PULMONARY ARTERY DENERVATION REDUCES CLINICAL WORSENING IN PULMONARY HYPERTENSION, INCLUDING HEART FAILURE-RELATED DISEASE: A META-ANALYSIS

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Background

Pulmonary hypertension due to left heart disease (group 2 PH) accounts for 60–85% of all PH and is among the strongest predictors of hospitalization, right ventricular failure, and death in heart failure, yet no drug therapy has ever been approved for it; PAH-specific agents have repeatedly failed or caused harm in this population (Humbert et al., *European Respiratory Society/ESC Guidelines*, 2023; Ilonze et al., *JACC: Heart Failure*, 2024). This is one of the largest unmet therapeutic needs in cardiovascular medicine. Pulmonary artery denervation (PADN), a catheter-based ablation of the sympathetic fibers and baroreceptors at the pulmonary artery bifurcation, targets the sympathetic overactivation common to both heart failure and PH. Until recently, PADN was classified as experimental because trials were small and did not reflect contemporary guideline-directed medical therapy (GDMT) (Humbert et al., 2023). The landmark PADN-HF-PH randomized trial 2026 has now, for the first time, demonstrated a reduction in hard clinical events on a background of modern GDMT. We synthesized the totality of randomized and observational evidence to quantify the magnitude, consistency, and mechanistic coherence of PADN's benefit and to define where it is clinically actionable.

Methods

We performed a random-effects meta-analysis of 10 studies of PADN in PH, including 4 randomized controlled trials and the pivotal PADN-HF-PH trial. Clinical outcomes were compared against control as odds ratios (OR); hemodynamic and functional outcomes were analyzed as mean differences. Pre-specified analyses included restriction to group 2 (heart failure–related) PH, a sensitivity analysis removing the 6-minute walk distance component from the composite worsening endpoint, and assessment of concordance between clinical and hemodynamic effects.

Results

PADN reduced clinical worsening with striking consistency (3 RCTs, n = 490; OR 0.40, 95% CI 0.26–0.62; I^2 = 0%), corresponding to an absolute risk reduction of 17.5% and a number needed to treat of just 6 (95% CI 4–10). The effect was fully preserved when the walk-distance component was removed (OR 0.39), confirming that the benefit is driven by hard events rather than a soft functional measure — directly mirroring the pivotal trial, in which worsening was reduced by 52% even after exclusion of the 6-minute walk distance. Critically, the benefit held in the most therapy-refractory population — group 2 PH (OR 0.44, 95% CI 0.28–0.70) — the exact group for which no approved therapy exists. Rehospitalization fell substantially (OR 0.16, 95% CI 0.04–0.70). Mortality did not differ (OR 0.62, 95% CI 0.32–1.19), consistent with the pivotal trial being underpowered for survival.

The clinical benefit was underpinned by concordant, large-magnitude hemodynamic and functional gains: mean pulmonary artery pressure fell by 11.8 mm Hg, pulmonary vascular resistance by 4.9 Wood units, cardiac output rose by 0.56 L/min, right ventricular function improved, and 6-minute walk distance increased by 92 m — a pattern closely matching contemporaneous independent syntheses (Cekirdekci and Onar, 2026; Abouzid et al, 2025). This coherence between a mechanistic target (sympathetic overdrive), proximate hemodynamics, and downstream clinical events is the signature of a disease-modifying intervention rather than a symptomatic one.

Conclusions and Clinical Impact

Added to GDMT, PADN prevents approximately one clinical worsening event for every 6 patients treated, including in heart failure–related PH — a population in which, until now, no therapy has shown benefit and PAH drugs have failed. The effect is internally consistent (I^2 = 0% for the primary outcome), robust to removal of its softest component, and mechanistically concordant across hemodynamics, right ventricular function, and clinical events. These findings reposition PADN from an experimental curiosity to the leading candidate therapy for an orphaned, high-mortality condition and provide the quantitative, pooled rationale to prioritize it for guideline evaluation. A demonstrated mortality benefit remains

unproven and is the explicit charge of ongoing adequately powered, sham-controlled trials, which should determine guideline adoption.

OUTCOMES OF PULMONARY ARTERY DENERVATION (PADN) IN PULMONARY HYPERTENSION

Clinical Outcomes (PADN vs Control)

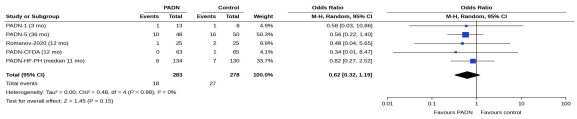


Table 1- Forest plot of all-cause mortality

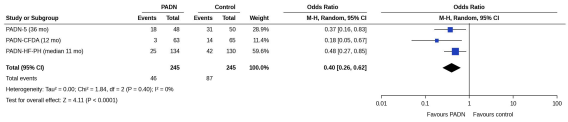


Table 2- Forest plot of clinical worsening

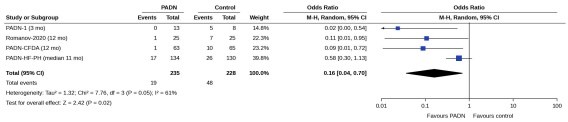


Table 3- Forest plot of rehospitalization

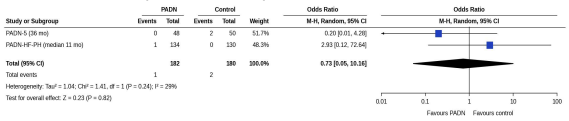


Table 4- Forest plot of heart or lung transplantation

Exercise Capacity

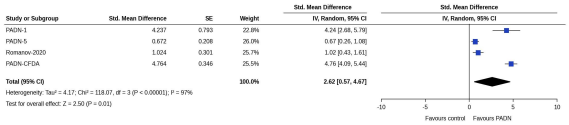


Table 5- Forest plot of 6-minute walk distance, post-PADN versus control (standardized mean difference)

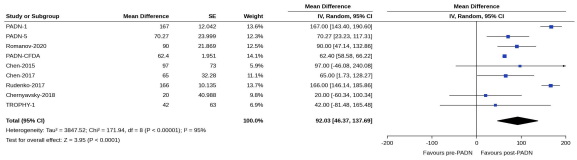


Table 6- Forest plot of 6-minute walk distance, post-PADN versus pre-PADN (mean difference, m)

Hemodynamics (Post-PADN vs Pre-PADN)

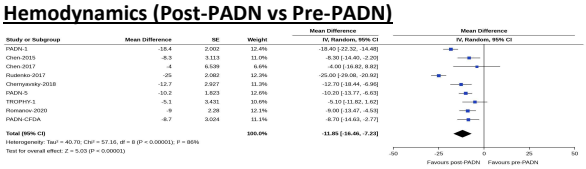


Table 7- Forest plot of mean pulmonary artery pressure (mean difference, mm Hg)

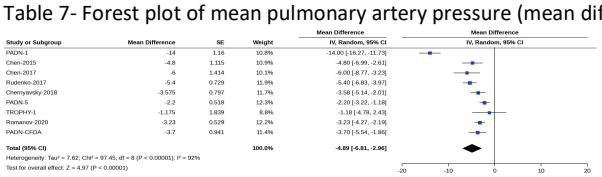


Table 8- Forest plot of pulmonary vascular resistance (mean difference, Wood units)



Table 9- Forest plot of cardiac output (mean difference, L/min)

Right Ventricular Function and Biomarker

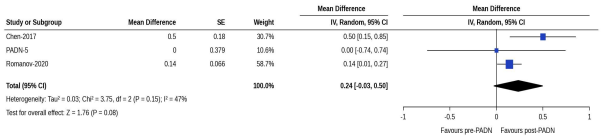


Table 10- Forest plot of TAPSE, post-PADN versus pre-PADN (mean difference)

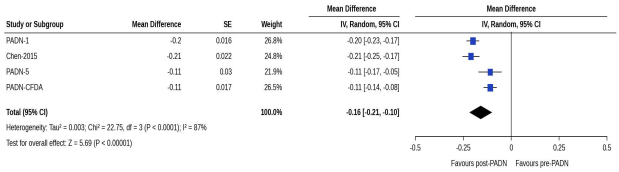


Table 11- Forest plot of RV Tei index, post-PADN versus pre-PADN (mean difference)

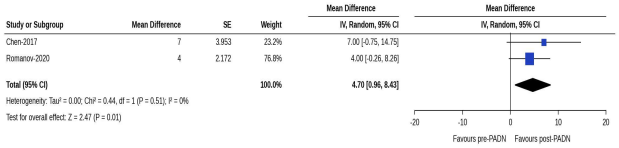


Table 12- Forest plot of RV fractional area change, post-PADN versus pre-PADN (mean difference, %)

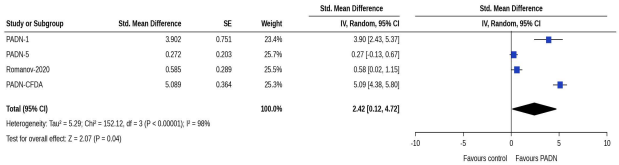


Table 13- Forest plot of NT-proBNP, post-PADN versus control (standardized mean difference)

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