Giant T-U waves precede torsades de pointes in long QT syndrome: a systematic electrocardiographic analysis in patients with acquired and congenital QT prolongation. *J Am Coll Cardiol* 2009;**54**:143–149.
903. Orr CF, Ahlskog JE. Frequency, characteristics, and risk factors for amiodarone neurotoxicity. *Arch Neurol* 2009;**66**:865–869.

904. Lai SW, Lin CL, Liao KF, Lin CY. Amiodarone use and risk of acute pancreatitis: a population-based case-control study. *Heart Rhythm* 2015;**12**:163–166.
905. Epstein AE, Olshansky B, Naccarelli GV, Kennedy JI Jr, Murphy EJ, Goldschlager N. Practical management guide for clinicians who treat patients with amiodarone. *Am J Med* 2016;**129**:468–475.
906. Basaria S, Cooper DS. Amiodarone and the thyroid. *Am J Med* 2005;**118**:706–714.
907. Colby R, Geyer H. Amiodarone-induced pulmonary toxicity. *JAAPA* 2017;**30**:23–26.
908. Van Gelder IC, Crijns HJ, Van Gilst WH, Van Wijk LM, Hamer HP, Lie KI. Efficacy and safety of flecainide acetate in the maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation or atrial flutter. *Am J Cardiol* 1989;**64**:1317–1321.
909. Anderson JL, Gilbert EM, Alpert BL, Henthorn RW, Waldo AL, Bhandari AK, Hawkinson RW, Pritchett EL. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy. A multicenter, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. Flecainide Supraventricular Tachycardia Study Group. *Circulation* 1989;**80**:1557–1570.
910. Stroobandt R, Stiels B, Hoebrechts R. Propafenone for conversion and prophylaxis of atrial fibrillation. Propafenone Atrial Fibrillation Trial Investigators. *Am J Cardiol* 1997;**79**:418–423.
911. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, et alet alMortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**:781–788.
912. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 1992;**20**:527–532.
913. Podrid PJ, Anderson JL. Safety and tolerability of long-term propafenone therapy for supraventricular tachyarrhythmias. The Propafenone Multicenter Study Group. *Am J Cardiol* 1996;**78**:430–434.
914. Brembilla-Perrot B, Laporte F, Sellal JM, Schwartz J, Olivier A, Zinzius PY, Manenti V, Beurrier D, Andronache M, Louis P, Selton O, de la Chaise AT, De Chillou C. 1: 1 atrial-flutter. Prevalence and clinical characteristics. *Int J Cardiol* 2013;**168**:3287–3290.
915. Gao X, Guha A, Buck B, Patel D, Snider MJ, Boyd M, Afzal M, Badin A, Godara H, Liu Z, Tyler J, Weiss R, Kalbfleisch S, Hummel J, Augostini R, Houmsse M, Daoud EG. Initiation and outcomes with Class Ic antiarrhythmic drug therapy. *Indian Pacing Electrophysiol J* 2018;**18**:68–72.
916. Richiardi E, Gaita F, Greco C, Gaschino G, Comba Costa G, Rosettani E, Brusca A. [Propafenone versus hydroquinidine in long-term pharmacological prophylaxis of atrial fibrillation]. *Cardiologia* 1992;**37**:123–127.
917. Chimienti M, Cullen MT, Jr., Casadei G. Safety of long-term flecainide and propafenone in the management of patients with symptomatic paroxysmal atrial fibrillation: report from theFlecainide and Propafenone Italian Study Investigators. *Am J Cardiol* 1996;**77**:60A–75A.
918. Reimold SC, Cantillon CO, Friedman PL, Antman EM. Propafenone versus sotalol for suppression of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 1993;**71**:558–563.
919. Aliot E, Denjoy I. Comparison of the safety and efficacy of flecainide versus propafenone in hospital out-patients with symptomatic paroxysmal atrial fibrillation/flutter. The Flecainide AF French Study Group. *Am J Cardiol* 1996;**77**:66A–71A.
920. Bellandi F, Simonetti I, Leoncini M, Frascarelli F, Giovannini T, Maioli M, Dabizzi RP. Long-term efficacy and safety of propafenone and sotalol for the maintenance of sinus rhythm after conversion of recurrent symptomatic atrial fibrillation. *Am J Cardiol* 2001;**88**:640–645.
921. Meinertz T, Lip GY, Lombardi F, Sadowski ZP, Kalsch B, Camez A, Hewkin A, Eberle S; ERAFT Investigators. Efficacy and safety of propafenone sustained release in the prophylaxis of symptomatic paroxysmal atrial fibrillation (The European Rythmol/Rytmonorm Atrial Fibrillation Trial [ERAFT] Study). *Am J Cardiol* 2002;**90**:1300–1306.
922. Pritchett EL, Page RL, Carlson M, Undesser K, Fava G; Rythmol Atrial Fibrillation Trial (RAFT) Investigators. Efficacy and safety of sustained-release propafenone (propafenone SR) for patients with atrial fibrillation. *Am J Cardiol* 2003;**92**:941–946.
923. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ; Athena Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–678.
924. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol* 2010;**21**:597–605.
925. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH, for the EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–999.
926. Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003;**24**:1481–1487.
927. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study G. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
928. Wu C, Tcherny-Lessenot S, Dai W, Wang Y, Kechemir H, Gandhi S, Lin S, Juhaeri J. Assessing the risk for peripheral neuropathy in patients treated with dronedarone compared with that in other antiarrhythmics. *Clin Ther* 2018;**40**:450–455.e1.
929. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009;**54**:1089–1095.
930. Gao S, Dai W, Zhang L, Juhaeri J, Wang Y, Caubel P. Risk of cardiovascular events, stroke, congestive heart failure, interstitial lung disease, and acute liver injury: dronedarone versus amiodarone and other antiarrhythmics. *J Atr Fibrillation* 2013;**6**:890.
931. Pisters R, Hohnloser SH, Connolly SJ, Torp-Pedersen C, Naditch-Brule L, Page RL, Crijns HJ; ATHENA Investigators. Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial. *Europace* 2014;**16**:174–181.
932. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH;PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–2276.
933. Friberg L. Safety of dronedarone in routine clinical care. *J Am Coll Cardiol* 2014;**63**:2376–2384.
934. Friberg L. Ventricular arrhythmia and death among atrial fibrillation patients using anti-arrhythmic drugs. *Am Heart J* 2018;**205**:118–127.
935. Khan MH, Rochlani Y, Aronow WS. Efficacy and safety of dronedarone in the treatment of patients with atrial fibrillation. *Expert Opin Drug Saf* 2017;**16**:1407–1412.
936. Vamos M, Hohnloser SH. Amiodarone and dronedarone: an update. *Trends Cardiovasc Med* 2016;**26**:597–602.
937. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol* 2007;**64**:785–791.
938. Vijayalakshmi K, Whittaker VJ, Sutton A, Campbell P, Wright RA, Hall JA, Harcombe AA, Linker NJ, Stewart MJ, Davies A, de Belder MA. A randomized trial of prophylactic antiarrhythmic agents (amiodarone and sotalol) in patients with atrial fibrillation for whom direct current cardioversion is planned. *Am Heart J* 2006;**151**:863.e1-6.
939. Capucci A, Botto G, Molon G, Spampinato A, Favale S, Proclemer A, Porfilio A, Marotta T, Vimercati M, Boriani G; DAPHNE Study Investigators. The Drug And Pace Health cliNical Evaluation (DAPHNE) study: a randomized trial comparing sotalol versus beta-blockers to treat symptomatic atrial fibrillation in patients with brady-tachycardia syndrome implanted with an antitachycardia pacemaker. *Am Heart J* 2008;**156**:373.e1-8.
940. Juul-Moller S, Edvardsson N, Rehnqvist-Ahlberg N. Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. *Circulation* 1990;**82**:1932–199.
941. MacNeil DJ, Davies RO, Deitchman D. Clinical safety profile of sotalol in the treatment of arrhythmias. *Am J Cardiol* 1993;**72**:44A–50A.
942. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagne P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**:913–920.
943. Andersen SS, Hansen ML, Gislason GH, Schramm TK, Folke F, Fosbol E, Abildstrom SZ, Madsen M, Kober L, Torp-Pedersen C. Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study. *Europace* 2009;**11**:886–891.
944. Crijns HJ, Gosselink AT, Lie KI. Propafenone versus disopyramide for maintenance of sinus rhythm after electrical cardioversion of chronic atrial fibrillation: a randomized, double-blind study. PRODIS Study Group. *Cardiovasc Drugs Ther* 1996;**10**:145–152.

945. Lloyd EA, Gersh BJ, Forman R. The efficacy of quinidine and disopyramide in the maintenance of sinus rhythm after electroconversion from atrial fibrillation. A double-blind study comparing quinidine, disopyramide and placebo. *S Afr Med J* 1984;**65**:367–369.
946. Karlson BW, Torstensson I, Abjorn C, Jansson SO, Peterson LE. Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation. A placebo-controlled one-year follow-up study. *Eur Heart J* 1988;**9**:284–290.
947. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990;**82**:1106–1116.
948. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJ, Simantirakis E, Atar D, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) pilot general registry. *Europace* 2014;**16**:308–319.
949. Dagres N, Lewalter T, Lip GY, Pison L, Proclemer A, Blomstrom-Lundqvist C, Scientific Initiatives Committee EHRA. Current practice of antiarrhythmic drug therapy for prevention of atrial fibrillation in Europe: the European Heart Rhythm Association survey. *Europace* 2013;**15**:478–481.
950. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251–1258.
951. Goette A, Staack T, Rocken C, Arndt M, Geller JC, Huth C, Ansorge S, Klein HU, Lendeckel U. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000;**35**:1669–1677.
952. Thanigaimani S, Lau DH, Agbaedeng T, Elliott AD, Mahajan R, Sanders P. Molecular mechanisms of atrial fibrosis: implications for the clinic. *Expert Rev Cardiovasc Ther* 2017;**15**:247–256.
953. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol* 2003;**41**:2197–2204.
954. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 2010;**55**:2299–2307.
955. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;**45**:1832–1839.
956. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, McMurray JJ, Olsson L, Rouleau JL, Young JB, Yusuf S. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;**152**:86–92.
957. McMurray JJ, Young JB, Dunlap ME, Granger CB, Hainer J, Michelson EL, Earle S, Olofsson B, Ostergren J, Yusuf S, Swedberg K, Pfeffer MA, CHARM Investigators. Relationship of dose of background angiotensin-converting enzyme inhibitor to the benefits of candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial. *Am Heart J* 2006;**151**:985–991.
958. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;**45**:712–719.
959. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. *Am Heart J* 2006;**152**:217–222.
960. Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH, Nieminen MS, Edelman JM, Hille DA, Dahlof B. Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. *JAMA* 2006;**296**:1242–1248.
961. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA; CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
962. Marott SC, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of atrial fibrillation: a nationwide study. *Eur Heart J* 2014;**35**:1205–1214.
963. Goette A, Schon N, Kirchhof P, Breithardt G, Fetsch T, Hausler KG, Klein HU, Steinbeck G, Wegscheider K, Meinertz T. Angiotensin II-antagonist in paroxysmal atrial fibrillation (ANTIPAF) trial. *Circ Arrhythm Electrophysiol* 2012;**5**:43–51.
964. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. *Europace* 2011;**13**:610–625.
965. Reil JC, Hohl M, Selejan S, Lipp P, Drautz F, Kazakow A, Munz BM, Muller P, Steendijk P, Reil GH, Allessie MA, Bohm M, Neuberger HR. Aldosterone promotes atrial fibrillation. *Eur Heart J* 2012;**33**:2098–2108.
966. Reil JC, Tauchnitz M, Tian Q, Hohl M, Linz D, Oberhofer M, Kaestner L, Reil GH, Thiele H, Steendijk P, Bohm M, Neuberger HR, Lipp P. Hyperaldosteronism induces left atrial systolic and diastolic dysfunction. *Am J Physiol Heart Circ Physiol* 2016;**311**:H1014–H1023.
967. Tsai CT, Chiang FT, Tseng CD, Hwang JJ, Kuo KT, Wu CK, Yu CC, Wang YC, Lai LP, Lin JL. Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. *J Am Coll Cardiol* 2010;**55**:758–770.
968. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
969. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, Vincent J, Pitt B; EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. *J Am Coll Cardiol* 2012;**59**:1598–1603.
970. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, Anand IS, O'Meara E, Rouleau JL, Sweitzer NK, Fang JC, Saksena S, Pitt B, Pfeffer MA, Solomon SD. Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial. *JACC Heart Fail* 2018;**6**:689–697.
971. Neefs J, van den Berg NW, Limpens J, Berger WR, Boekholdt SM, Sanders P, de Groot JR. Aldosterone pathway blockade to prevent atrial fibrillation: a systematic review and meta-analysis. *Int J Cardiol* 2017;**231**:155–161.
972. Kuhlkamp V, Schirdewan A, Stangl K, Homberg M, Ploch M, Beck OA. Use of metoprolol CR/XL to maintain sinus rhythm after conversion from persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 2000;**36**:139–146.
973. Nergardh AK, Rosenqvist M, Nordlander R, Frick M. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a randomized double-blind placebo-controlled study. *Eur Heart J* 2007;**28**:1351–1357.
974. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med* 2016;**374**:1744–1753.
975. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW, PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ* 2011;**342**:d1250.
976. Pinho-Gomes AC, Reilly S, Brandes RP, Casadei B. Targeting inflammation and oxidative stress in atrial fibrillation: role of 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibition with statins. *Antioxid Redox Signal* 2014;**20**:1268–1285.
977. Humphries KH, Lee M, Sheldon R, Ramanathan K, Dorian P, Green M, Kerr CR; CARAF Investigators. Statin use and recurrence of atrial fibrillation after successful cardioversion. *Am Heart J* 2007;**154**:908–913.
978. Bianconi L, Calo L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. *Europace* 2011;**13**:174–181.
979. Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, Latini R, Libby P, Lombardi F, O'Gara PT, Page RL, Tavazzi L, Tognoni G; OPERA Investigators. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. *JAMA* 2012;**308**:2001–2011.
980. Yamashita T, Inoue H, Okumura K, Kodama I, Aizawa Y, Atarashi H, Ohe T, Ohtsu H, Kato T, Kamakura S, Kumagai K, Kurachi Y, Koretsune Y, Saikawa T, Sakurai M, Sato T, Sugi K, Nakaya H, Hirai M, Hirayama A, Fukatani M, Mitamura H, Yamazaki T, Watanabe E, Ogawa S; J-RHYTHM II Investigators. Randomized trial of angiotensin II-receptor blocker vs. dihydropiridine calcium channel blocker in the treatment of paroxysmal atrial fibrillation with hypertension (J-RHYTHM II study). *Europace* 2011;**13**:473–479.
981. Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, Ferrante D, Badra R, Figal J, Ramos S, Tognoni G, Doval HC; GESICA Investigators. Omega-3 fatty

acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J Am Coll Cardiol* 2013;**61**:463–468.
982. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**304**:2363–2372.
983. Kochiadakis GE, Marketou ME, Igoumenidis NE, Chrysostomakis SI, Mavrakis HE, Kaleboubas MD, Vardas PE. Amiodarone, sotalol, or propafenone in atrial fibrillation: which is preferred to maintain normal sinus rhythm?*Pacing Clin Electrophysiol* 2000;**23**:1883–1887.
984. Boriani G, Biffi M, Capucci A, Botto GL, Broffoni T, Rubino I, Della Casa S, Sanguinetti M, Magnani B. Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease. A randomized, controlled trial. *Ann Intern Med* 1997;**126**:621–625.
985. Ehrlich JR, Look C, Kostev K, Israel CW, Goette A. Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany. *Int J Cardiol* 2019;**278**:126–132.
986. Camm AJ. Hopes and disappointments with antiarrhythmic drugs. *Int J Cardiol* 2017;**237**:71–74.
987. De Vecchis R. Long-term antiarrhythmic drug treatment after atrial fibrillation ablation: does a too obstinate rhythm control strategy bring serious risk of proarrhythmia to ablated patients?*Eur Heart J Cardiovasc Pharmacother* 2019;**5**:117–118.
988. Fabritz L, Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects: individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol* 2010;**106**:263–268.
989. Reimold FR, Reynolds MR. Proarrhythmia and death with antiarrhythmic drugs for atrial fibrillation, and the unfulfilled promise of comparative effectiveness research. *Am Heart J* 2018;**205**:128–130.
990. Coughtrie AL, Behr ER, Layton D, Marshall V, Camm AJ, Shakir SAW. Drugs and life-threatening ventricular arrhythmia risk: results from the DARE study cohort. *BMJ Open* 2017;**7**:e016627.
991. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shah R. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a policy conference of the European Society of Cardiology. *Eur Heart J* 2000;**21**:1216–1231.
992. Milan DJ, Saul JP, Somberg JC, Molnar J. Efficacy of intravenous and oral sotalol in pharmacologic conversion of atrial fibrillation: a systematic review and meta-analysis. *Cardiology* 2017;**136**:52–60.
993. Agusala K, Oesterle A, Kulkarni C, Caprio T, Subacius H, Passman R. Risk prediction for adverse events during initiation of sotalol and dofetilide for the treatment of atrial fibrillation. *Pacing Clin Electrophysiol* 2015;**38**:490–498.
994. Lin CY, Lin YJ, Lo LW, Chen YY, Chong E, Chang SL, Chung FP, Chao TF, Hu YF, Tuan TC, Liao JN, Chang Y, Chien KL, Chiou CW, Chen SA. Factors predisposing to ventricular proarrhythmia during antiarrhythmic drug therapy for atrial fibrillation in patients with structurally normal heart. *Heart Rhythm* 2015;**12**:1490–1500.
995. Kaab S, Hinterseer M, Nabauer M, Steinbeck G. Sotalol testing unmasks altered repolarization in patients with suspected acquired long-QT-syndrome – a case-control pilot study using i.v. sotalol. *Eur Heart J* 2003;**24**:649–657.
996. Lehtonen A, Fodstad H, Laitinen-Forsblom P, Toivonen L, Kontula K, Swan H. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. *Heart Rhythm* 2007;**4**:603–607.
997. Patten M, Maas R, Bauer P, Luderitz B, Sonntag F, Dluzniewski M, Hatala R, Opolski G, Muller HW, Meinertz T; SOPAT Investigators. Suppression of paroxysmal atrial tachyarrhythmias – results of the SOPAT trial. *Eur Heart J* 2004;**25**:1395–1404.
998. Fetsch T, Bauer P, Engberding R, Koch HP, Lukl J, Meinertz T, Oeff M, Seipel L, Trappe HJ, Treese N, Breithardt G; Prevention of Atrial Fibrillation after Cardioversion Investigators. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J* 2004;**25**:1385–1394.
999. Vallurupalli S, Pothineni NV, Deshmukh A, Paydak H. Utility of routine exercise testing to detect rate-related QRS widening in patients without structural heart disease on class Ic antiarrhythmic agents (flecainide and propafenone). *Am J Cardiol* 2015;**116**:730–732.
1000. Parkash R, Wells GA, Sapp JL, Healey JS, Tardif J-C, Greiss I, Rivard L, Roux J-F, Gula L, Nault I. Effect of aggressive blood pressure control on the recurrence of atrial fibrillation after catheter ablation: a randomized, open-label clinical trial (SMAC-AF [Substrate Modification With Aggressive Blood Pressure Control]). *Circulation* 2017;**135**:1788–1798.
1001. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, Alonso A. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. *Circ Arrhythm Electrophysiol* 2014;**7**:620–625.
1002. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study). *Eur Heart J* 2006;**27**:96–106.
1003. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity – results of a meta-analysis. *Am Heart J* 2008;**155**:310–315.
1004. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;**292**:2471–2477.
1005. Baek YS, Yang PS, Kim TH, Uhm JS, Park J, Pak HN, Lee MH, Joung B. Associations of abdominal obesity and new-onset atrial fibrillation in the general population. *J Am Heart Assoc* 2017;**6**.
1006. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant trials. *Stroke* 2017;**48**:857–866.
1007. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
1008. Cha YM, Friedman PA, Asirvatham SJ, Shen WK, Munger TM, Rea RF, Brady PA, Jahangir A, Monahan KH, Hodge DO, Meverden RA, Gersh BJ, Hammill SC, Packer DL. Catheter ablation for atrial fibrillation in patients with obesity. *Circulation* 2008;**117**:2583–2590.
1009. Ector J, Dragusin O, Adriaenssens B, Huybrechts W, Willems R, Ector H, Heidbuchel H. Obesity is a major determinant of radiation dose in patients undergoing pulmonary vein isolation for atrial fibrillation. *J Am Coll Cardiol* 2007;**50**:234–242.
1010. Shoemaker MB, Muhammad R, Farrell M, Parvez B, White BW, Streur M, Stubblefield T, Rytlewski J, Parvathaneni S, Nagarakanti R, Roden DM, Saavedra P, Ellis C, Whalen SP, Darbar D. Relation of morbid obesity and female gender to risk of procedural complications in patients undergoing atrial fibrillation ablation. *Am J Cardiol* 2013;**111**:368–373.
1011. Ettinger PO, Wu CF, De La Cruz C Jr, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the 'holiday heart': alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;**95**:555–562.
1012. Conen D, Albert CM. Alcohol consumption and risk of atrial fibrillation: how much is too much?*J Am Coll Cardiol* 2014;**64**:290–292.
1013. Liang Y, Mente A, Yusuf S, Gao P, Sleight P, Zhu J, Fagard R, Lonn E, Teo KK; ONTARGET and TRANSCEND Investigators. Alcohol consumption and the risk of incident atrial fibrillation among people with cardiovascular disease. *CMAJ* 2012;**184**:E857–866.
1014. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;**64**:281–289.
1015. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Alcohol intake and prognosis of atrial fibrillation. *Heart* 2013;**99**:1093–1099.
1016. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–28.
1017. Lavie CJ, Thomas RJ, Squires RW, Allison TG, Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clin Proc* 2009;**84**:373–383.
1018. Mont L. Arrhythmias and sport practice. *Heart* 2010;**96**:398–405.
1019. Menezes AR, Lavie CJ, De Schutter A, Milani RV, O'Keefe J, DiNicolantonio JJ, Morin DP, Abi-Samra FM. Lifestyle modification in the prevention and treatment of atrial fibrillation. *Prog Cardiovasc Dis* 2015;**58**:117–125.
1020. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ* 1998;**316**:1784–1785.
1021. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, Jenni R, Oechslin E, Luthi P, Scharf C, Marti B, Attenhofer Jost CH. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J* 2008;**29**:71–78.
1022. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace* 2008;**10**:618–623.

1023. Nielsen JR, Wachtell K, Abdulla J. The relationship between physical activity and risk of atrial fibrillation – a systematic review and meta-analysis. *J Atr Fibrillation* 2013;**5**:789.
1024. Risom SS, Zwisler AD, Johansen PP, Sibilitz KL, Lindschou J, Gluud C, Taylor RS, Svendsen JH, Berg SK. Exercise-based cardiac rehabilitation for adults with atrial fibrillation. *Cochrane Database Syst Rev* 2017;**2**:CD011197.
1025. Dzeshka MS, Shantsila A, Shantsila E, Lip GYH. Atrial fibrillation and hypertension. *Hypertension* 2017;**70**:854–861.
1026. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
1027. Kim TH, Yang PS, Yu HT, Jang E, Shin H, Kim HY, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, Joung B, Lip GYH. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. *Eur Heart J* 2019;**40**:809–819.
1028. Lip GY, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;**28**:752–759.
1029. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, Pokushalov EA, Romanov AB. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020;**323**:248–255.
1030. Du X, Ninomiya T, de Galan B, Abadir E, Chalmers J, Pillai A, Woodward M, Cooper M, Harrap S, Hamet P, Poulter N, Lip GY, Patel A, Group AC. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J* 2009;**30**:1128–1135.
1031. Pallisgaard JL, Schjerning AM, Lindhardt TB, Procida K, Hansen ML, Torp-Pedersen C, Gislason GH. Risk of atrial fibrillation in diabetes mellitus: a nationwide cohort study. *Eur J Prev Cardiol* 2016;**23**:621–627.
1032. Rizzo MR, Sasso FC, Marfella R, Siniscalchi M, Paolisso P, Carbonara O, Capoluongo MC, Lascar N, Pace C, Sardu C, Passavanti B, Barbieri M, Mauro C, Paolisso G. Autonomic dysfunction is associated with brief episodes of atrial fibrillation in type 2 diabetes. *J Diabetes Complications* 2015;**29**:88–92.
1033. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. *Int J Cardiol* 2005;**105**:315–318.
1034. Lee SR, Choi EK, Rhee TM, Lee HJ, Lim WH, Kang SH, Han KD, Cha MJ, Cho Y, Oh IY, Oh S. Evaluation of the association between diabetic retinopathy and the incidence of atrial fibrillation: a nationwide population-based study. *Int J Cardiol* 2016;**223**:953–957.
1035. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation* 2015;**131**:e29–322.
1036. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, Thomas A, Papademetriou V. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes study). *Am J Cardiol* 2014;**114**:1217–1222.
1037. Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, Wen MS, Chen WJ, Yeh YH, See LC. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. *Cardiovasc Diabetol* 2014;**13**:123.
1038. Zhang Z, Zhang X, Korantzopoulos P, Letsas KP, Tse G, Gong M, Meng L, Li G, Liu T. Thiazolidinedione use and atrial fibrillation in diabetic patients: a meta-analysis. *BMC Cardiovasc Disord* 2017;**17**:96.
1039. Bell DSH, Goncalves E. Atrial fibrillation and type 2 diabetes: prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab* 2019;**21**:210–217.
1040. Patti G, Di Gioia G, Cavallari I, Nenna A. Safety and efficacy of nonvitamin K antagonist oral anticoagulants versus warfarin in diabetic patients with atrial fibrillation: a study-level meta-analysis of phase III randomized trials. *Diabetes Metab Res Rev* 2017;**33**.
1041. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P, Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol* 2014;**63**:2141–2147.
1042. Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, Baranowski B, Hussein A, Saliba W, Wazni O. Association between pre-ablation glycemic control and outcomes among patients with diabetes undergoing atrial fibrillation ablation. *JACC Clin Electrophysiol* 2019;**5**:897–903.
1043. Linz D, Baumert M, Catcheside P, Floras J, Sanders P, Levy P, Cowie MR, Doug McEvoy R. Assessment and interpretation of sleep disordered breathing severity in cardiology: clinical implications and perspectives. *Int J Cardiol* 2018;**271**:281–288.
1044. Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. *Circulation* 2004;**110**:364–367.
1045. Goudis CA, Ketikoglou DG. Obstructive sleep and atrial fibrillation: pathophysiological mechanisms and therapeutic implications. *Int J Cardiol* 2017;**230**:293–300.
1046. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD, Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;**5**:263–276.
1047. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, Kalman JM, Sanders P. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. *JAMA Cardiol* 2018;**3**:532–540.
1048. Fein AS, Shvilkin A, Shah D, Haffajee CI, Das S, Kumar K, Kramer DB, Zimetbaum PJ, Buxton AE, Josephson ME, Anter E. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;**62**:300–305.
1049. Neilan TG, Farhad H, Dodson JA, Shah RV, Abbasi SA, Bakker JP, Michaud GF, van der Geest R, Blankstein R, Steigner M, John RM, Jerosch-Herold M, Malhotra A, Kwong RY. Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. *J Am Heart Assoc* 2013;**2**:e000421.
1050. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ, Al-Mallah MH. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. *Am J Cardiol* 2015;**116**:1767–1773.
1051. Shukla A, Aizer A, Holmes D, Fowler S, Park DS, Bernstein S, Bernstein N, Chinitz L. Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: a meta-analysis. *JACC Clin Electrophysiol* 2015;**1**:41–51.
1052. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol* 2015;**66**:985–996.
1053. Bonfanti L, Annovi A, Sanchis-Gomar F, Saccenti C, Meschi T, Ticinesi A, Cervellin G. Effectiveness and safety of electrical cardioversion for acute-onset atrial fibrillation in the emergency department: a real-world 10-year single center experience. *Clin Exp Emerg Med* 2019;**6**:64–69.
1054. Scheuermeyer FX, Grafstein E, Stenstrom R, Innes G, Heslop C, MacPhee J, Pourvali R, Heilbron B, McGrath L, Christenson J. Thirty-day and 1-year outcomes of emergency department patients with atrial fibrillation and no acute underlying medical cause. *Ann Emerg Med* 2012;**60**:755–765.e2.
1055. Boriani G, Proietti M, Laroche C, Diemberger I, Popescu MI, Riahi S, Shantsila A, Dan GA, Tavazzi L, Maggioni AP, Lip GYH; EORP-A Pilot General Registry Investigators. Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general registry. *Int J Cardiol* 2018;**271**:68–74.
1056. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Dan GA, Kalarus Z, Tavazzi L, Maggioni AP, Lip GY. 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) general pilot registry. *Europace* 2016;**18**:648–657.
1057. Gulizia MM, Cemin R, Colivicchi F, De Luca L, Di Lenarda A, Boriani G, Di Pasquale G, Nardi F, Scherillo M, Lucci D, Fabbri G, Maggioni AP; BLITZ-AF Investigators. Management of atrial fibrillation in the emergency room and in the cardiology ward: the BLITZ AF study. *Europace* 2019;**21**:230–238.
1058. Gonzalez-Pacheco H, Marquez MF, Arias-Mendoza A, Alvarez-Sangabriel A, Eid-Lidt G, Gonzalez-Hermosillo A, Azar-Manzur F, Altamirano-Castillo A, Briseno-Cruz JL, Garcia-Martinez A, Mendoza-Garcia S, Martinez-Sanchez C.

Clinical features and in-hospital mortality associated with different types of atrial fibrillation in patients with acute coronary syndrome with and without ST elevation. *J Cardiol* 2015;**66**:148–154.
1059. Krijthe BP, Leening MJ, Heeringa J, Kors JA, Hofman A, Franco OH, Witteman JC, Stricker BH. Unrecognized myocardial infarction and risk of atrial fibrillation: the Rotterdam Study. *Int J Cardiol* 2013;**168**:1453–1457.
1060. Chao TF, Huang YC, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Hsieh MH, Lip GY, Chen SA. Acute myocardial infarction in patients with atrial fibrillation with a CHA2DS2-VASc score of 0 or 1: a nationwide cohort study. *Heart Rhythm* 2014;**11**:1941–1947.
1061. Sanclemente C, Yeste M, Suarez C, Coll R, Aguilar E, Sahuquillo JC, Lerma R, Monreal M; FRENA Investigators. Predictors of outcome in stable outpatients with peripheral artery disease. *Intern Emerg Med* 2014;**9**:69–77.
1062. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2015;**131**:1843–1850.
1063. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med* 2014;**174**:107–114.
1064. Kralev S, Schneider K, Lang S, Suselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PLoS One* 2011;**6**:e24964.
1065. Guimaraes PO, Zakroysky P, Goyal A, Lopes RD, Kaltenbach LA, Wang TY. Usefulness of antithrombotic therapy in patients with atrial fibrillation and acute myocardial infarction. *Am J Cardiol* 2019;**123**:12–18.
1066. Erez A, Goldenberg I, Sabbag A, Nof E, Zahger D, Atar S, Pollak A, Dobrecky-Merye I, Beigel R, Matetzky S, Glikson M, Beinart R. Temporal trends and outcomes associated with atrial fibrillation observed during acute coronary syndrome: real-world data from the Acute Coronary Syndrome Israeli Survey (ACSIS), 2000–2013. *Clin Cardiol* 2017;**40**:275–280.
1067. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
1068. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
1069. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K, ESC Scientific Document Group. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;**21**:192–193.
1070. Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J* 2019;**40**:3757–3767.
1071. Potpara TS, Mujovic N, Proietti M, Dagres N, Hindricks G, Collet JP, Valgimigli M, Heidbuchel H, Lip GYH. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. *Europace* 2020;**22**:33–46.
1072. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;**381**:1103–1113.
1073. Karjalainen PP, Vikman S, Niemela M, Porela P, Ylitalo A, Vaittinen MA, Puurunen M, Airaksinen TJ, Nyman K, Vahlberg T, Airaksinen KE. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. *Eur Heart J* 2008;**29**:1001–1010.
1074. Vranckx P, Leebeek FW, Tijssen JG, Koolen J, Stammen F, Herman JP, de Winter RJ, van THAW, Backx B, Lindeboom W, Kim SY, Kirsch B, van Eickels M, Misselwitz F, Verheugt FW. Peri-procedural use of rivaroxaban in elective percutaneous coronary intervention to treat stable coronary artery disease. The X-PLORER trial. *Thromb Haemost* 2015;**114**:258–267.
1075. Vranckx P, Verheugt FW, de Maat MP, Ulmans VA, Regar E, Smits P, ten Berg JM, Lindeboom W, Jones RL, Friedman J, Reilly P, Leebeek FW. A randomised study of dabigatran in elective percutaneous coronary intervention in stable coronary artery disease patients. *EuroIntervention* 2013;**8**:1052–1060.
1076. Fiedler KA, Maeng M, Mehilli J, Schulz-Schupke S, Byrne RA, Sibbing D, Hoppmann P, Schneider S, Fusaro M, Ott I, Kristensen SD, Ibrahim T, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sarafoff N. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol* 2015;**65**:1619–1629.
1077. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Kober L, Torp-Pedersen C, Hansen ML. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol* 2013;**62**:981–989.
1078. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM, for the WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;**381**:1107–1115.
1079. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH; RE-DUAL PCI Steering Committee Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;**377**:1513–1524.
1080. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, Korjian S, Daaboul Y, Lip GY, Cohen M, Husted S, Peterson ED, Fox KA. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;**375**:2423–2434.
1081. Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med* 2019;**380**:1509–1524.
1082. Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, Batushkin V, Campo G, Lysak Z, Vakaliuk I, Milewski K, Laeis P, Reimitz PE, Smolnik R, Zierhut W, Goette A. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet* 2019;**394**:1335–1343.
1083. Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, Oldgren J, Ten Berg JM, Kimura T, Hohnloser SH, Lip GYH, Bhatt DL. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2018;**39**:1726–1735a.
1084. Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Gibson CM, Alexander JH. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. *JAMA Cardiol* 2019:pii:2735647.
1085. Andreou I, Briasoulis A, Pappas C, Ikonomidis I, Alexopoulos D. Ticagrelor versus clopidogrel as part of dual or triple antithrombotic therapy: a systematic review and meta-analysis. *Cardiovasc Drugs Ther* 2018;**32**:287–294.
1086. Fu A, Singh K, Abunassar J, Malhotra N, Le May M, Labinaz M, Glover C, Marquis JF, Froeschl M, Dick A, Hibbert B, Chong AY, So DY; CAPITAL Investigators. Ticagrelor in triple antithrombotic therapy: predictors of ischemic and bleeding complications. *Clin Cardiol* 2016;**39**:19–23.
1087. Jackson LR, 2nd, Ju C, Zettler M, Messenger JC, Cohen DJ, Stone GW, Baker BA, Effron M, Peterson ED, Wang TY. Outcomes of patients with acute myocardial infarction undergoing percutaneous coronary intervention receiving an oral anticoagulant and dual antiplatelet therapy: a comparison of clopidogrel versus prasugrel from the TRANSLATE-ACS study. *JACC Cardiovasc Interv* 2015;**8**:1880–1889.
1088. Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, Kastrati A. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. *J Am Coll Cardiol* 2013;**61**:2060–2066.
1089. Verlinden NJ, Coons JC, Iasella CJ, Kane-Gill SL. Triple antithrombotic therapy with aspirin, P2Y12 inhibitor, and warfarin after percutaneous coronary

intervention: an evaluation of prasugrel or ticagrelor versus clopidogrel. *J Cardiovasc Pharmacol Ther* 2017;**22**:546–551.
1090. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H, ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
1091. Pikija S, Sztriha LK, Sebastian Mutzenbach J, Golaszewski SM, Sellner J. Idarucizumab in dabigatran-treated patients with acute ischemic stroke receiving alteplase: a systematic review of the available evidence. *CNS Drugs* 2017;**31**:747–757.
1092. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke* 2001;**32**:2333–2337.
1093. Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* 1983;**14**:688–693.
1094. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet* 2000;**355**:1205–1210.
1095. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke* 2007;**38**:423–430.
1096. von Kummer R, Broderick JP, Campbell BC, Demchuk A, Goyal M, Hill MD, Treurniet KM, Majoie CB, Marquering HA, Mazya MV, San Roman L, Saver JL, Strbian D, Whiteley W, Hacke W. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic*stroke and reperfusion therapy*. *Stroke* 2015;**46**:2981–2986.
1097. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. *Stroke* 2008;**39**:2249–2256.
1098. Kablau M, Kreisel SH, Sauer T, Binder J, Szabo K, Hennerici MG, Kern R. Predictors and early outcome of hemorrhagic transformation after acute ischemic stroke. *Cerebrovasc Dis* 2011;**32**:334–341.
1099. Seiffge DJ, Werring DJ, Paciaroni M, Dawson J, Warach S, Milling TJ, Engelter ST, Fischer U, Norrving B. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol* 2019;**18**:117–126.
1100. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, Chondrogianni M, Bovi P, Carletti M, Cappellari M, Zedde M, Ntaios G, Karagkiozi E, Athanasakis G, Makaritsis K, Silvestrelli G, Lanari A, Ciccone A, Putaala J, Tomppo L, Tatlisumak T, Abdul-Rahim AH, Lees KR, Alberti A, Venti M, Acciarresi M, D'Amore C, Becattini C, Mosconi MG, Cimini LA, Soloperto R, Masotti L, Vannucchi V, Lorenzini G, Tassi R, Guideri F, Acampa M, Martini G, Sohn SI, Marcheselli S, Mumoli N, De Lodovici ML, Bono G, Furie KL, Tadi P, Yaghi S, Toni D, Letteri F, Tassinari T, Kargiotis O, Lotti EM, Flomin Y, Mancuso M, Maccarrone M, Giannini N, Bandini F, Pezzini A, Poli L, Padovani A, Scoditti U, Denti L, Consoli D, Galati F, Sacco S, Carolei A, Tiseo C, Gourbali V, Orlandi G, Giuntini M, Chiti A, Giorli E, Gialdini G, Corea F, Ageno W, Bellesini M, Colombo G, Monaco S, Maimone Baronello M, Karapanayiotides T, Caso V. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) study. *J Am Heart Assoc* 2017;**6**.
1101. Seiffge DJ, Traenka C, Polymeris A, Hert L, Peters N, Lyrer P, Engelter ST, Bonati LH, De Marchis GM. Early start of DOAC after ischemic stroke: risk of intracranial hemorrhage and recurrent events. *Neurology* 2016;**87**:1856–1862.
1102. Arihiro S, Todo K, Koga M, Furui E, Kinoshita N, Kimura K, Yamagami H, Terasaki T, Yoshimura S, Shiokawa Y, Kamiyama K, Takizawa S, Okuda S, Okada Y, Nagakane Y, Kameda T, Hasegawa Y, Shibuya S, Ito Y, Nakashima T, Takamatsu K, Nishiyama K, Matsuki T, Homma K, Takasugi J, Tokunaga K, Sato S, Kario K, Kitazono T, Toyoda K; SAMURAI Study Investigators. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: the SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. *Int J Stroke* 2016;**11**:565–574.
1103. Hong KS, Kwon SU, Lee SH, Lee JS, Kim YJ, Song TJ, Kim YD, Park MS, Kim EG, Cha JK, Sung SM, Yoon BW, Bang OY, Seo WK, Hwang YH, Ahn SH, Kang DW, Kang HG, Yu KH, Phase 2 exploratory clinical study to assess the effects of xarelto versus warfarin on ischemia B, hospital stay in acute cerebral infarction patients with non-valvular atrial fibrillation study G. Rivaroxaban vs warfarin sodium in the ultra-early period after atrial fibrillation-related mild ischemic stroke: a randomized clinical trial. *JAMA Neurol* 2017;**74**:1206–1215.
1104. Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: an updated systematic review and meta-analysis of randomized controlled trials. *Int J Stroke* 2017;**12**:589–596.
1105. Gonzalez ME, Klein FR, Riccio PM, Cassara FP, Munoz Giacomelli F, Racosta JM, Roberts ES, Sposato, LA. Atrial fibrillation detected after acute ischemic stroke: evidence supporting the neurogenic hypothesis. *J Stroke Cerebrovasc Dis* 2013;**22**:e486–491.
1106. Sposato LA, Cerasuolo JO, Cipriano LE, Fang J, Fridman S, Paquet M, Saposnik G. Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence. *Neurology* 2018;**90**:e924–e931.
1107. Steinberg BA, Shrader P, Pieper K, Thomas L, Allen LA, Ansell J, Chan PS, Ezekowitz MD, Fonarow GC, Freeman JV, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli GV, Reiffel JA, Singer, DE, Peterson ED, Piccini, JP; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) II Investigators. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). *J Am Heart Assoc* 2018;**7**:e007633.
1108. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ; NAVIGATE ESUS Investigators. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med* 2018;**378**:2191–2201.
1109. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmunzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; RE-SPECT ESUS Steering Committee Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–1917.
1110. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, Haeusler KG, Mikulik R, Kasner SE, Toni D, Arauz A, Ntaios G, Hankey GJ, Perera K, Pagola J, Shuaib A, Lutsep H, Yang X, Uchiyama S, Endres M, Coutts SB, Karlinski M, Czlonkowska A, Molina CA, Santo G, Berkowitz SD, Hart RG, Connolly SJ. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol* 2019.
1111. Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nagele T, Brachmann J, Jung W, Gahn G, Schmid E, Baezner H, Keller T, Petzold GC, Schrickel JW, Liman J, Wachter R, Schon F, Schabet M, Lindner A, Ludolph AC, Kimmig H, Jander S, Schlegel U, Gawaz M, Ziemann U. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): rationale and study design. *Int J Stroke* 2017;**12**:985–990.
1112. Li Y-G, Bisson A, Bodin A, Herbert J, Grammatico-Guillon L, Joung B, Wang Y-T, Lip GYH, Fauchier L. C2HEST score and prediction of incident atrial fibrillation in poststroke patients: a French nationwide study. *J Am Heart Assoc* 2019;**8**:e012546.
1113. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Cote R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–2477.
1114. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–2486.
1115. Wachter R, Groschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jurries F, Messerschmid A, Behnke N, Groschel S, Uphaus T, Grings A, Ibis T, Klimpe S, Wagner-Heck M, Arnold M, Protsenko E, Heuschmann PU, Conen D, Weber-Kruger M; Find-AF(randomised) Investigators and Coordinators. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial. *Lancet Neurol* 2017;**16**:282–290.
1116. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Kohrmann M, Wachter R, Rosin L, Kirchhof P. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke* 2013;**44**:3357–3364.
1117. Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ, Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke* 2014;**45**:520–526.

1118. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;**14**:377–387.
1119. Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, Diener HC, Di Lazzaro V, Rymer MM, Hogge L, Rogers TB, Ziegler PD, Assar MD. Predictors for atrial fibrillation detection after cryptogenic stroke: results from CRYSTAL AF. *Neurology* 2016;**86**:261–269.
1120. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M, Davidson T. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2015;**17**:207–214.
1121. Yong JH, Thavorn K, Hoch JS, Mamdani M, Thorpe KE, Dorian P, Sharma M, Laupacis A, Gladstone DJ, on behalf of the EMBRACE Steering Committee. Potential cost-effectiveness of ambulatory cardiac rhythm monitoring after cryptogenic stroke. *Stroke* 2016;**47**:2380–2385.
1122. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007;**50**:309–315.
1123. Wilson D, Ambler G, Lee KJ, Lim JS, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, Wong YK, Mak HKF, Prats-Sanchez L, Martinez-Domeno A, Inamura S, Yoshifuji K, Arsava EM, Horstmann S, Purrucker J, Lam BYK, Wong A, Kim YD, Song TJ, Schrooten M, Lemmens R, Eppinger S, Gattringer T, Uysal E, Tanriverdi Z, Bornstein NM, Assayag EB, Hallevi H, Tanaka J, Hara H, Coutts SB, Hert L, Polymeris A, Seiffge DJ, Lyrer P, Algra A, Kappelle J, Al-Shahi Salman R, Jager HR, Lip GYH, Mattle HP, Panos LD, Mas JL, Legrand L, Karayiannis C, Phan T, Gunkel S, Christ N, Abrigo J, Leung T, Chu W, Chappell F, Makin S, Hayden D, Williams DJ, Kooi ME, van Dam-Nolen DHK, Barbato C, Browning S, Wiegertjes K, Tuladhar AM, Maaijwee N, Guevarra C, Yatawara C, Mendyk AM, Delmaire C, Kohler S, van Oostenbrugge R, Zhou Y, Xu C, Hilal S, Gyanwali B, Chen C, Lou M, Staals J, Bordet R, Kandiah N, de Leeuw FE, Simister R, van der Lugt A, Kelly PJ, Wardlaw JM, Soo Y, Fluri F, Srikanth V, Calvet D, Jung S, Kwa VIH, Engelter ST, Peters N, Smith EE, Yakushiji Y, Orken DN, Fazekas F, Thijs V, Heo JH, Mok V, Veltkamp R, Ay H, Imaizumi T, Gomez-Anson B, Lau KK, Jouvent E, Rothwell PM, Toyoda K, Bae HJ, Marti-Fabregas J, Werring DJ. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol* 2019;**18**:653–665.
1124. Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, Sheth KN, Hanley DF, Ziai WC, Kamel H. Restarting anticoagulant therapy after intracranial hemorrhage: a systematic review and meta-analysis. *Stroke* 2017;**48**:1594–1600.
1125. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di Pasquale G, Yusuf S. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010;**9**:1157–1163.
1126. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, Alings M, Goto S, Lewis BS, Rosenqvist M, Hanna M, Mohan P, Alexander JH, Diener HC; ARISTOTLE Committees and Investigators. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012;**11**:503–511.
1127. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, Diener HC, Donnan GA, Halperin JL, Mahaffey KW, Mas JL, Massaro A, Norrving B, Nessel CC, Paolini JF, Roine RO, Singer DE, Wong L, Califf RM, Fox KA, Hacke W; ROCKET AF Steering Committee Investigators. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;**11**:315–322.
1128. Rost NS, Giugliano RP, Ruff CT, Murphy SA, Crompton AE, Norden AD, Silverman S, Singhal AB, Nicolau JC, SomaRaju B, Mercuri MF, Antman EM, Braunwald E. Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48). *Stroke* 2016;**47**:2075–2082.
1129. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, O'Donnell M, Hohnloser SH, Hankey GJ, Shestakovska O, Yusuf S. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol* 2012;**11**:225–231.
1130. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993;**342**:1255–1262.
1131. Cuker A. Laboratory measurement of the non-vitamin K antagonist oral anticoagulants: selecting the optimal assay based on drug, assay availability, and clinical indication. *J Thromb Thrombolysis* 2016;**41**:241–247.
1132. Salmonson T, Dogne JM, Janssen H, Garcia Burgos J, Blake P. Non-vitamin-K oral anticoagulants and laboratory testing: now and in the future: views from a workshop at the European Medicines Agency (EMA). *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:42–47.
1133. Chai-Adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost* 2015;**13**:1790–1798.
1134. Anderson I, Cifu AS. Management of bleeding in patients taking oral anticoagulants. *JAMA* 2018;**319**:2032–2033.
1135. Milling TJ Jr, Refaai MA, Sarode R, Lewis B, Mangione A, Durn BL, Harman A, Lee ML, Goldstein JN. Safety of a four-factor prothrombin complex concentrate versus plasma for vitamin K antagonist reversal: an integrated analysis of two phase IIIb clinical trials. *Acad Emerg Med* 2016;**23**:466–475.
1136. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kam CW, Kamphuisen PW, Kreuzer J, Levy JH, Royle G, Sellke FW, Stangier J, Steiner T, Verhamme P, Wang B, Young L, Weitz JI. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med* 2017;**377**:431–441.
1137. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Demchuk AM, Pallin DJ, Concha M, Goodman S, Leeds J, Souza S, Siegal DM, Zotova E, Meeks B, Ahmad S, Nakamya J, Milling TJ Jr; ANNEXA Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* 2019;**380**:1326–1335.
1138. Levi M, Moore KT, Castillejos CF, Kubitza D, Berkowitz SD, Goldhaber SZ, Raghoebar M, Patel MR, Weitz JI, Levy JH. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost* 2014;**12**:1428–1436.
1139. Nagalla S, Thomson L, Oppong Y, Bachman B, Chervoneva I, Kraft WK. Reversibility of apixaban anticoagulation with a four-factor prothrombin complex concentrate in healthy volunteers. *Clin Transl Sci* 2016;**9**:176–180.
1140. Zahir H, Brown KS, Vandell AG, Desai M, Maa JF, Dishy V, Lomeli B, Feussner A, Feng W, He L, Grosso MA, Lanz HJ, Antman EM. Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation* 2015;**131**:82–90.
1141. Isnard R, Bauer F, Cohen-Solal A, Damy T, Donal E, Galinier M, Hagege A, Jourdain P, Leclercq C, Sabatier R, Trochu JN, Cohen A. Non-vitamin K antagonist oral anticoagulants and heart failure. *Arch Cardiovasc Dis* 2016;**109**:641–650.
1142. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015;**17**:1192–1200.
1143. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, LeBlanc MH, Masoudi FA, Ross HJ, Roussin A, Sussex B. 2017 comprehensive update of the Canadian Cardiovascular Society Guidelines for the management of heart failure. *Can J Cardiol* 2017;**33**:1342–1433.
1144. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, Kistler PM, Briffa T, Wong J, Abhayaratna W, Thomas L, Audehm R, Newton P, O'Loughlin J, Branagan M, Connell C. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the prevention, detection, and management of heart failure in Australia 2018. *Heart Lung Circ* 2018;**27**:1123–1208.
1145. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
1146. Kelly JP, DeVore AD, Wu J, Hammill BG, Sharma A, Cooper LB, Felker GM, Piccini JP, Allen LA, Heidenreich PA, Peterson ED, Yancy CW, Fonarow GC, Hernandez AF. Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from Get With The Guidelines-Heart Failure. *J Am Heart Assoc* 2019;**8**:e011560.
1147. Filippatos G, Farmakis D. How to use beta-blockers in heart failure with reduced ejection fraction and atrial fibrillation. *J Am Coll Cardiol* 2017;**69**:2897–2900.

1148. Nielsen PB, Larsen TB, Gorst-Rasmussen A, Skjoth F, Lip GY. beta-Blockers in atrial fibrillation patients with or without heart failure: association with mortality in a nationwide cohort study. *Circ Heart Fail* 2016;**9**:e002597.
1149. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011.
1150. Barbash IM, Minha S, Ben-Dor I, Dvir D, Torguson R, Aly M, Bond E, Satler LF, Pichard AD, Waksman R. Predictors and clinical implications of atrial fibrillation in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;**85**:468–477.
1151. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, Misu K, Asano R, Nagayama M, Sumiyoshi T, Kasegawa H, Hosoda S. Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. *Eur Heart J* 2005;**26**:1866–1872.
1152. Maan A, Heist EK, Passeri J, Inglessis I, Baker J, Ptaszek L, Vlahakes G, Ruskin JN, Palacios I, Sundt T, Mansour M. Impact of atrial fibrillation on outcomes in patients who underwent transcatheter aortic valve replacement. *Am J Cardiol* 2015;**115**:220–226.
1153. Ngaage DL, Schaff HV, Barnes SA, Sundt TM 3rd, Mullany CJ, Dearani JA, Daly RC, Orszulak TA. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery?*Ann Thorac Surg* 2006;**82**:1392–1399.
1154. Ngaage DL, Schaff HV, Mullany CJ, Barnes S, Dearani JA, Daly RC, Orszulak TA, Sundt TM 3rd. Influence of preoperative atrial fibrillation on late results of mitral repair: is concomitant ablation justified?*Ann Thorac Surg* 2007;**84**:434–442.
1155. Lim E, Barlow CW, Hosseinpour AR, Wisbey C, Wilson K, Pidgeon W, Charman S, Barlow JB, Wells FC. Influence of atrial fibrillation on outcome following mitral valve repair. *Circulation* 2001;**104**:I59–63.
1156. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Babuty D, Angoulvant D, Lip GY, Fauchier L. Prognostic value of CHA2DS2-VASc score in patients with 'non-valvular atrial fibrillation' and valvular heart disease: the Loire Valley Atrial Fibrillation Project. *Eur Heart J* 2015;**36**:1822–1830.
11547. Lip GYH, Jensen M, Melgaard L, Skjoth F, Nielsen PB, Larsen TB. Stroke and bleeding risk scores in patients with atrial fibrillation and valvular heart disease: evaluating 'valvular heart disease' in a nationwide cohort study. *Europace* 2019;**21**:33–40.
1158. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br Med J* 1964;**1**:1209–1212.
1159. Philippart R, Brunet-Bernard A, Clementy N, Bourguignon T, Mirza A, Angoulvant D, Babuty D, Lip GY, Fauchier L. Oral anticoagulation, stroke and thromboembolism in patients with atrial fibrillation and valve bioprosthesis. The Loire Valley Atrial Fibrillation Project. *Thromb Haemost* 2016;**115**:1056–1063.
1160. Siontis KC, Yao X, Gersh BJ, Noseworthy PA. Direct oral anticoagulants in patients with atrial fibrillation and valvular heart disease other than significant mitral stenosis and mechanical valves: a meta-analysis. *Circulation* 2017;**135**:714–716.
1161. Kim JY, Kim SH, Myong JP, Kim YR, Kim TS, Kim JH, Jang SW, Oh YS, Lee MY, Rho TH. Outcomes of direct oral anticoagulants in patients with mitral stenosis. *J Am Coll Cardiol* 2019;**73**:1123–1131.
1162. Bisson A, Bodin A, Clementy N, Bernard A, Babuty D, Lip GYH, Fauchier L. Stroke, thromboembolism and bleeding in patients with atrial fibrillation according to the EHRA valvular heart disease classification. *Int J Cardiol* 2018;**260**:93–98.
1163. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**:66–74.
1164. Dangas GD, Tijssen JGP, Wohrle J, Sondergaard L, Gilard M, Mollmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimaraes AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schafer U, Seeger J, Tchetche D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S, for the GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:120–129.
1165. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoon ML, Van de Werf, F; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;**369**:1206–1214.
1166. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. *Nat Rev Nephrol* 2018;**14**:337–351.
1167. Albertsen IE, Rasmussen LH, Overvad TF, Graungaard T, Larsen TB, Lip GY. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. *Stroke* 2013;**44**:1329–1336.
1168. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;**367**:625–635.
1169. Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. *Can J Cardiol* 2013;**29**:S71–78.
1170. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant* 2012;**27**:3816–3822.
1171. Banerjee A, Fauchier L, Vourc'h P, Andres CR, Taillandier S, Halimi JM, Lip GYH. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2014;**145**:1370–1382.
1172. Fauchier L, Bisson A, Clementy N, Vourc'h P, Angoulvant D, Babuty D, Halimi JM, Lip GYH. Changes in glomerular filtration rate and outcomes in patients with atrial fibrillation. *Am Heart J* 2018;**198**:39–45.
1173. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, Braunwald E. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 2016;**134**:24–36.
1174. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation* 2014;**129**:961–970.
1175. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011;**32**:2387–2394.
1176. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012;**33**:2821–2830.
1177. Coleman CI, Kreutz R, Sood NA, Bunz TJ, Eriksson D, Meinecke AK, Baker WL. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. *Am J Med* 2019;**132**:1078–1083.
1178. Ha JT, Neuen BL, Cheng LP, Jun M, Toyama T, Gallagher MP, Jardine MJ, Sood MM, Garg AX, Palmer SC, Mark PB, Wheeler DC, Jha V, Freedman B, Johnson DW, Perkovic V, Badve SV. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2019;**171**:181–189.
1179. Pokorney SD. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation (RENAL-AF). Presentation at the American Heart Association Annual Scientific Sessions (AHA 2019), Philadelphia, PA, 16 November 2019.
1180. Violi F, Davi G, Hiatt W, Lip GY, Corazza GR, Perticone F, Proietti M, Pignatelli P, Vestri AR, Basili S; ARAPACIS Study Investigators. Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation: implications for risk and therapy. *J Am Coll Cardiol* 2013;**62**:2255–2256.
1181. Bruere H, Fauchier L, Bernard Brunet A, Pierre B, Simeon E, Babuty D, Clementy N. History of thyroid disorders in relation to clinical outcomes in atrial fibrillation. *Am J Med* 2015;**128**:30–37.
1182. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of atrial fibrillation in the post-thyrotoxic state. *Am J Med* 1982;**72**:903–906.
1183. Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. *Europace* 2014;**16**:477–484.
1184. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013;**145**:105–112.e15.
1185. Caldeira D, Barra M, Ferreira A, Rocha A, Augusto A, Pinto FJ, Costa J, Ferreira JJ. Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. *Aliment Pharmacol Ther* 2015;**42**:1239–1249.
1186. Kolb JM, Flack KF, Chatterjee-Murphy P, Desai J, Wallentin LC, Ezekowitz M, Connolly S, Reilly P, Brueckmann M, Ilgenfritz J, Aisenberg J. Locations and mucosal lesions responsible for major gastrointestinal bleeding in patients on warfarin or dabigatran. *Dig Dis Sci* 2018;**63**:1878–1889.
1187. Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. *Thromb Haemost* 2015;**114**:819–825.

1188. O'Dea D, Whetteckey J, Ting N. A prospective, randomized, open-label study to evaluate two management strategies for gastrointestinal symptoms in patients newly on treatment with dabigatran. *Cardiol Ther* 2016;**5**:187–201.
1189. Lai HC, Chien WC, Chung CH, Lee WL, Wu TJ, Wang KY, Liu CN, Liu TJ. Atrial fibrillation, liver disease, antithrombotics and risk of cerebrovascular events: a population-based cohort study. *Int J Cardiol* 2016;**223**:829–837.
1190. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol* 2011;**57**:173–180.
1191. Potpara TS, Lip GY. Drug-induced liver injury with oral anticoagulants: a threat or not?*Heart* 2017;**103**:809–811.
1192. Hoolwerf EW, Kraaijpoel N, Buller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: a systematic review. *Thromb Res* 2018;**170**:102–108.
1193. Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, Mueck W. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct factor Xa inhibitor. *Br J Clin Pharmacol* 2013;**76**:89–98.
1194. Bonde AN, Blanche P, Staerk L, Gerds TA, Gundlund A, Gislason G, Torp-Pedersen C, Lip GYH, Hlatky MA, Olesen JB. Oral anticoagulation among atrial fibrillation patients with anaemia: an observational cohort study. *Eur Heart J* 2019.
1195. Arun M, Brauneis D, Doros G, Shelton AC, Sloan JM, Quillen K, Ruberg FL, Sanchorawala V, Varga C. The incidence of atrial fibrillation among patients with AL amyloidosis undergoing high-dose melphalan and stem cell transplantation: experience at a single institution. *Bone Marrow Transplant* 2017;**52**:1349–1351.
1196. Yuan M, Tse G, Zhang Z, Han X, Wu WKK, Li G, Xia Y, Liu T. The incidence of atrial fibrillation with trastuzumab treatment: a systematic review and meta-analysis. *Cardiovasc Ther* 2018;**36**:e12475.
1197. Ganatra S, Sharma A, Shah S, Chaudhry GM, Martin DT, Neilan TG, Mahmood SS, Barac A, Groarke JD, Hayek SS, Dani S, Venesy D, Patten R, Nohria A. Ibrutinib-associated atrial fibrillation. *JACC Clin Electrophysiol* 2018;**4**:1491–1500.
1198. Boriani G, Corradini P, Cuneo A, Falanga A, Foa R, Gaidano G, Ghia PP, Martelli M, Marasca R, Massaia M, Mauro FR, Minotti G, Molica S, Montillo M, Pinto A, Tedeschi A, Vitolo U, Zinzani PL. Practical management of ibrutinib in the real life: focus on atrial fibrillation and bleeding. *Hematol Oncol* 2018;**36**:624–632.
1199. Yun S, Vincelette ND, Acharya U, Abraham I. Risk of atrial fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic review and pooled analysis of four randomized controlled trials. *Clin Lymphoma Myeloma Leuk* 2017;**17**:31–37.e13.
1200. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;**155**:469–473.
1201. Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *J Am Heart Assoc* 2017;**6**:e005155.
1202. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000,*and implications on the projections for future prevalence. Circulation* 2006;**114**:119–125.
1203. Ohlmeier C, Mikolajczyk R, Haverkamp W, Garbe E. Incidence, prevalence, and antithrombotic management of atrial fibrillation in elderly Germans. *Europace* 2013;**15**:1436–1444.
1204. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–2375.
1205. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, Maywald U, Bauersachs R, Breithardt G. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace* 2013;**15**:486–493.
1206. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014;**6**:213–220.
1207. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol* 2010;**56**:827–837.
1208. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–554.
1209. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun M, MaCurdy TE, Worrall C, Kelman JA. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015;**131**:157–164.
1210. Biteker M, Basaran O, Dogan V, Altun I, Ozpamuk Karadeniz F, Tekkesin AI, Cakilli Y, Turkkan C, Hamidi M, Demir V, Gursoy MO, Tek Ozturk M, Aksan G, Seyis S, Balli M, Alici MH, Bozyel S. Real-world clinical characteristics and treatment patterns of individuals aged 80 and older with nonvalvular atrial fibrillation: results from the ReAl-life Multicenter Survey Evaluating Stroke Study. *J Am Geriatr Soc* 2017;**65**:1684–1690.
1211. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke* 2000;**31**:822–827.
1212. Ghaswalla PK, Harpe SE, Slattum PW. Warfarin use in nursing home residents: results from the 2004 national nursing home survey. *Am J Geriatr Pharmacother* 2012;**10**:25–36.e2.
1213. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660–666.
1214. Oqab Z, Pournazari P, Sheldon RS. What is the impact of frailty on prescription of anticoagulation in elderly patients with atrial fibrillation? A systematic review and meta-analysis. *J Atr Fibrillation* 2018;**10**:1870.
1215. Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GYH, on behalf of the AF Gen Pilot Investigators. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace* 2017;**19**:722–733.
1216. Singh P, Arrevad PS, Peterson GM, Bereznicki LR. Evaluation of antithrombotic usage for atrial fibrillation in aged care facilities. *J Clin Pharm Ther* 2011;**36**:166–171.
1217. Annoni G, Mazzola P. Real-world characteristics of hospitalized frail elderly patients with atrial fibrillation: can we improve the current prescription of anticoagulants?*J Geriatr Cardiol* 2016;**13**:226–232.
1218. Deandrea S, Bravi F, Turati F, Lucenteforte E, La Vecchia C, Negri E. Risk factors for falls in older people in nursing homes and hospitals. A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2013;**56**:407–415.
1219. Phelan EA, Mahoney JE, Voit JC, Stevens JA. Assessment and management of fall risk in primary care settings. *Med Clin North Am* 2015;**99**:281–293.
1220. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;**125**:773–778.
1221. Garwood CL, Corbett TL. Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *Ann Pharmacother* 2008;**42**:523–532.
1222. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med* 2007;**147**:590–592.
1223. Jacobs LG, Billett HH, Freeman K, Dinglas C, Jumaquio L. Anticoagulation for stroke prevention in elderly patients with atrial fibrillation, including those with falls and/or early-stage dementia: a single-center, retrospective, observational study. *Am J Geriatr Pharmacother* 2009;**7**:159–166.
1224. Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). *Age Ageing* 2007;**36**:151–156.
1225. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc* 2014;**62**:857–864.
1226. Siu CW, Tse HF. Net clinical benefit of warfarin therapy in elderly Chinese patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;**7**:300–306.
1227. Alnsasra H, Haim M, Senderey AB, Reges O, Leventer-Roberts M, Arnson Y, Leibowitz M, Hoshen M, Avgil-Tsadok M. Net clinical benefit of anticoagulant treatments in elderly patients with nonvalvular atrial fibrillation: experience from the real world. *Heart Rhythm* 2019;**16**:31–37.
1228. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HC, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;**123**:2363–2372.
1229. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, Breithardt G, Singer DE, Becker RC, Hacke W, Paolini JF, Nessel CC, Mahaffey KW, Califf RM, Fox KA; ROCKET AF Steering Committee Investigators. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K

Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation* 2014;**130**:138–146.
1230. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, Hylek EM, Jansky P, Lopes RD, Ruzyllo W, Thomas L, Wallentin L. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J* 2014;**35**:1864–1872.
1231. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iekushi K, Yamanaka S, Tajiri M; J-ROCKET AF Study Investigators. Rivaroxaban vs. warfarin in Japanese patients with non-valvular atrial fibrillation in relation to age. *Circ J* 2014;**78**:1349–1356.
1232. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, Nordio F, Murphy SA, Kimura T, Jin J, Lanz H, Mercuri M, Braunwald E, Antman, EM. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc* 2016;**5**:e003432.
1233. Kim IS, Kim HJ, Kim TH, Uhm JS, Joung B, Lee MH, Pak HN. Non-vitamin K antagonist oral anticoagulants have better efficacy and equivalent safety compared to warfarin in elderly patients with atrial fibrillation: a systematic review and meta-analysis. *J Cardiol* 2018;**72**:105–112.
1234. Ng KH, Shestakovska O, Connolly SJ, Eikelboom JW, Avezum A, Diaz R, Lanas F, Yusuf S, Hart RG. Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. *Age Ageing* 2016;**45**:77–83.
1235. Ruiz Ortiz M, Muniz J, Rana Miguez P, Roldan I, Marin F, Asuncion Esteve-Pastor M Cequier A, Martinez-Selles M, Bertomeu V, Anguita M; FANTASIIA Study Investigators. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. *Europace* 2018;**20**:1577–1583.
1236. Deitelzweig S, Keshishian A, Li X, Kang A, Dhamane AD, Luo X, Balachander N, Rosenblatt L, Mardekian J, Pan X, Nadkarni A, Di Fusco M, Garcia Reeves AB, Yuce H, Lip GYH. Comparisons between oral anticoagulants among older nonvalvular atrial fibrillation patients. *J Am Geriatr Soc* 2019;**67**:1662–1671.
1237. Dillinger JG, Aleil B, Cheggour S, Benhamou Y, Bejot Y, Marechaux S, Delluc A, Bertoletti L, Lellouche N. Dosing issues with non-vitamin K antagonist oral anticoagulants for the treatment of non-valvular atrial fibrillation: why we should not underdose our patients. *Arch Cardiovasc Dis* 2018;**111**:85–94.
1238. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, Meeder JG, Prins MH, Levy S, Crijns HJ; Euro Heart Survey Investigators. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J* 2007;**153**:1006–1012.
1239. Fumagalli S, Said SAM, Laroche C, Gabbai D, Marchionni N, Boriani G, Maggioni AP, Popescu MI, Rasmussen LH, Crijns H, Lip GYH; EORP-AF Investigators. Age-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in europe: the EORP-AF General Pilot Registry (EURObservational Research Programme-Atrial Fibrillation). *JACC Clin Electrophysiol* 2015;**1**:326–334.
1240. Paciullo F, Proietti M, Bianconi V, Nobili A, Pirro M, Mannucci PM, Lip GYH, Lupattelli G; REPOSI Investigators. Choice and outcomes of rate control versus rhythm control in elderly patients with atrial fibrillation: a report from the REPOSI Study. *Drugs Aging* 2018;**35**:365–373.
1241. Shariff N, Desai RV, Patel K, Ahmed MI, Fonarow GC, Rich MW, Aban IB, Banach M, Love TE, White M, Aronow WS, Epstein AE, Ahmed A. Rate-control versus rhythm-control strategies and outcomes in septuagenarians with atrial fibrillation. *Am J Med* 2013;**126**:887–893.
1242. Purmah Y, Proietti M, Laroche C, Mazurek M, Tahmatzidis D, Boriani G, Novo S, Lip GYH; EORP-AF General Pilot Registry Investigators. Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation. *Europace* 2018;**20**:243–252.
1243. Abdin A, Yalin K, Lyan E, Sawan N, Liosis S, Meyer-Saraei R, Elsner C, Lange SA, Heeger CH, Eitel C, Eitel I, Tilz RR. Safety and efficacy of cryoballoon ablation for the treatment of atrial fibrillation in elderly patients. *Clin Res Cardiol* 2019;**108**:167–174.
1244. Bhargava M, Marrouche NF, Martin DO, Schweikert RA, Saliba W, Saad EB, Bash D, Williams-Andrews M, Rossillo A, Erciyes D, Khaykin Y, Burkhardt JD, Joseph G, Tchou PJ, Natale A. Impact of age on the outcome of pulmonary vein isolation for atrial fibrillation using circular mapping technique and cooled-tip ablation catheter. *J Cardiovasc Electrophysiol* 2004;**15**:8–13.
1245. Bulava A, Hanis J, Dusek L. Clinical outcomes of radiofrequency catheter ablation of atrial fibrillation in octogenarians-10-year experience of a one high-volume center. *J Geriatr Cardiol* 2017;**14**:575–581.
1246. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Lappe DL, Muhlestein JB, Nelson J, Day JD. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in octogenarians. *Pacing Clin Electrophysiol* 2010;**33**:146–152.
1247. Heeger CH, Bellmann B, Fink T, Bohnen JE, Wissner E, Wohlmuth P, Rottner L, Sohns C, Tilz RR, Mathew S, Reissmann B, Lemes C, Maurer T, Luker J, Sultan A, Plenge T, Goldmann B, Ouyang F, Kuck KH, Metzner I, Metzner A, Steven D, Rillig A. Efficacy and safety of cryoballoon ablation in the elderly: a multicenter study. *Int J Cardiol* 2019;**278**:108–113.
1248. Kis Z, Noten AM, Martirosyan M, Hendriks AA, Bhagwandien R, Szili-Torok T. Comparison of long-term outcome between patients aged <65 years vs. >/=65 years after atrial fibrillation ablation. *J Geriatr Cardiol* 2017;**14**:569–574.
1249. Lim T, Day D, Weiss P, Crandall BG, May HAT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Lappe DL, Mahapatra S, Bunch TJ. More aggressive left atrial ablation in elderly patients does not increase procedural complications. *J Innov Card Rhythm Manag* 2011;**2**:206–211.
1250. Lin T, Du X, Bai R, Chen YW, Yu RH, Long DY, Tang RB, Sang CH, Li SN, Ma CS, Dong JZ. Long-term results of single-procedure catheter ablation for atrial fibrillationin pre- and post-menopausal women. *J Geriatr Cardiol* 2014;**11**:120–125.
1251. Lioni L, Letsas KP, Efremidis M, Vlachos K, Giannopoulos G, Kareliotis V, Deftereos S, Sideris A. Catheter ablation of atrial fibrillation in the elderly. *J Geriatr Cardiol* 2014;**11**:291–295.
1252. Metzner I, Wissner E, Tilz RR, Rillig A, Mathew S, Schmidt B, Chun J, Wohlmuth P, Deiss S, Lemes C, Maurer T, Fink T, Heeger C, Ouyang F, Kuck KH, Metzner A. Ablation of atrial fibrillation in patients >/=75 years: long-term clinical outcome and safety. *Europace* 2016;**18**:543–549.
1253. Santangeli P, Di Biase L, Mohanty P, Burkhardt JD, Horton R, Bai R, Mohanty S, Pump A, Gibson D, Couts L, Hongo R, Beheiry S, Natale A. Catheter ablation of atrial fibrillation in octogenarians: safety and outcomes. *J Cardiovasc Electrophysiol* 2012;**23**:687–693.
1254. Tan HW, Wang XH, Shi HF, Yang GS, Zhou L, Gu JN, Jiang WF, Liu X. Efficacy, safety and outcome of catheter ablation for atrial fibrillation in octogenarians. *Int J Cardiol* 2010;**145**:147–148.
1255. Zado E, Callans DJ, Riley M, Hutchinson M, Garcia F, Bala R, Lin D, Cooper J, Verdino R, Russo AM, Dixit S, Gerstenfeld E, Marchlinski FE. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol* 2008;**19**:621–626.
1256. Abugattas JP, Iacopino S, Moran D, De Regibus V, Takarada K, Mugnai G, Stroker E, Coutino-Moreno HE, Choudhury R, Storti C, De Greef Y, Paparella G, Brugada P, de Asmundis C, Chierchia GB. Efficacy and safety of the second generation cryoballoon ablation for the treatment of paroxysmal atrial fibrillation in patients over 75 years: a comparison with a younger cohort. *Europace* 2017;**19**:1798–1803.
1257. Bunch TJ, May HT, Bair TL, Jacobs V, Crandall BG, Cutler M, Weiss JP, Mallender C, Osborn JS, Anderson JL, Day JD. The impact of age on 5-year outcomes after atrial fibrillation catheter ablation. *J Cardiovasc Electrophysiol* 2016;**27**:141–146.
1258. Guiot A, Jongnarangsin K, Chugh A, Suwanagool A, Latchamsetty R, Myles JD, Jiang Q, Crawford T, Good E, Pelosi F Jr, Bogun F, Morady F, Oral H. Anticoagulant therapy and risk of cerebrovascular events after catheter ablation of atrial fibrillation in the elderly. *J Cardiovasc Electrophysiol* 2012;**23**:36–43.
1259. Kusumoto F, Prussak K, Wiesinger M, Pullen T, Lynady C. Radiofrequency catheter ablation of atrial fibrillation in older patients: outcomes and complications. *J Interv Card Electrophysiol* 2009;**25**:31–35.
1260. Liu Y, Huang H, Huang C, Zhang S, Ma C, Liu X, Yang Y, Cao K, Wu S, Wang F; National Atrial Fibrillation Working Group of Chinese Society of Pacing and Electrophysiology. Catheter ablation of atrial fibrillation in Chinese elderly patients. *Int J Cardiol* 2011;**152**:266–267.
1261. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. *J Am Coll Cardiol* 2012;**59**:143–149.
1262. Spragg DD, Dalal D, Cheema A, Scherr D, Chilukuri K, Cheng A, Henrikson CA, Marine JE, Berger RD, Dong J, Calkins H. Complications of catheter ablation for atrial fibrillation: incidence and predictors. *J Cardiovasc Electrophysiol* 2008;**19**:627–631.
1263. Srivatsa UN, Danielsen B, Anderson I, Amsterdam E, Pezeshkian N, Yang Y, White RH. Risk predictors of stroke and mortality after ablation for atrial fibrillation: the California experience 2005–2009. *Heart Rhythm* 2014;**11**:1898–1903.
1264. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J* 2018;**39**:453–460.
1265. Jacobs V, Woller SC, Stevens S, May HT, Bair TL, Anderson JL, Crandall BG, Day JD, Johanning K, Long Y, Mallender C, Olson JL, Osborn JS, Weiss JP, Bunch TJ. Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm* 2014;**11**:2206–2213.
1266. Jacobs V, Woller SC, Stevens SM, May HT, Bair TL, Crandall BG, Cutler M, Day JD, Weiss JP, Osborn JS, Mallender C, Anderson JL, Bunch TJ. Percent

time with a supratherapeutic INR in atrial fibrillation patients also using an antiplatelet agent is associated with long-term risk of dementia. *J Cardiovasc Electrophysiol* 2015;**26**:1180–1186.
1267. Jacobs V, May HT, Bair TL, Crandall BG, Cutler MJ, Day JD, Mallender C, Osborn JS, Stevens SM, Weiss JP, Woller SC, Bunch TJ. Long-term population-based cerebral ischemic event and cognitive outcomes of direct oral anticoagulants compared with warfarin among long-term anticoagulated patients for atrial fibrillation. *Am J Cardiol* 2016;**118**:210–214.
1268. Zhang C, Gu ZC, Shen L, Pan MM, Yan YD, Pu J, Liu XY, Lin HW. Non-vitamin K antagonist oral anticoagulants and cognitive impairment in atrial fibrillation: insights from the meta-analysis of over 90,000 patients of randomized controlled trials and real-world studies. *Front Aging Neurosci* 2018;**10**:258.
1269. Sogaard M, Skjoth F, Jensen M, Kjaeldgaard JN, Lip GYH, Larsen TB, Nielsen PB. Nonvitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients and risk of dementia: a nationwide propensity-weighted cohort study. *J Am Heart Assoc* 2019;**8**:e011358.
1270. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J* 2019;**40**:2327–2335.
121. Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community?*Eur J Clin Pharmacol* 2001;**57**:589–594.
1272. Salas M, In't Veld BA, van der Linden PD, Hofman A, Breteler M, Stricker BH. Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. *Clin Pharmacol Ther* 2001;**70**:561–566.
1273. Jensen AS, Idorn L, Norager B, Vejlstrup N, Sondergaard L. Anticoagulation in adults with congenital heart disease: the who, the when and the how?*Heart* 2015;**101**:424–429.
1274. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017;**69**:1363–1371.
1275. Caldeira D, David C, Costa J, Ferreira JJ, Pinto FJ. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2018;**4**:111–118.
1276. Ammash NM, Phillips SD, Hodge DO, Connolly HM, Grogan MA, Friedman PA, Warnes CA, Asirvatham SJ. Outcome of direct current cardioversion for atrial arrhythmias in adults with congenital heart disease. *Int J Cardiol* 2012;**154**:270–274.
1277. Feltes TF, Friedman RA. Transesophageal echocardiographic detection of atrial thrombi in patients with nonfibrillation atrial tachyarrhythmias and congenital heart disease. *J Am Coll Cardiol* 1994;**24**:1365–1370.
1278. Roos-Hesselink J, Meijboom F, Spitaels S, van Domburg R, van Rijen E, Utens E, Bogers A, Simoons M, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21–33 years. *Eur Heart J* 2003;**24**:190–197.
1279. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Bejot Y, Vuillier F, Detante O, Guidoux C, Canaple S, Vaduva C, Dequatre-Ponchelle N, Sibon I, Garnier P, Ferrier A, Timsit S, Robinet-Borgomano E, Sablot D, Lacour JC, Zuber M, Favrole P, Pinel JF, Apoil M, Reiner P, Lefebvre C, Guerin P, Piot C, Rossi R, Dubois-Rande JL, Eicher JC, Meneveau N, Lusson JR, Bertrand B, Schleich JM, Godart F, Thambo JB, Leborgne L, Michel P, Pierard L, Turc G, Barthelet M, Charles-Nelson A, Weimar C, Moulin T, Juliard JM, Chatellier G; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med* 2017;**377**:1011–1021.
1280. Gutierrez SD, Earing MG, Singh AK, Tweddell JS, Bartz PJ. Atrial tachyarrhythmias and the Cox-maze procedure in congenital heart disease. *Congenit Heart Dis* 2013;**8**:434–439.
1281. Kobayashi J, Yamamoto F, Nakano K, Sasako Y, Kitamura S, Kosakai Y. Maze procedure for atrial fibrillation associated with atrial septal defect. *Circulation* 1998;**98**:II399–402.
1282. Shim H, Yang JH, Park PW, Jeong DS, Jun TG. Efficacy of the maze procedure for atrial fibrillation associated with atrial septal defect. *Korean J Thorac Cardiovasc Surg* 2013;**46**:98–103.
1283. Sherwin ED, Triedman JK, Walsh EP. Update on interventional electrophysiology in congenital heart disease: evolving solutions for complex hearts. *Circ Arrhythm Electrophysiol* 2013;**6**:1032–1040.
1284. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704–709.
1285. Zellerhoff S, Pistulli R, Monnig G, Hinterseer M, Beckmann BM, Kobe J, Steinbeck G, Kaab S, Haverkamp W, Fabritz L, Gradaus R, Breithardt G, Schulze-Bahr E, Bocker D, Kirchhof P. Atrial arrhythmias in long-QT syndrome under daily life conditions: a nested case control study. *J Cardiovasc Electrophysiol* 2009;**20**:401–407.
1286. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT syndrome: a familial cause of sudden death. *Circulation* 2003;**108**:965–970.
1287. Borggrefe M, Wolpert C, Antzelevitch C, Veltmann C, Giustetto C, Gaita F, Schimpf R. Short QT syndrome. Genotype-phenotype correlations. *J Electrocardiol* 2005;**38**:75–80.
1288. Giustetto C, Di Monte F, Wolpert C, Borggrefe M, Schimpf R, Sbragia P, Leone G, Maury P, Anttonen O, Haissaguerre M, Gaita F. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. *Eur Heart J* 2006;**27**:2440–2447.
1289. Giustetto C, Schimpf R, Mazzanti A, Scrocco C, Maury P, Anttonen O, Probst V, Blanc JJ, Sbragia P, Dalmasso P, Borggrefe M, Gaita F. Long-term follow-up of patients with short QT syndrome. *J Am Coll Cardiol* 2011;**58**:587–595.
1290. Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011;**57**:802–812.
1291. Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P, Haissaguerre M, Clementy J. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;**25**:879–884.
1292. Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, Morita H, Nishii N, Watanabe A, Tada T, Murakami M, Miyaji K, Hiramatsu S, Nakagawa K, Tanaka M, Miura A, Kimura H, Fuke S, Sumita W, Sakuragi S, Urakawa S, Iwasaki J, Ohe T. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol* 2008;**51**:1169–1175.
1293. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J Am Coll Cardiol* 2008;**51**:1149–1153.
1294. Rodriguez-Manero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, de Asmundis C, Chierchia GB, Wauters K, Rao JY, Bayrak F, Van Malderen S, Brugada P. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. *Am J Cardiol* 2013;**111**:362–367.
1295. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, Komatsu Y, Marquie C, Rosa A, Diallo A, Cassagneau R, Loizeau C, Martins R, Field ME, Derval N, Miyazaki S, Denis A, Nogami A, Ritter P, Gourraud JB, Ploux S, Rollin A, Zemmoura A, Lamaison D, Bordachar P, Pierre B, Jais P, Pasquie JL, Hocini M, Legal F, Defaye P, Boveda S, Iesaka Y, Mabo P, Haissaguerre M. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study – part 2. *Circulation* 2013;**128**:1739–1747.
1296. Hernandez-Ojeda J, Arbelo E, Borras R, Berne P, Tolosana JM, Gomez-Juanatey A, Berruezo A, Campuzano O, Sarquella-Brugada G, Mont L, Brugada R, Brugada J. Patients with Brugada syndrome and implanted cardioverter-defibrillators: long-term follow-up. *J Am Coll Cardiol* 2017;**70**:1991–2002.
1297. Sumitomo N, Sakurada H, Taniguchi K, Matsumura M, Abe O, Miyashita M, Kanamaru H, Karasawa K, Ayusawa M, Fukamizu S, Nagaoka I, Horie M, Harada K, Hiraoka M. Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. *Circ J* 2007;**71**:1606–1609.
1298. Sy RW, Gollob MH, Klein GJ, Yee R, Skanes AC, Gula LJ, Leong-Sit P, Gow RM, Green MS, Birnie DH, Krahn AD. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2011;**8**:864–871.
1299. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;**3**:e001002.
1300. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465–472.
1301. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, Rastegar H, Estes NAM, Maron MS, Maron BJ. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017;**136**:2420–2436.
1302. Rowin EJ, Orfanos A, Estes NAM, Wang W, Link MS, Maron MS, Maron BJ. Occurrence and natural history of clinically silent episodes of atrial fibrillation in hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:1862–1865.
1303. van Velzen HG, Theuns DA, Yap SC, Michels M, Schinkel AF. Incidence of device-detected atrial fibrillation and long-term outcomes in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:100–105.
1304. Klopotowski M, Kwapiszewska A, Kukula K, Jamiolkowski J, Dabrowski M, Derejko P, Oreziak A, Baranowski R, Spiewak M, Marczak M, Klisiewicz A, Szepietowska B, Chmielak Z, Witkowski A. Clinical and echocardiographic parameters as risk factors for atrial fibrillation in patients with hypertrophic cardiomyopathy. *Clin Cardiol* 2018;**41**:1336–1340.
1305. Choi YJ, Choi EK, Han KD, Jung JH, Park J, Lee E, Choe W, Lee SR, Cha MJ, Lim WH, Oh S. Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: a nationwide population-based study. *Int J Cardiol* 2018;**273**:130–135.

1306. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010;**106**:720–722.
1307. Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, te Riele AS, Judge DP, Tandri H, Calkins H. Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2013;**10**:1661–1668.
1308. Saguner AM, Ganahl S, Kraus A, Baldinger SH, Medeiros-Domingo A, Saguner AR, Mueller-Burri SA, Wolber T, Haegeli LM, Krasniqi N, Tanner FC, Steffel J, Brunckhorst C, Duru F. Clinical role of atrial arrhythmias in patients with arrhythmogenic right ventricular dysplasia. *Circ J* 2014;**78**:2854–2861.
1309. Bourfiss M, Te Riele AS, Mast TP, Cramer MJ, Van Der Heijden JF, Van Veen TA, Loh P, Dooijes D, Hauer RN, Velthuis BK. Influence of genotype on structural atrial abnormalities and atrial fibrillation or flutter in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Cardiovasc Electrophysiol* 2016;**27**:1420–1428.
1310. Mussigbrodt A, Knopp H, Efimova E, Weber A, Bertagnolli L, Hilbert S, Kosiuk J, Dinov B, Bode K, Kircher S, Dagres N, Richter S, Sommer P, Husser D, Bollmann A, Hindricks G, Arya A. Supraventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy associate with long-term outcome after catheter ablation of ventricular tachycardias. *Europace* 2018;**20**:1182–1187.
1311. Tonet JL, Castro-Miranda R, Iwa T, Poulain F, Frank R, Fontaine GH. Frequency of supraventricular tachyarrhythmias in arrhythmogenic right ventricular dysplasia. *Am J Cardiol* 1991;**67**:1153.
1312. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, Edvardsen T, Haugaa KH. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J* 2018;**39**:853–860.
1313. van Rijsingen IA, Nannenberg EA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Grasso M, Serio A, Jenkins S, Rowland C, Richard P, Wilde AA, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Christiaans I, Pinto YM. Gender-specific differences in major cardiac events and mortality in lamin A/C mutation carriers. *Eur J Heart Fail* 2013;**15**:376–384.
1314. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016;**68**:2299–2307.
1315. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, Mannarino S, Gambarin F, Favalli V, Grasso M, Agozzino M, Campana C, Gavazzi A, Febo O, Marini M, Landolina M, Mortara A, Piccolo G, Vigano M, Tavazzi L, Arbustini E. Long-term outcome and risk stratification in dilated cardiolaminopathies. *J Am Coll Cardiol* 2008;**52**:1250–1260.
1316. Stollberger C, Blazek G, Winkler-Dworak M, Finsterer J. Atrial fibrillation in left ventricular noncompaction with and without neuromuscular disorders is associated with a poor prognosis. *Int J Cardiol* 2009;**133**:41–45.
1317. Aras D, Tufekcioglu O, Ergun K, Ozeke O, Yildiz A, Topaloglu S, Deveci B, Sahin O, Kisacik HL, Korkmaz S. Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. *J Card Fail* 2006;**12**:726–733.
1318. Li S, Zhang C, Liu N, Bai H, Hou C, Wang J, Song L, Pu J. Genotype-positive status is associated with poor prognoses in patients with left ventricular noncompaction cardiomyopathy. *J Am Heart Assoc* 2018;**7**:e009910.
1319. Pappone C, Radinovic A, Manguso F, Vicedomini G, Sala S, Sacco FM, Ciconte G, Saviano M, Ferrari M, Sommariva E, Sacchi S, Ciaccio C, Kallergis EM, Santinelli V. New-onset atrial fibrillation as first clinical manifestation of latent Brugada syndrome: prevalence and clinical significance. *Eur Heart J* 2009;**30**:2985–2992.
1320. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;**16**:394–396.
1321. Peters S. Atrial arrhythmias in arrhythmogenic cardiomyopathy: at the beginning or at the end of the disease story?*Circ J* 2015;**79**:446.
1322. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ, Jr., Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Muehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–1724.
1323. Olesen MS, Yuan L, Liang B, Holst AG, Nielsen N, Nielsen JB, Hedley PL, Christiansen M, Olesen SP, Haunso S, Schmitt N, Jespersen T, Svendsen JH. High prevalence of long QT syndrome-associated SCN5A variants in patients with early-onset lone atrial fibrillation. *Circ Cardiovasc Genet* 2012;**5**:450–459.
1324. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, Giachino D, Bianchi F, Barbonaglia L, Ferraro A. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: prevalence, management, and correlation with prognosis. *Heart Rhythm* 2014;**11**:259–265.
1325. Conte G, Dewals W, Sieira J, de Asmundis C, Ciconte G, Chierchia GB, Di Giovanni G, Baltogiannis G, Saitoh Y, Levinstein M, La Meir M, Wellens F, Pappaert G, Brugada P. Drug-induced Brugada syndrome in children: clinical features, device-based management, and long-term follow-up. *J Am Coll Cardiol* 2014;**63**:2272–2279.
1326. Lee SE, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B. Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. *Heart* 2017;**103**:1496–1501.
1327. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517–2524.
1328. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation* 2000;**102**:858–864.
1329. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, Bloise R, Catalano O, Moro G, Tibollo V, Morini M, Bellazzi R, Napolitano C, Bagnardi V, Priori SG. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol* 2016;**68**:2540–2550.
1330. Pizzale S, Gollob MH, Gow R, Birnie DH. Sudden death in a young man with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:1319–1321.
1331. Roses-Noguer F, Jarman JW, Clague JR, Till J. Outcomes of defibrillator therapy in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2014;**11**:58–66.
1332. van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, Aiba T, Wada Y, Ingles J, Leren IS, Rudic B, Schwartz PJ, Maltret A, Sacher F, Skinner JR, Krahn AD, Roston TM, Tfelt-Hansen J, Swan H, Robyns T, Ohno S, Roberts JD, van den Berg MP, Kammeraad JA, Probst V, Kannankeril PJ, Blom NA, Behr ER, Borggrefe M, Haugaa KH, Semsarian C, Horie M, Shimizu W, Till JA, Leenhardt A, Ackerman MJ, Wilde AA. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J* 2019;**40**:2953–2961.
1333. Sugiyasu A, Oginosawa Y, Nogami A, Hata Y. A case with catecholaminergic polymorphic ventricular tachycardia unmasked after successful ablation of atrial tachycardias from pulmonary veins. *Pacing Clin Electrophysiol* 2009;**32**:e21–24.
1334. Veltmann C, Kuschyk J, Schimpf R, Streitner F, Schoene N, Borggrefe M, Wolpert C. Prevention of inappropriate ICD shocks in patients with Brugada syndrome. *Clin Res Cardiol* 2010;**99**:37–44.
1335. Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med* 1979;**301**:1080–1085.
1336. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, Calkins H, Corrado D, Deftereos SG, Diller GP, Gomez-Doblas JJ, Gorenek B, Grace A, Ho SY, Kaski JC, Kuck KH, Lambiase PD, Sacher F, Sarquella-Brugada G, Suwalski P, Zaza A; ESC Scientific Document Group. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:655–720.
1337. Morady F, DiCarlo LA, Jr., Baerman JM, De Buitleir M. Effect of propranolol on ventricular rate during atrial fibrillation in the Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol* 1987;**10**:492–496.
1338. Sellers TD Jr, Bashore TM, Gallagher JJ. Digitalis in the pre-excitation syndrome. Analysis during atrial fibrillation. *Circulation* 1977;**56**:260–267.
1339. Glatter KA, Dorostkar PC, Yang Y, Lee RJ, Van Hare GF, Keung E, Modin G, Scheinman MM. Electrophysiological effects of ibutilide in patients with accessory pathways. *Circulation* 2001;**104**:1933–1939.
1340. Ludmer PL, McGowan NE, Antman EM, Friedman PL. Efficacy of propafenone in Wolff-Parkinson-White syndrome: electrophysiologic findings and long-term follow-up. *J Am Coll Cardiol* 1987;**9**:1357–1363.
1341. Boahene KA, Klein GJ, Yee R, Sharma AD, Fujimura O. Termination of acute atrial fibrillation in the Wolff-Parkinson-White syndrome by procainamide and propafenone: importance of atrial fibrillatory cycle length. *J Am Coll Cardiol* 1990;**16**:1408–1414.
1342. Crijns HJ, den Heijer P, van Wijk LM, Lie KI. Successful use of flecainide in atrial fibrillation with rapid ventricular rate in the Wolff-Parkinson-White syndrome. *Am Heart J* 1988;**115**:1317–1321.
1343. Simonian SM, Lotfipour S, Wall C, Langdorf MI. Challenging the superiority of amiodarone for rate control in Wolff-Parkinson-White and atrial fibrillation. *Intern Emerg Med* 2010;**5**:421–426.

1344. Vaidya VR, Arora S, Patel N, Badheka AO, Patel N, Agnihotri K, Billimoria Z, Turakhia MP, Friedman PA, Madhavan M, Kapa S, Noseworthy PA, Cha YM, Gersh B, Asirvatham SJ, Deshmukh AJ. Burden of arrhythmia in pregnancy. *Circulation* 2017;**135**:619–621.
1345. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, van Veldhuisen DJ; Zahara Investigators. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007;**49**:2303–2311.
1346. Opotowsky AR, Siddiqi OK, D'Souza B, Webb GD, Fernandes SM, Landzberg MJ. Maternal cardiovascular events during childbirth among women with congenital heart disease. *Heart* 2012;**98**:145–151.
1347. Lee MS, Chen W, Zhang Z, Duan L, Ng A, Spencer HT, Kwan DM, Shen AY. Atrial fibrillation and atrial flutter in pregnant women – a population-based study. *J Am Heart Assoc* 2016;**5**:e003182.
1348. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol* 2008;**31**:538–541.
1349. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA; ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–3241.
1350. Wang YC, Chen CH, Su HY, Yu MH. The impact of maternal cardioversion on fetal haemodynamics. *Eur J Obstet Gynecol Reprod Biol* 2006;**126**:268–269.
1351. Moore JS, Teefey P, Rao K, Berlowitz MS, Chae SH, Yankowitz J. Maternal arrhythmia: a case report and review of the literature. *Obstet Gynecol Surv* 2012;**67**:298–312.
1352. Page RL. Treatment of arrhythmias during pregnancy. *Am Heart J* 1995;**130**:871–876.
1353. Barnes EJ, Eben F, Patterson D. Direct current cardioversion during pregnancy should be performed with facilities available for fetal monitoring and emergency caesarean section. *BJOG* 2002;**109**:1406–1407.
1354. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME, Keegan R, Kim YH, Knight BP, Kuck KH, Lane DA, Lip GYH, Malmborg H, Oral H, Pappone C, Themistoclakis S, Wood KA, Blomstrom-Lundqvist C. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE). *Eur Heart J* 2018;**39**:1442–1445.
1355. Kockova R, Kocka V, Kiernan T, Fahy GJ. Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. *J Cardiovasc Electrophysiol* 2007;**18**:545–547.
1356. Lip GY, Beevers M, Churchill D, Shaffer LM, Beevers DG. Effect of atenolol on birth weight. *Am J Cardiol* 1997;**79**:1436–1438.
1357. Heidbuchel H, Anne W, Willems R, Adriaenssens B, Van de Werf F, Ector H. Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. *Int J Cardiol* 2006;**107**:67–72.
1358. Calvo N, Ramos P, Montserrat S, Guasch E, Coll-Vinent B, Domenech M, Bisbal F, Hevia S, Vidorreta S, Borras R, Falces C, Embid C, Montserrat JM, Berruezo A, Coca A, Sitges M, Brugada J, Mont L. Emerging risk factors and the dose-response relationship between physical activity and lone atrial fibrillation: a prospective case-control study. *Europace* 2016;**18**:57–63.
1359. Crump C, Sundquist J, Winkleby MA, Sundquist K. Height, weight, and aerobic fitness level in relation to the risk of atrial fibrillation. *Am J Epidemiol* 2018;**187**:417–426.
1360. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G. Long-lasting sport practice and lone atrial fibrillation. *Eur Heart J* 2002;**23**:477–482.
1361. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J; GIRAFA Investigators. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. *Europace* 2008;**10**:15–20.
1362. Guasch E, Mont L. Diagnosis, pathophysiology, and management of exercise-induced arrhythmias. *Nat Rev Cardiol* 2017;**14**:88–101.
1363. Stein R, Medeiros CM, Rosito GA, Zimerman LI, Ribeiro JP. Intrinsic sinus and atrioventricular node electrophysiologic adaptations in endurance athletes. *J Am Coll Cardiol* 2002;**39**:1033–1038.
1364. Calvo N, Mont L, Tamborero D, Berruezo A, Viola G, Guasch E, Nadal M, Andreu D, Vidal B, Sitges M, Brugada J. Efficacy of circumferential pulmonary vein ablation of atrial fibrillation in endurance athletes. *Europace* 2010;**12**:30–36.
1365. Koopman P, Nuyens D, Garweg C, La Gerche A, De Buck S, Van Casteren L, Alzand B, Willems R, Heidbuchel H. Efficacy of radiofrequency catheter ablation in athletes with atrial fibrillation. *Europace* 2011;**13**:1386–1393.
1366. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572–1577.
1367. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation* 2008;**118**:800–807.
1368. Thelle DS, Selmer R, Gjesdal K, Sakshaug S, Jugessur A, Graff-Iversen S, Tverdal A, Nystad W. Resting heart rate and physical activity as risk factors for lone atrial fibrillation: a prospective study of 309,540 men and women. *Heart* 2013;**99**:1755–1760.
1369. O'Brien B, Burrage PS, Ngai JY, Prutkin JM, Huang CC, Xu X, Chae SH, Bollen BA, Piccini JP, Schwann NM, Mahajan A, Ruel M, Body SC, Sellke FW, Mathew J, Muehlschlegel JD. Society of Cardiovascular Anesthesiologists/European Association of Cardiothoracic Anaesthetists practice advisory for the management of perioperative atrial fibrillation in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2019;**33**:12–26.
1370. Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, Rahman F, McManus DD, Tadros TM, Levy D, Vasan RS, Larson MG, Ellinor PT, Benjamin EJ. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. *Circulation* 2015;**131**:1648–1655.
1371. Dobrev D, Aguilar M, Heijman J, Guichard JB, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol* 2019;**16**:417–436.
1372. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol* 2008;**51**:793–801.
1373. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, Ailawadi G, Kirkwood KA, Perrault LP, Parides MK, Smith RL 2nd, Kern JA, Dussault G, Hackmann AE, Jeffries NO, Miller MA, Taddei-Peters WC, Rose EA, Weisel RD, Williams DL, Mangusan RF, Argenziano M, Moquete EG, O'Sullivan KL, Pellerin M, Shah KJ, Gammie JS, Mayer ML, Voisine P, Gelijns AC, O'Gara PT, Mack MJ, CTSN. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med* 2016;**374**:1911–1921.
1374. Amar D. Postthoracotomy atrial fibrillation. *Curr Opin Anaesthesiol* 2007;**20**:43–47.
1375. Philip I, Berroeta C, Leblanc I. Perioperative challenges of atrial fibrillation. *Curr Opin Anaesthesiol* 2014;**27**:344–352.
1376. Lowres N, Mulcahy G, Jin K, Gallagher R, Neubeck L, Freedman B. Incidence of postoperative atrial fibrillation recurrence in patients discharged in sinus rhythm after cardiac surgery: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2018;**26**:504–511.
1377. Lee SH, Kang DR, Uhm JS, Shim J, Sung JH, Kim JY, Pak HN, Lee MH, Joung B. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. *Am Heart J* 2014;**167**:593–600.e1.
1378. Konstantino Y, Zelnik Yovel D, Friger MD, Sahar G, Knyazer B, Amit G. Postoperative atrial fibrillation following coronary artery bypass graft surgery predicts long-term atrial fibrillation and stroke. *Isr Med Assoc J* 2016;**18**:744–748.
1379. Lin MH, Kamel H, Singer DE, Wu YL, Lee M, Ovbiagele B. Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality. *Stroke* 2019;**50**:1364–1371.
1380. AlTurki A, Marafi M, Proietti R, Cardinale D, Blackwell R, Dorian P, Bessissow A, Vieira L, Greiss I, Essebag V, Healey JS, Huynh T. Major adverse cardiovascular events associated with postoperative atrial fibrillation after noncardiac surgery: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2020;**13**:e007437.
1381. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, Barash PG, Hsu PH, Mangano DT; Investigators of the Ischemia Research and Education Foundation, Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–1729.
1382. Villareal RP, Hariharan R, Liu BC, Kar B, Lee VV, Elayda M, Lopez JA, Rasekh A, Wilson JM, Massumi A. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. *J Am Coll Cardiol* 2004;**43**:742–748.
1383. Cardinale D, Sandri MT, Colombo A, Salvatici M, Tedeschi I, Bacchiani G, Beggiato M, Meroni CA, Civelli M, Lamantia G, Colombo N, Veglia F, Casiraghi M, Spaggiari L, Venturino M, Cipolla CM. Prevention of Atrial Fibrillation in High-risk Patients Undergoing Lung Cancer Surgery: the PRESAGE Trial. *Ann Surg* 2016;**264**:244–251.
1384. Ojima T, Nakamori M, Nakamura M, Katsuda M, Hayata K, Kato T, Kitadani J, Tabata H, Takeuchi A, Yamaue H. Randomized clinical trial of landiolol hydrochloride for the prevention of atrial fibrillation and postoperative complications after oesophagectomy for cancer. *Br J Surg* 2017;**104**:1003–1009.
1385. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, Whitlock RP. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. *Cochrane Database Syst Rev* 2013:CD003611.

1386. Ozaydin M, Icli A, Yucel H, Akcay S, Peker O, Erdogan D, Varol E, Dogan A, Okutan H. Metoprolol vs. carvedilol or carvedilol plus N-acetyl cysteine on post-operative atrial fibrillation: a randomized, double-blind, placebo-controlled study. *Eur Heart J* 2013;**34**:597–604.
1387. O'Neal JB, Billings FTt, Liu X, Shotwell MS, Liang Y, Shah AS, Ehrenfeld JM, Wanderer JP, Shaw AD. Effect of preoperative beta-blocker use on outcomes following cardiac surgery. *Am J Cardiol* 2017;**120**:1293–1297.
1388. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**:1839–1847.
1389. Zhu J, Wang C, Gao D, Zhang C, Zhang Y, Lu Y, Gao Y. Meta-analysis of amiodarone versus beta-blocker as a prophylactic therapy against atrial fibrillation following cardiac surgery. *Intern Med J* 2012;**42**:1078–1087.
1390. Auer J, Weber T, Berent R, Puschmann R, Hartl P, Ng CK, Schwarz C, Lehner E, Strasser U, Lassnig E, Lamm G, Eber B; Study of Prevention of Postoperative Atrial Fibrillation. A comparison between oral antiarrhythmic drugs in the prevention of atrial fibrillation after cardiac surgery: the pilot study of prevention of postoperative atrial fibrillation (SPPAF), a randomized, placebo-controlled trial. *Am Heart J* 2004;**147**:636–643.
1391. Buckley MS, Nolan PE Jr, Slack MK, Tisdale JE, Hilleman DE, Copeland JG. Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta-analysis of dose response and timing of initiation. *Pharmacotherapy* 2007;**27**:360–368.
1392. Riber LP, Christensen TD, Jensen HK, Hoejsgaard A, Pilegaard HK. Amiodarone significantly decreases atrial fibrillation in patients undergoing surgery for lung cancer. *Ann Thorac Surg* 2012;**94**:339–344; discussion 345–346.
1393. Tisdale JE, Wroblewski HA, Wall DS, Rieger KM, Hammoud ZT, Young JV, Kesler KA. A randomized trial evaluating amiodarone for prevention of atrial fibrillation after pulmonary resection. *Ann Thorac Surg* 2009;**88**:886–893; discussion 894–895.
1394. Yuan X, Du J, Liu Q, Zhang L. Defining the role of perioperative statin treatment in patients after cardiac surgery: a meta-analysis and systematic review of 20 randomized controlled trials. *Int J Cardiol* 2017;**228**:958–966.
1395. Fairley JL, Zhang L, Glassford NJ, Bellomo R. Magnesium status and magnesium therapy in cardiac surgery: a systematic review and meta-analysis focusing on arrhythmia prevention. *J Crit Care* 2017;**42**:69–77.
1396. Tabbalat RA, Hamad NM, Alhaddad IA, Hammoudeh A, Akasheh BF, Khader Y. Effect of ColchiciNe on the InciDence of atrial fibrillation in open heart surgery patients: END-AF trial. *Am Heart J* 2016;**178**:102–107.
1397. Ali-Hasan-Al-Saegh S, Mirhosseini SJ, Liakopoulos O, Sabashnikov A, Dehghan HR, Sedaghat-Hamedani F, Kayvanpour E, Ghaffari N, Vahabzadeh V, Aghabagheri M, Mozayan MR, Popov AF. Posterior pericardiotomy in cardiac surgery: systematic review and meta-analysis. *Asian Cardiovasc Thorac Ann* 2015;**23**:354–362.
1398. Hu XL, Chen Y, Zhou ZD, Ying J, Hu YH, Xu GH. Posterior pericardiotomy for the prevention of atrial fibrillation after coronary artery bypass grafting: a meta-analysis of randomized controlled trials. *Int J Cardiol* 2016;**215**:252–256.
1399. Wang W, Mei YQ, Yuan XH, Feng XD. Clinical efficacy of epicardial application of drug-releasing hydrogels to prevent postoperative atrial fibrillation. *J Thorac Cardiovasc Surg* 2016;**151**:80–85.
1400. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D; Dexamethasone for Cardiac Surgery Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012;**308**:1761–1767.
1401. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum A, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S, Yusuf S; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;**386**:1243–1253.
1402. Saxena A, Dinh DT, Smith JA, Shardey GC, Reid CM, Newcomb AE. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). *Am J Cardiol* 2012;**109**:219–225.
1403. Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, Tarazi R, Shroyer AL, Sethi GK, Grover FL, Hammermeister KE. Atrial fibrillation after cardiac surgery: a major morbid event?*Ann Surg* 1997;**226**:501–511; discussion 511–513.
1404. Gialdini G, Nearing K, Bhave PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**:616–622.
1405. Horwich P, Buth KJ, Legare JF. New onset postoperative atrial fibrillation is associated with a long-term risk for stroke and death following cardiac surgery. *J Card Surg* 2013;**28**:8–13.
1406. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardiothorac Surg* 2010;**37**:1353–1359.
1407. Rubin DA, Nieminski KE, Reed GE, Herman MV. Predictors, prevention, and long-term prognosis of atrial fibrillation after coronary artery bypass graft operations. *J Thorac Cardiovasc Surg* 1987;**94**:331–335.
1408. Butt JH, Xian Y, Peterson ED, Olsen PS, Rorth R, Gundlund A, Olesen JB, Gislason GH, Torp-Pedersen C, Kober L, Fosbol EL. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation. *JAMA Cardiol* 2018;**3**:417–424.
1409. Butt JH, Olesen JB, Havers-Borgersen E, Gundlund A, Andersson C, Gislason GH, Torp-Pedersen C, Kober L, Fosbol EL. Risk of thromboembolism associated with atrial fibrillation following noncardiac surgery. *J Am Coll Cardiol* 2018;**72**:2027–2036.
1410. POISE Study group., Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**:1839–1847.
1411. Leonardi M, Bissett J. Prevention of atrial fibrillation. *Curr Opin Cardiol* 2005;**20**:417–423.
1412. Roberts JD, Dewland TA, Glidden DV, Hoffmann TJ, Arking DE, Chen LY, Psaty BM, Olgin JE, Alonso A, Heckbert SR, Marcus GM. Impact of genetic variants on the upstream efficacy of renin-angiotensin system inhibitors for the prevention of atrial fibrillation. *Am Heart J* 2016;**175**:9–17.
1413. Pena JM, MacFadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. *Eur Heart J* 2012;**33**:531–537.
1414. Maggioni AP, Fabbri G, Lucci D, Marchioli R, Franzosi MG, Latini R, Nicolosi GL, Porcu M, Cosmi F, Stefanelli S, Tognoni G; GISSI-HF Investigators. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial. *Eur Heart J* 2009;**30**:2327–2336.
1415. Zhou X, Du JL, Yuan J, Chen YQ. Statin therapy is beneficial for the prevention of atrial fibrillation in patients with coronary artery disease: a meta-analysis. *Eur J Pharmacol* 2013;**707**:104–111.
1416. Fang WT, Li HJ, Zhang H, Jiang S. The role of statin therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. *Br J Clin Pharmacol* 2012;**74**:744–756.
1417. Macfarlane PW, Murray H, Sattar N, Stott DJ, Ford I, Buckley B, Jukema JW, Westendorp RG, Shepherd J. The incidence and risk factors for new onset atrial fibrillation in the PROSPER study. *Europace* 2011;**13**:634–639.
1418. Haywood LJ, Ford CE, Crow RS, Davis BR, Massie BM, Einhorn PT, Williard A; ALLHAT Collaborative Research Group. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *J Am Coll Cardiol* 2009;**54**:2023–2031.
1419. Schwartz GG, Chaitman BR, Goldberger JJ, Messig M. High-dose atorvastatin and risk of atrial fibrillation in patients with prior stroke or transient ischemic attack: analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Am Heart J* 2011;**161**:993–999.
1420. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials. *Curr Opin Cardiol* 2013;**28**:7–18.
1421. Yang Q, Qi X, Li Y. The preventive effect of atorvastatin on atrial fibrillation: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2014;**14**:99.
1422. Martino A, Pezzi L, Magnano R, Salustri E, Penco M, Calo L. Omega 3 and atrial fibrillation: where are we?*World J Cardiol* 2016;**8**:114–119.
1423. Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T, Gillis AM, Haugaa KH, Lip GYH, Van Gelder I, Malik M, Poole J, Potpara T, Savelieva I, Sarkozy A; ESC Scientific Document Group. Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace* 2018;**20**:1565–1565ao.
1424. Potpara TS, Marinkovic JM, Polovina MM, Stankovic GR, Seferovic PM, Ostojic MC, Lip GY. Gender-related differences in presentation, treatment and long-term outcome in patients with first-diagnosed atrial fibrillation and structurally normal heart: the Belgrade atrial fibrillation study. *Int J Cardiol* 2012;**161**:39–44.
1425. Potpara TS, Blomstrom-Lundqvist C. Sex-related differences in atrial fibrillation: can we discern true disparities from biases?*Heart* 2017;**103**:979–981.

1426. Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, Gersh B, Hylek E, Kowey PR, Reiffel JA, Naccarelli GV, Chan PS, Spertus JA, Peterson ED; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Investigators and Patients. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol* 2016;**1**:282–291.
1427. Lang C, Seyfang L, Ferrari J, Gattringer T, Greisenegger S, Willeit K, Toell T, Krebs S, Brainin M, Kiechl S, Willeit J, Lang W, Knoflach M; Austrian Stroke Registry Collaborators. Do women with atrial fibrillation experience more severe strokes? Results from the Austrian Stroke Unit Registry. *Stroke* 2017;**48**:778–780.
1428. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol* 2012;**110**:1799–1802.
1429. Rienstra M, Van Veldhuisen DJ, Hagens VE, Ranchor AV, Veeger NJ, Crijns HJ, Van Gelder IC; RACE Investigators. Gender-related differences in rhythm control treatment in persistent atrial fibrillation: data of the Rate Control Versus Electrical Cardioversion (RACE) study. *J Am Coll Cardiol* 2005;**46**:1298–1306.
1430. Lehmann MH, Timothy KW, Frankovich D, Fromm BS, Keating M, Locati EH, Taggart RT, Towbin JA, Moss AJ, Schwartz PJ, Vincent GM. Age-gender influence on the rate-corrected QT interval and the QT-heart rate relation in families with genotypically characterized long QT syndrome. *J Am Coll Cardiol* 1997;**29**:93–99.
1431. Zylla MM, Brachmann J, Lewalter T, Hoffmann E, Kuck KH, Andresen D, Willems S, Eckardt L, Tebbenjohanns J, Spitzer SG, Schumacher B, Hochadel M, Senges J, Katus HA, Thomas D. Sex-related outcome of atrial fibrillation ablation: insights from the German Ablation Registry. *Heart Rhythm* 2016;**13**:1837–1844.
1432. Patel N, Deshmukh A, Thakkar B, Coffey JO, Agnihotri K, Patel A, Ainani N, Nalluri N, Patel N, Patel N, Patel N, Badheka AO, Kowalski M, Hendel R, Viles-Gonzalez J, Noseworthy PA, Asirvatham S, Lo K, Myerburg RJ, Mitrani RD. Gender, race, and health insurance status in patients undergoing catheter ablation for atrial fibrillation. *Am J Cardiol* 2016;**117**:1117–1126.
1433. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrialfibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;**532**:h7013.
1434. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, Kalarus Z, Crijns HJ, Oliveira MM, Tavazzi L, Maggioni AP, Boriani G. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *Europace* 2015;**17**:1777–1786.
1435. Proietti M, Nobili A, Raparelli V, Napoleone L, Mannucci PM, Lip GY; REPOSI Investigators. Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation: insights from the REPOSI study. *Clin Res Cardiol* 2016;**105**:912–920.
1436. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, Schilling RJ, Schmitt J, Zamorano JL. Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention oF thromboemolic events – European Registry in Atrial Fibrillation (PREFER in AF). *Europace* 2014;**16**:6–14.
1437. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, Petrescu L, Darabantiu D, Crijns HJ, Kirchhof P, Vardas P, Tavazzi L, Maggioni AP, Boriani G. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme – Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 2014;**35**:3365–3376.
1438. Jortveit J, Pripp AH, Langorgen J, Halvorsen S. Poor adherence to guideline recommendations among patients with atrial fibrillation and acute myocardial infarction. *Eur J Prev Cardiol* 2019:2047487319841940.
1439. Potpara TS, Dan GA, Trendafilova E, Goda A, Kusljugic Z, Manola S, Music L, Musetescu R, Badila E, Mitic G, Paparisto V, Dimitrova ES, Polovina MM, Petranov SL, Djergo H, Loncar D, Bijedic A, Brusich S, Lip GY; Balkan-AF Investigators. Stroke prevention in atrial fibrillation and 'real world' adherence to guidelines in the Balkan region: the BALKAN-AF*Survey*. *Sci Rep* 2016;**6**:20432.
1440. Kim H, Kim TH, Cha MJ, Lee JM, Park J, Park JK, Kang KW, Shim J, Uhm JS, Kim J, Park HW, Choi EK, Kim JB, Kim C, Lee YS, Joung B. A prospective survey of atrial fibrillation management for real-world guideline adherence: COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) Registry. *Korean Circ J* 2017;**47**:877–887.
1441. Miyazawa K, Li YG, Rashed WA, Al Mahmeed W, Shehab A, Zubaid M, Lip GYH. Secondary stroke prevention and guideline adherent antithrombotic treatment in patients with atrial fibrillation: insights from the Gulf Survey of Atrial Fibrillation events (Gulf SAFE). *Int J Cardiol* 2019;**274**:126–131.
1442. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, Cools F, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Kayani G, Koretsune Y, Mantovani LG, Misselwitz F, Oh S, Turpie AG, Verheugt FW, Kakkar AK; GARFIELD-AF Investigators. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart* 2017;**103**:307–314.
1443. Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ, Ezekowitz MD, Fonarow GC, Gersh BJ, Goldhaber S, Haas S, Hacke W, Kowey PR, Ansell J, Mahaffey KW, Naccarelli G, Reiffel JA, Turpie A, Verheugt F, Piccini JP, Kakkar A, Peterson ED, Fox KAA, Garfield AF; ORBIT-AF Investigators. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *Am Heart J* 2017;**194**:132–140.
1444. Leef GC, Perino AC, Askari M, Fan J, Ho PM, Olivier CB, Longo L, Mahaffey KW, Turakhia MP. Appropriateness of direct oral anticoagulant dosing in patients with atrial fibrillation: insights from the Veterans Health Administration. *J Pharm Pract* 2019:897190019828270.
1445. Dupree L, DeLosSantos M, Smotherman C. Evaluation of adherence to guideline-directed antithrombotic therapy for atrial fibrillation at hospital discharge. *J Cardiovasc Pharmacol Ther* 2018;**23**:502–508.
1446. Heidbuchel H, Dagres N, Antz M, Kuck KH, Lazure P, Murray S, Carrera C, Hindricks G, Vahanian A. Major knowledge gaps and system barriers to guideline implementation among European physicians treating patients with atrial fibrillation: a European Society of Cardiology international educational needs assessment. *Europace* 2018;**20**:1919–1928.
1447. Desteghe L, Germeys J, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Delesie M, Dendale P, Heidbuchel H. Effectiveness and usability of an online tailored education platform for atrial fibrillation patients undergoing a direct current cardioversion or pulmonary vein isolation. *Int J Cardiol* 2018;**272**:123–129.
1448. Marquez-Contreras E, Martell-Claros N, Marquez-Rivero S, Hermida-Campa E, Gracia-Diez C, Sanchez-Lopez E, Gil-Guillen V; Compliance and Inertia Working Group, Spanish Society of Hypertension (SEH-LELHA). Strategies for improving dabigatran adherence for stroke prevention in patients with non-valvular atrial fibrillation: education and drug intake reminders (FACILITA study). *Curr Med Res Opin* 2018;**34**:1301–1308.
1449. Piccini JP, Xu H, Cox M, Matsouaka RA, Fonarow GC, Butler J, Curtis AB, Desai N, Fang M, McCabe PJ, Page Ii RL, Turakhia M, Russo AM, Knight BP, Sidhu M, Hurwitz JL, Ellenbogen KA, Lewis WR; Get With The Guidelines-AFIB Clinical Working Group and Hospitals. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation* 2019;**139**:1497–1506.
1450. Richardson KM, Singh J, Munoz D, Damp JB, Mendes LA. Improving practice guideline adherence through peer feedback: impact of an ambulatory cardiology curriculum. *Teach Learn Med* 2018;**30**:328–336.
1451. Ferguson C, Hickman LD, Phillips J, Newton PJ, Inglis SC, Lam L, Bajorek BV. An mHealth intervention to improve nurses' atrial fibrillation and anticoagulation knowledge and practice: the EVICOAG study. *Eur J Cardiovasc Nurs* 2019;**18**:7–15.
1452. Siebenhofer A, Ulrich LR, Mergenthal K, Berghold A, Pregartner G, Kemperdick B, Schulz-Rothe S, Rauck S, Harder S, Gerlach FM, Petersen JJ. Primary care management for patients receiving long-term antithrombotic treatment: a cluster-randomized controlled trial. *PLoS One* 2019;**14**:e0209366.
1453. Heidenreich PA, Solis P, Estes NAM 3rd, Fonarow GC, Jurgens CY, Marine JE, McManus DD, McNamara RL. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on performance measures. *J Am Coll Cardiol* 2016;**68**:525–568.
1454. Lewis WR, Piccini JP, Turakhia MP, Curtis AB, Fang M, Suter RE, Page RL, 2nd, Fonarow GC. Get With The Guidelines AFIB: novel quality improvement registry for hospitalized patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2014;**7**:770–777.
1455. Friedman DJ, Al-Khatib SM. Measuring quality in electrophysiology. *J Interv Card Electrophysiol* 2016;**47**:5–10.
1456. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;**3**:692–694.
1457. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010;**8**:202–204.

1458. Diederichsen SZ, Haugan KJ, Brandes A, Lanng MB, Graff C, Krieger D, Kronborg C, Holst AG, Kober L, Hojberg S, Svendsen JH. Natural history of subclinical atrial fibrillation detected by implanted loop recorders. *J Am Coll Cardiol* 2019;**74**:2771–2781.
1459. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsky MT, Turkel M, Waldo AL; RATE Registry Investigators. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes. *Circulation* 2016;**134**:1130–1140.
1460. Pastori D, Miyazawa K, Li Y, Szekely O, Shahid F, Farcomeni A, Lip GYH. Atrial high-rate episodes and risk of major adverse cardiovascular events in patients with cardiac implantable electronic devices. *Clin Res Cardiol* 2020;**109**:96–102.
1461. Gonzalez M, Keating RJ, Markowitz SM, Liu CF, Thomas G, Ip JE, Lerman BB, Cheung JW. Newly detected atrial high rate episodes predict long-term mortality outcomes in patients with permanent pacemakers. *Heart Rhythm* 2014;**11**:2214–2221.
1462. Gorenek BC, Bax J, Boriani G, Chen SA, Dagres N, Glotzer TV, Healey JS, Israel CW, Kudaiberdieva G, Levin LA, Lip GYH, Martin D, Okumura K, Svendsen JH, Tse HF, Botto GLC-C; ESC Scientific Document Group. Device-detected subclinical atrial tachyarrhythmias: definition, implications and management – an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace* 2017;**19**:1556–1578.
1463. Nasir JM, Pomeroy W, Marler A, Hann M, Baykaner T, Jones R, Stoll R, Hursey K, Meadows A, Walker J, Kindsvater S. Predicting determinants of atrial fibrillation or flutter for therapy elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) study. *Heart Rhythm* 2017;**14**:955–961.
1464. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, Pouliot E, Ziegler PD; REVEAL AF Investigators. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. *JAMA Cardiol* 2017;**2**:1120–1127.
1465. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke risk as a function of atrial fibrillation duration and CHA2DS2-VASc score. *Circulation* 2019;**140**:1639–1646.
1466. Celikyurt U, Knecht S, Kuehne M, Reichlin T, Muehl A, Spies F, Osswald S, Sticherling C. Incidence of new-onset atrial fibrillation after cavotricuspid isthmus ablation for atrial flutter. *Europace* 2017;**19**:1776–1780.
1467. Bertaglia E, Bonso A, Zoppo F, Proclemer A, Verlato R, Coro L, Mantovan R, Themistoclakis S, Raviele A, Pascotto P; North-Eastern Italian Study on Atrial Flutter Ablation Investigators. Different clinical courses and predictors of atrial fibrillation occurrence after transisthmic ablation in patients with preablation lone atrial flutter, coexistent atrial fibrillation, and drug induced atrial flutter. *Pacing Clin Electrophysiol* 2004;**27**:1507–1512.
1468. Nabar A, Rodriguez LM, Timmermans C, van Mechelen R, Wellens HJ. Class IC antiarrhythmic drug induced atrial flutter: electrocardiographic and electrophysiological findings and their importance for long term outcome after right atrial isthmus ablation. *Heart* 2001;**85**:424–429.
1469. Enriquez A, Sarrias A, Villuendas R, Ali FS, Conde D, Hopman WM, Redfearn DP, Michael K, Simpson C, De Luna AB, Bayes-Genis A, Baranchuk A. New-onset atrial fibrillation after cavotricuspid isthmus ablation: identification of advanced interatrial block is key. *Europace* 2015;**17**:1289–1293.
1470. Maskoun W, Pino MI, Ayoub K, Llanos OL, Almomani A, Nairooz R, Hakeem A, Miller J. Incidence of atrial fibrillation after atrial flutter ablation. *JACC Clin Electrophysiol* 2016;**2**:682–690.
1471. Reithmann C, Hoffmann E, Spitzlberger G, Dorwarth U, Gerth A, Remp T, Steinbeck G. Catheter ablation of atrial flutter due to amiodarone therapy for paroxysmal atrial fibrillation. *Eur Heart J* 2000;**21**:565–572.
1472. Vadmann H, Nielsen PB, Hjortshoj SP, Riahi S, Rasmussen LH, Lip GY, Larsen TB. Atrial flutter and thromboembolic risk: a systematic review. *Heart* 2015;**101**:1446–1455.
1473. Van Gelder IC, Crijns HJ, Van Gilst WH, Verwer R, Lie KI. Prediction of uneventful cardioversion and maintenance of sinus rhythm from direct-current electrical cardioversion of chronic atrial fibrillation and flutter. *Am J Cardiol* 1991;**68**:41–46.
1474. Gillis AM, Unterberg-Buchwald C, Schmidinger H, Massimo S, Wolfe K, Kavaney DJ, Otterness MF, Hohnloser SH; GEM III AT Worldwide Investigators. Safety and efficacy of advanced atrial pacing therapies for atrial tachyarrhythmias in patients with a new implantable dual chamber cardioverter-defibrillator. *J Am Coll Cardiol* 2002;**40**:1653–1659.
1475. Crijns HJ, Van Gelder IC, Kingma JH, Dunselman PH, Gosselink AT, Lie KI. Atrial flutter can be terminated by a class III antiarrhythmic drug but not by a class IC drug. *Eur Heart J* 1994;**15**:1403–1408.
1476. Ellenbogen KA, Stambler BS, Wood MA, Sager PT, Wesley RC, Jr., Meissner MC, Zoble RG, Wakefield LK, Perry KT, Vanderlugt JT. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study. *J Am Coll Cardiol* 1996;**28**:130–136.
1477. Falk RH, Pollak A, Singh SN, Friedrich T. Intravenous dofetilide, a class III antiarrhythmic agent, for the termination of sustained atrial fibrillation or flutter. Intravenous Dofetilide Investigators. *J Am Coll Cardiol* 1997;**29**:385–390.
1478. Singh S, Zoble RG, Yellen L, Brodsky MA, Feld GK, Berk M, Billing CB, Jr. Efficacy and safety of oral dofetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000;**102**:2385–2390.
1479. Crozier IG, Ikram H, Kenealy M, Levy L. Flecainide acetate for conversion of acute supraventricular tachycardia to sinus rhythm. *Am J Cardiol* 1987;**59**:607–609.
1480. Murdock CJ, Kyles AE, Yeung-Lai-Wah JA, Qi A, Vorderbrugge S, Kerr CR. Atrial flutter in patients treated for atrial fibrillation with propafenone. *Am J Cardiol* 1990;**66**:755–757.
1481. Da Costa A, Thevenin J, Roche F, Romeyer-Bouchard C, Abdellaoui L, Messier M, Denis L, Faure E, Gonthier R, Kruszynski G, Pages JM, Bonijoly S, Lamaison D, Defaye P, Barthelemy JC, Gouttard T, Isaaz K; Loire-Ardèche-Drôme-Isère-Puy-de-Dôme Trial of Atrial Flutter Investigators. Results from the Loire-Ardèche-Drôme-Isère-Puy-de-Dome (LADIP) trial on atrial flutter, a multicentric prospective randomized study comparing amiodarone and radiofrequency ablation after the first episode of symptomatic atrial flutter. *Circulation* 2006;**114**:1676–1681.
1482. Schwartzman D, Callans DJ, Gottlieb CD, Dillon SM, Movsowitz C, Marchlinski FE. Conduction block in the inferior vena caval-tricuspid valve isthmus: association with outcome of radiofrequency ablation of type I atrial flutter. *J Am Coll Cardiol* 1996;**28**:1519–1531.
1483. Wasmer K, Monnig G, Bittner A, Dechering D, Zellerhoff S, Milberg P, Kobe J, Eckardt L. Incidence, characteristics, and outcome of left atrial tachycardias after circumferential antral ablation of atrial fibrillation. *Heart Rhythm* 2012;**9**:1660–1666.
1484. Satomi K, Bansch D, Tilz R, Chun J, Ernst S, Antz M, Greten H, Kuck KH, Ouyang F. Left atrial and pulmonary vein macroreentrant tachycardia associated with double conduction gaps: a novel type of man-made tachycardia after circumferential pulmonary vein isolation. *Heart Rhythm* 2008;**5**:43–51.
1485. Chugh A, Oral H, Lemola K, Hall B, Cheung P, Good E, Tamirisa K, Han J, Bogun F, Pelosi F Jr, Morady F. Prevalence, mechanisms, and clinical significance of macroreentrant atrial tachycardia during and following left atrial ablation for atrial fibrillation. *Heart Rhythm* 2005;**2**:464–471.
1486. Goette A, Auricchio A, Boriani G, Braunschweig F, Terradellas JB, Burri H, Camm AJ, Crijns H, Dagres N, Deharo JC, Dobrev D, Hatala R, Hindricks G, Hohnloser SH, Leclercq C, Lewalter T, Lip GYH, Merino JL, Mont L, Prinzen F, Proclemer A, Purerfellner H, Savelieva I, Schilling R, Steffel J, van Gelder IC, Zeppenfeld K, Zupan I, Heidbuchel H. EHRA White Paper: knowledge gaps in arrhythmia management – status 2019. *Europace* 2019;**21**:993–994.
1487. De With RR, Marcos EG, Dudink E, Spronk HM, Crijns H, Rienstra M, Van Gelder IC. Atrial fibrillation progression risk factors and associated cardiovascular outcome in well-phenotyped patients: data from the AF-RISK study. *Europace* 2020;**22**:352–360.
1488. Andrade JG, Deyell MW, Lee AY, Macle L. Sex differences in atrial fibrillation. *Canadian J Cardiol* 2018;**34**:429–436.
1489. Potpara TS, Ferro C, Lip GYH, Dan GA, Lenarczyk R, Mallamaci F, Ortiz A, Sarafidis P, Ekart R, Dagres N. Management of atrial fibrillation in patients with chronic kidney disease in clinical practice: a joint European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) physician-based survey. *Europace* 2020;**22**:496–505.
1490. Al-Khatib SM, Benjamin EJ, Buxton AE, Calkins H, Chung MK, Curtis AB, Desvigne-Nickens P, Jais P, Packer DL, Piccini JP, Rosenberg Y, Russo AM, Wang PJ, Cooper LS, Go AS, Workshop C. Research needs and priorities for catheter ablation of atrial fibrillation: a report from a National Heart, Lung, and Blood Institute Virtual Workshop. *Circulation* 2020;**141**:482–492.
1491. Nielsen JC, Lin YJ, de Oliveira Figueiredo MJ, Sepehri Shamloo A, Alfie A, Boveda S, Dagres N, Di Toro D, Eckhardt LL, Ellenbogen K, Hardy C, Ikeda T,

Jaswal A, Kaufman E, Krahn A, Kusano K, Kutyifa V, Lim HS, Lip GYH, Nava-Townsend S, Pak HN, RodrÚguez Diez G, Sauer W, Saxena A, Svendsen JH, Vanegas D, Vaseghi M, Wilde A, Bunch TJ; ESC Scientific Document Group, Buxton AE, Calvimontes G, Chao TF, Eckardt L, Estner H, Gillis AM, Isa R, Kautzner J, Maury P, Moss JD, Nam GB, Olshansky B, Pava Molano LF, Pimentel M, Prabhu M, Tzou WS, Sommer P, Swampillai J, Vidal A, Deneke T, Hindricks G, Leclercq C. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *Europace* 2020;**22**:1147–1148.

1492. Blessberger H, Lewis SR, Pritchard MW, Fawcett LJ, Domanovits H, Schlager O, Wildner B, Kammler J, Steinwender C. Perioperative beta-blockers for preventing surgery-related mortality and morbidity in adults undergoing cardiac surgery. *Cochrane Database Syst Rev* 2019 23;**9**:CD013435.