

CRITICAL APPRAISAL

Pulmonary Artery Denervation for Group 2 Pulmonary Hypertension: A Modern Solution to an Age-Old Problem?

Ahmed Ghoneem, MD^a; Rosa Cruz Torres, MD^a; Vikas Aggarwal, MD^a

^a Division of Cardiology, Henry Ford Hospital, Detroit, Michigan, USA

Pulmonary hypertension is a common and consequential final pathway of cardiovascular and pulmonary disease, affecting an estimated 31.5 million people worldwide. More than half of that burden, roughly 16 million people, is attributable to pulmonary hypertension associated with left heart disease (PH-LHD), or World Health Organization group 2 pulmonary hypertension.¹ Despite its prevalence and strong association with heart failure hospitalization, right ventricular failure, and death, PH-LHD has no approved therapy directed at the pulmonary circulation.^{2,3} Treatment is limited to the underlying heart failure or valvular disease, while attempts to repurpose pulmonary arterial hypertension drugs have been neutral or harmful.⁴⁻⁶ This therapeutic gap invites a device-based analogy. Calcific aortic valve disease carries a comparable global burden of approximately 12.6 million cases and likewise has no medical therapy capable of reversing the fixed disease process, yet surgical and then transcatheter aortic valve replacement transformed its prognosis.⁷ Against that precedent, the PADN-HF-PH trial asks whether pulmonary artery denervation (PADN) might offer a procedural solution where pharmacotherapy has reached its limits.⁸

PH-LHD is not a single disease. Elevated left-sided filling pressure initially produces passive, postcapillary pulmonary hypertension; in some patients, sustained exposure is accompanied by pulmonary vasoconstriction, remodeling, increased pulmonary vascular resistance (PVR), right ventricular-pulmonary arterial uncoupling, and right ventricular failure. This distinction separates isolated postcapillary pulmonary hypertension (IpcPH; PVR ≤ 2 Wood units) from combined precapillary and postcapillary pulmonary hypertension (CpcPH; PVR > 2 Wood units), the latter generally carrying a worse prognosis.^{2,9}

Sympathetic activation is integral to both heart failure and pulmonary vascular dysfunction. PADN uses radiofrequency ablation near the distal main pulmonary artery and its bifurcation to interrupt sympathetic fibers, with the aim of lowering pulmonary vascular tone and afterload rather than adding another vasodilator.⁸ The PADN program has evolved over more than a decade (**Figure 1**). The first-in-human and phase II studies established feasibility but were small, nonrandomized, and uncontrolled.^{10,11} PADN-5 produced striking functional and hemodynamic signals in CpcPH, but interpretation was complicated by a control regimen that included sildenafil, a

therapy that is unproven and potentially harmful in PH-LHD.^{4,12,13} PADN-CFDA provided sham-controlled evidence in group 1 pulmonary arterial hypertension, a physiology that cannot be assumed to translate to group 2 disease.¹⁴ An early feasibility study of intravascular ultrasound denervation is a reminder that PADN is a family of procedures rather than a single standardized technique.¹⁵ PADN-HF-PH was therefore the program's most consequential test: a larger randomized evaluation on a background of contemporary heart failure therapy.¹⁶

WHAT PADN-HF-PH ADDS

Zhang and colleagues enrolled 264 symptomatic patients with right heart catheterization-confirmed PH-LHD at 25 centers in China, randomly assigning 134 to PADN plus guideline-directed medical therapy (GDMT) and 130 to GDMT alone.⁸ Baseline characteristics included 53% with preserved ejection fraction, 44.7% with IpcPH, and 55.3% with CpcPH. Median mean pulmonary artery pressure was 30 mm Hg, wedge pressure 19 mm Hg, and PVR 2.3 Wood units. Background therapy was contemporary: approximately 79% received a sodium-glucose cotransporter 2 (SGLT2) inhibitor, 83% a beta-blocker, 83% a mineralocorticoid receptor antagonist, and 95% renin-angiotensin system or neprilysin inhibition. PADN was completed in all assigned patients, with a median procedure time of 101 minutes and no procedural complications other than two access-site hematomas. However, fluoroscopy time and radiation dose, as well as operator specialty, prior PADN experience, and procedural case volume, were not reported, limiting assessment of procedural efficiency and reproducibility.

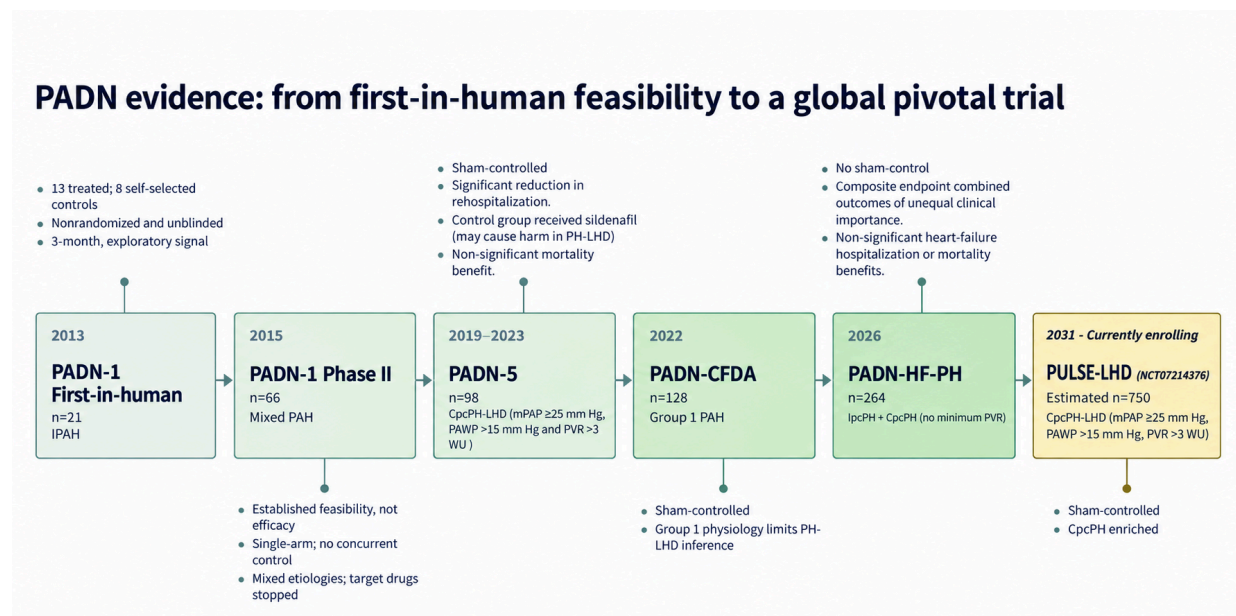
At a median follow-up of 338 days, clinical worsening occurred in 25 PADN-treated patients and 42 controls. The Kaplan-Meier-estimated 2-year incidence was 25.7% versus 51.5% (hazard ratio [HR], 0.49; 95% confidence interval [CI], 0.30-0.82; $P=0.006$). Recurrent events were also reduced (annualized rate, 36.3 vs. 56.3 per 100 patient-years; HR, 0.59; 95% CI, 0.39-0.89). Importantly, the finding was not driven solely by the 6-minute walk distance (6MWD), which had been the chief concern before publication: after excluding 6MWD decline, clinical worsening remained lower with PADN (20.8% vs. 40.3%; HR, 0.48; 95% CI, 0.27-0.86). Heart failure hospitalization favored PADN numerically (24.8% vs. 33.0%; HR, 0.56; 95% CI, 0.30-1.04), as did outpatient worsening requiring

intravenous therapy (16.5% vs. 32.2%; HR, 0.58; 95% CI, 0.31-1.11). Death was similar between arms (6 vs. 7 patients).

These results are difficult to dismiss as a simple exercise-training or expectancy effect. The treatment signal persisted in sensitivity analyses and even when the most subjective component was removed. Concordant improvements in 6MWD, Kansas City

Cardiomyopathy Questionnaire (KCCQ) score, natriuretic peptide levels, biventricular function, estimated right-sided pressures, and tricuspid regurgitation support biologic activity. Acute reductions in pulmonary pressure, PVR, and wedge pressure, along with increased cardiac output, provide mechanistic coherence. Consistency across clinical, functional, biomarker, and echocardiographic domains is the trial's greatest strength.

FIGURE 1



Pulmonary artery denervation (PADN): from first-in-human feasibility to a global pivotal trial. Timeline of pulmonary artery denervation (PADN) using radiofrequency energy showing the year, sample size, population, and principal design features and limitations of each study. CpcPH = combined precapillary and postcapillary pulmonary hypertension; GDMT = guideline-directed medical therapy; IPAH = idiopathic pulmonary arterial hypertension; IpcPH = isolated postcapillary pulmonary hypertension; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PAWP = pulmonary artery wedge pressure; PH-LHD = pulmonary hypertension associated with left heart disease; PVR = pulmonary vascular resistance; WU = Wood units.

A STRONG SIGNAL WITH IMPORTANT CAVEATS

The greatest limitation of PADN-HF-PH was the open-label design without including a sham procedure (Table 1). Patients, treating clinicians, research personnel, and outcome assessors knew the treatment allocation. Although events were independently adjudicated and imaging and biomarker analyses were blinded, decisions to admit a patient or escalate diuretics are precisely the outcomes most sensitive to knowledge of treatment. The reduced 6MWD decline seen in the treatment group is reassuring, but that endpoint was secondary, unadjusted for multiplicity, and neither heart failure hospitalization nor mortality reached significance on its own. The trial establishes a strong signal of reduced clinical worsening; it does not establish a survival or hospitalization benefit.

Mechanistic interpretation is also incomplete. The investigators documented acute hemodynamic improvement, but right heart catheterization was not repeated during follow-up, so a sustained reduction in PVR, the most direct evidence that PADN modifies pulmonary vascular disease, cannot be demonstrated. This limitation is particularly important given the substantial clinical and hemodynamic heterogeneity of the study population, which

included patients with heart failure with reduced, mildly reduced, and preserved ejection fraction, as well as potentially different contributions from elevated left-sided filling pressures, pulmonary vascular remodeling, and right ventricular dysfunction. Patients were eligible without a minimum PVR, and nearly half had IpcPH, in which elevated pressure may largely reflect passive transmission from the left atrium. In the prespecified subgroup analysis, the confidence interval excluded unity only among patients with IpcPH (HR, 0.31; 95% CI, 0.12-0.79), whereas the effect was not significant in CpcPH (HR, 0.71; 95% CI, 0.39-1.28). Point estimates favored PADN in both groups, and neither subgroup analysis was powered or adjusted for multiplicity, so this is not evidence of true heterogeneity. It is, however, the opposite of what the pulmonary vascular hypothesis predicts. A small proof-of-principle study reporting improved left ventricular diastolic function after PADN in IpcPH offers one explanation, but if the dominant mechanism is left-sided rather than pulmonary vascular, then what PADN is and whom it should treat both change.¹⁷ The apparently larger effects in women and in patients with an ejection fraction above 40% should likewise be treated as hypothesis-generating. Future trials should prospectively define clinical and hemodynamic phenotypes, evaluate treatment effects across continuous measures such as PVR and ejection fraction, and determine whether PADN benefits the

broader PH-LHD population or a more narrowly defined responder phenotype.

Generalizability warrants equal caution. All patients were enrolled in China, were 75 years of age or younger, and had relatively preserved renal function and systemic perfusion. The advanced age, frailty, kidney disease, device therapy, and multimorbidity that characterize Western PH-LHD populations were underrepresented or excluded. Operator learning, reproducibility, and durability beyond the current follow-up remain unresolved, and the current data cannot tell us whether

reinnervation, progression of left heart disease, or recurrent pulmonary vascular remodeling will attenuate benefit, whether repeat denervation would be feasible after prior radiofrequency injury, or whether late pulmonary artery stenosis, aneurysmal change, or thrombosis will emerge outside the early procedural window. A procedure of roughly 100 minutes must ultimately justify its resource use not only against GDMT alone but also against structured heart failure care and optimized treatment of concomitant valve disease, atrial fibrillation, obesity, and sleep-disordered breathing.

TABLE 1
What PADN-HF-PH established and what remains to be shown

Domain	What PADN-HF-PH showed	What remains unresolved
Blinding	Open-label; events adjudicated and echocardiographic, hemodynamic and biomarker data analyzed blinded.	Patients, treating physicians and outcome assessors were unblinded, and admission and diuretic decisions are expectation-sensitive. A sham arm is required.
Primary endpoint	Clinical worsening 25.7% vs 51.5% (HR 0.49; 95% CI 0.30-0.82); effect persisted after removal of the 6-minute walk component (HR 0.48; 95% CI 0.27-0.86).	The composite combined outcomes of unequal importance; the analysis excluding walk distance was secondary and unadjusted for multiplicity.
Death and hospitalization	Death 6 vs 7 patients; heart failure hospitalization HR 0.56 (95% CI 0.30-1.04).	The trial was not powered for either. Confirmation requires adequate power for adjudicated cardiovascular death and heart failure hospitalization.
Hemodynamics	Acute falls in mean pulmonary artery pressure, pulmonary vascular resistance and wedge pressure with increased cardiac output at 10 minutes.	No repeat right heart catheterization during follow-up, so sustained reduction in pulmonary vascular resistance and improved right ventricular-pulmonary arterial coupling remain undemonstrated.
Phenotype	No minimum pulmonary vascular resistance for entry; 44.7% isolated postcapillary and 55.3% combined precapillary and postcapillary disease.	The confidence interval excluded unity only in isolated postcapillary disease (HR 0.31) and not in the combined phenotype (HR 0.71). Enrichment and analysis across continuous pulmonary vascular resistance are needed.
Generalizability	264 patients at 25 Chinese centers, 75 years of age or younger, with estimated glomerular filtration rate above 30 mL/min/1.73 m ² and cardiac index above 1.5 L/min/m ² .	Older, frailer patients with chronic kidney disease, device therapy and multimorbidity, who dominate Western practice, were underrepresented or excluded.
Durability and late safety	Procedural success 100%; two access-site hematomas and no other procedural complications; median follow-up 338 days.	Reinnervation, late pulmonary artery stenosis, aneurysm or thrombosis, and the feasibility and safety of repeat denervation are unknown.
Technique	Radiofrequency ablation at three sites, 150 seconds each under temperature control at 50°C.	Operator learning curve is undefined and the energy modality is not standardized across programs, differences in radiofrequency vs intravascular ultrasound.

CI = confidence interval; CpcPH = combined precapillary and postcapillary pulmonary hypertension; HR = hazard ratio; lpcPH = isolated postcapillary pulmonary hypertension; PADN = pulmonary artery denervation.

WHY THE SHAM ARM IS NOT A FORMALITY

Interventional cardiology has learned this lesson twice. ORBITA showed that an unblinded procedural benefit, taken as self-evident, could shrink substantially once patients were blinded, and SYMPPLICITY HTN-3 halted the first wave of renal denervation after a sham-controlled trial failed to reproduce open-label results.^{18,19} The instructive part is what followed: renal denervation was not abandoned but redesigned, and rigorously blinded trials such as SPYRAL HTN-OFF MED Pivotal ultimately demonstrated a real, if more modest, treatment effect.²⁰ A sham arm is not an obstacle placed in front of a promising therapy; it is the mechanism by which a promising therapy earns durable adoption. Given that PADN-HF-PH's benefit rests substantially on unblinded, expectation-sensitive endpoints such as outpatient diuretic escalation, the field should want that test rather than resist it.

FROM SIGNAL TO STANDARD

Our position is therefore straightforward. PADN-HF-PH is a well-conducted trial that provides the strongest signal yet for a pulmonary vascular intervention in group 2 pulmonary

hypertension, and it deserves to be treated as such. However, it should not change practice. Outside a clinical trial, PADN should not be offered to patients with PH-LHD based on these data, and reimbursement or guideline endorsement would be premature.

The ongoing international PULSE-LHD trial (NCT07214376) is therefore not redundant; it is the necessary next step. Its sham-controlled design and enrichment for CpcPH address the two central uncertainties remaining after PADN-HF-PH: expectation-sensitive bias and biological dilution from predominantly passive pulmonary hypertension. A confirmatory program should prioritize adequately powered, adjudicated cardiovascular death and heart failure hospitalization; serial invasive hemodynamics with assessment of right ventricular-pulmonary arterial coupling; a prespecified treatment-effect analysis across continuous PVR rather than a dichotomized phenotype; a standardized ablation technique with reporting of operator experience; and long-term pulmonary artery imaging for late stenosis, aneurysm, thrombosis, or loss of efficacy.

PADN-HF-PH moves pulmonary artery denervation beyond feasibility and into the category of therapies that plausibly could alter the course of PH-LHD. The magnitude of benefit, the

contemporary background therapy, the clean procedural safety profile, and the concordance of objective findings are all real. So is the fact that a common, heterogeneous syndrome treated with an irreversible ablative procedure demands a higher evidentiary threshold than an unblinded composite can provide. The right response to this trial is neither adoption nor dismissal, but referral of eligible patients to rigorously designed, sham-controlled trials.

ARTICLE INFORMATION

Ethics approval: This study did not involve human subjects. IRB approval was not required for this study.

Funding support: This research was not supported by a specific grant from any funding agency.

Author contributions: Ghoneem: conceptualization, resources, supervision, visualization, writing – original draft, writing – review & editing. Cruz Torres: conceptualization, formal analysis, investigation, validation, writing – review & editing. Aggarwal: conceptualization, writing – original draft.

Authorship criteria: All 3 listed authors have returned the ICMJE authorship attestation and confirmed all four ICMJE criteria.

Disclosures: Dr Aggarwal has served as a consultant for Jupiter Endovascular, Pulnovo Inc, Imperative Care, and Akura Medical; and has received research support from the American Heart Association, Imperative Care, AngioWave, Vena Medical, and Akura Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

AI use: The authors reported the use of artificial intelligence tools for manuscript editing and for figure generation. AI tools are not credited as authors, and the authors are responsible for all content. The journal used AI tools in copy-editing and proofreading; all changes were checked by the editorial team and approved by the authors.

Address for correspondence: Ahmed Ghoneem, MD, Division of Cardiology, Henry Ford Hospital, 2799 W Grand Blvd, K14, Detroit, MI 48202. Email: aghonee1 at hfhs dot org.

REFERENCES

1. Strange GA, Maron BA, Zeder K, et al. Global distribution of prognostically significant pulmonary pressure indicative of pulmonary hypertension. *J Glob Health*. 2025;15:04098. doi:10.7189/jogh.15.04098
2. Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J*. 2019;53(1):1801897. doi:10.1183/13993003.01897-2018
3. Ilonze OJ, Ebong IA, Guglin M, et al. Considerations in the diagnosis and management of pulmonary hypertension associated with left heart disease. *JACC Heart Fail*. 2024;12(8):1328-1342. doi:10.1016/j.jchf.2024.04.031
4. Bermejo J, Yotti R, Garcia-Orta R, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial. *Eur Heart J*. 2018;39(15):1255-1264. doi:10.1093/eurheartj/ehx700
5. Vachiéry JL, Delcroix M, Al-Hiti H, et al. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J*. 2018;51(2):1701886. doi:10.1183/13993003.01886-2017
6. Dachs TM, Duca F, Rettl R, et al. Riociguat in pulmonary hypertension and heart failure with preserved ejection fraction: the haemoDYNAMIC trial. *Eur Heart J*. 2022;43(36):3402-3413. doi:10.1093/eurheartj/ehac389
7. Yadgir S, Johnson CO, Aboyans V, et al. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. *Circulation*. 2020;141(21):1670-1680. doi:10.1161/CIRCULATIONAHA.119.043391
8. Zhang H, Wang Q, Liang M, et al. Pulmonary denervation for heart failure-related pulmonary hypertension. *N Engl J Med*. Published online August 30, 2026. doi:10.1056/NEJMoa2609056
9. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023;61(1):2200879. doi:10.1183/13993003.00879-2022
10. Chen SL, Zhang FF, Xu J, et al. Pulmonary artery denervation to treat pulmonary arterial hypertension: the single-center, prospective, first-in-man PADN-1 study (first-in-man pulmonary artery denervation for treatment of pulmonary artery hypertension). *J Am Coll Cardiol*. 2013;62(12):1092-1100. doi:10.1016/j.jacc.2013.05.075
11. Chen SL, Zhang H, Xie DJ, et al. Hemodynamic, functional, and clinical responses to pulmonary artery denervation in patients with pulmonary arterial hypertension of different causes: phase II results from the Pulmonary Artery Denervation-1 study. *Circ Cardiovasc Interv*. 2015;8(11):e002837. doi:10.1161/CIRCINTERVENTIONS.115.002837
12. Zhang H, Zhang J, Chen M, et al. Pulmonary artery denervation significantly increases 6-min walk distance for patients with combined pre- and post-capillary pulmonary hypertension associated with left heart failure: the PADN-5 study. *JACC Cardiovasc Interv*. 2019;12(3):274-284. doi:10.1016/j.jcin.2018.09.021
13. Zhang H, Kan J, Zhang J, et al. 3-year outcome in patients with combined precapillary and postcapillary pulmonary hypertension: results from PADN-5 trial. *JACC Heart Fail*. 2023;11(8):1135-1146. doi:10.1016/j.jchf.2023.05.016
14. Zhang H, Wei Y, Zhang C, et al. Pulmonary artery denervation for pulmonary arterial hypertension: a sham-controlled randomized PADN-CFDA trial. *JACC Cardiovasc Interv*. 2022;15(23):2412-2423. doi:10.1016/j.jcin.2022.09.013
15. Rothman AMK, Vachieri JL, Howard LS, et al. Intravascular ultrasound pulmonary artery denervation to treat pulmonary arterial hypertension (TROPHY1): multicenter, early feasibility study. *JACC Cardiovasc Interv*. 2020;13(8):989-999. doi:10.1016/j.jcin.2019.12.027
16. Wang Q, Zhang J, Zhang H, et al. Pulmonary artery denervation for the treatment of patients with pulmonary hypertension secondary to left-sided heart failure: rationale and design of the randomized controlled PADN-HF-PH trial. *Cardiology Discovery*. 2026;6(2):99-105. doi:10.1097/CD9.0000000000000181
17. Jiang X, Zhang H, Zhang J, et al. Pulmonary artery denervation improves left ventricular diastolic function in patients with isolated post-capillary pulmonary hypertension secondary to heart failure with preserved ejection fraction: a safety and proof-of-principle cohort study. *AsiaIntervention*. 2026;12(1):41-49. doi:10.4244/AIJ-D-25-00061
18. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet*. 2018;391(10115):31-40. doi:10.1016/S0140-6736(17)32714-9
19. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370(15):1393-1401. doi:10.1056/NEJMoa1402670
20. Böhm M, Kario K, Kandzari DE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet*. 2020;395(10234):1444-1451. doi:10.1016/S0140-6736(20)30554-7