Pulmonary Artery Denervation for Pulmonary Arterial Hypertension:

The Sham-Controlled Randomized PADN-CFDA trial

On Behalf of PADN-CFDA Trial Investigators

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Disclosure Statement of Financial Interest

I, Shao-Liang Chen, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- WHO Group I pulmonary arterial hypertension (***PAH***) is a progressive, debilitating disease
- Previous observational studies have demonstrated that pulmonary artery denervation (***PADN***) improves hemodynamic and exercise capacity in patients with PAH
- However, the safety and effectiveness of PADN have not been established in a randomized trial

Galiè N... Eur H J 2016; Frost A... Eur Respir J 2019; Benza RL... Chest 2012; Chen…JACC 2013

Aims

- To determine the safety and efficacy of PADN in Group I PAH patients

Study Flow Chart

Design

- **DESIGN:** Prospective, randomized, multi-center, sham-control clinical evaluation of pulmonary artery denervation (PADN) for patients with PAH
- **OBJECTIVE:** To evaluate the safety and efficacy of PADN treatment at 6-month follow-up
- **PRINCIPAL INVESTIGATOR**
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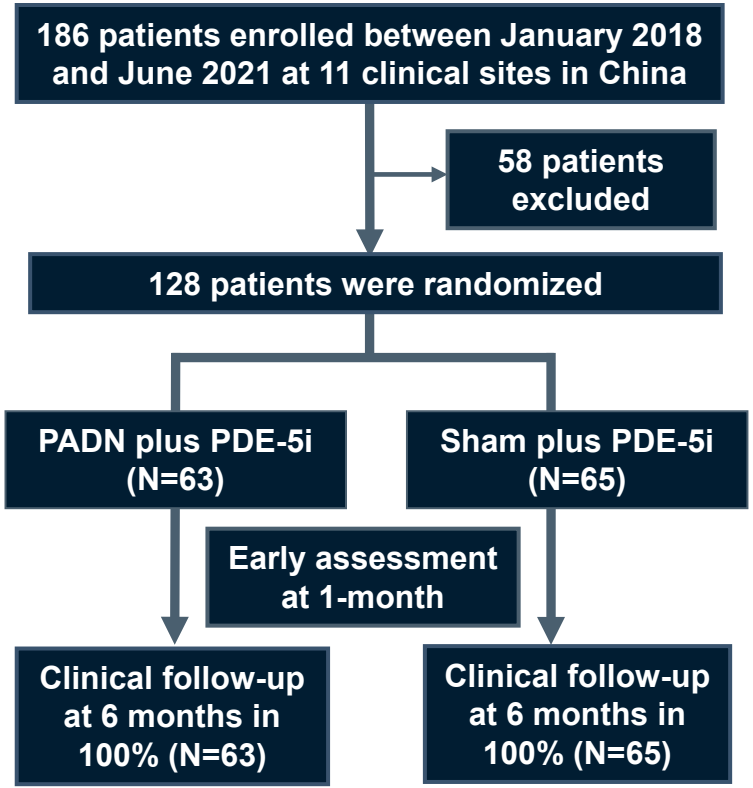


PDE-5i = phosphodiesterase-5 inhibitor

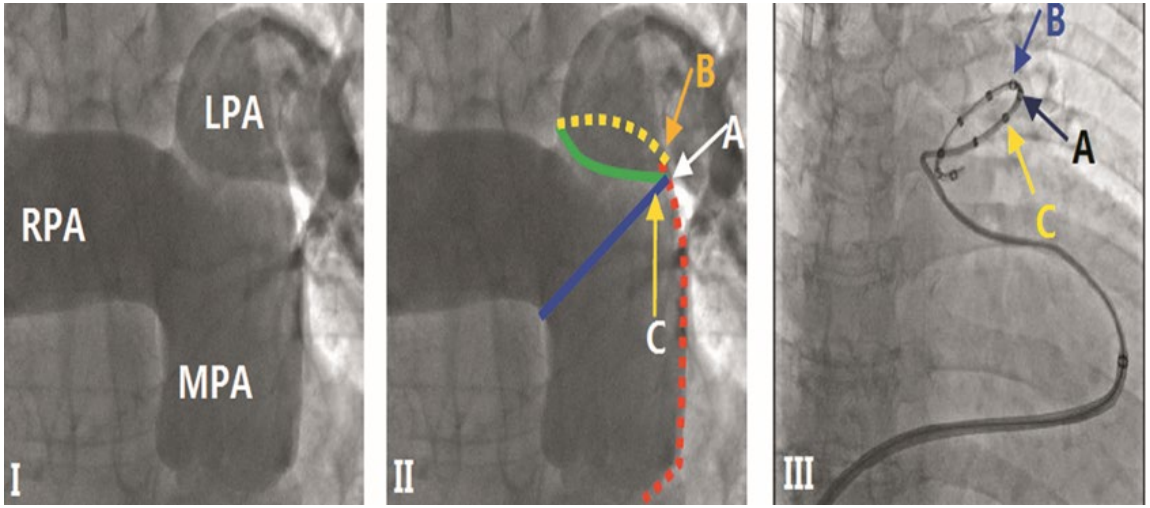
Major Inclusion Criteria

- Clinically stable patients aged 18 to 70 years with PAH who were not being treated with any PAH-specific medications for at least 30 days
- PAH was confirmed by right heart catheterization as:
  - mPAP ≥25 mmHg
  - PVR >3 WU
  - PAWP <15 mmHg
  - Negative acute vasoreactivity test (for idiopathic, heritable, or drug-induced PAH)

Major Exclusion Criteria

- Patients with Group II-V pulmonary hypertension
- Cardiac index <1.5 L/min/m^2
- Creatinine clearance <30 ml/min
- Inflammation or cancer
- Tricuspid valve or pulmonary valve stenosis
- Pulmonary veno-occlusive disease

PADN Procedure



- Target ablation sites (A, B and C)
- If sPAP or mPAP reduction <10% after ablation at A-C, additional ablations at ostial anterior LPA wall were performed

- The following ablation parameters were programmed at each point: temperature ≥45°C, energy ≤20 W, and time 120 seconds
- Control patients had a sham-procedure performed in which the PADN catheter was positioned at the target site but energy was not delivered

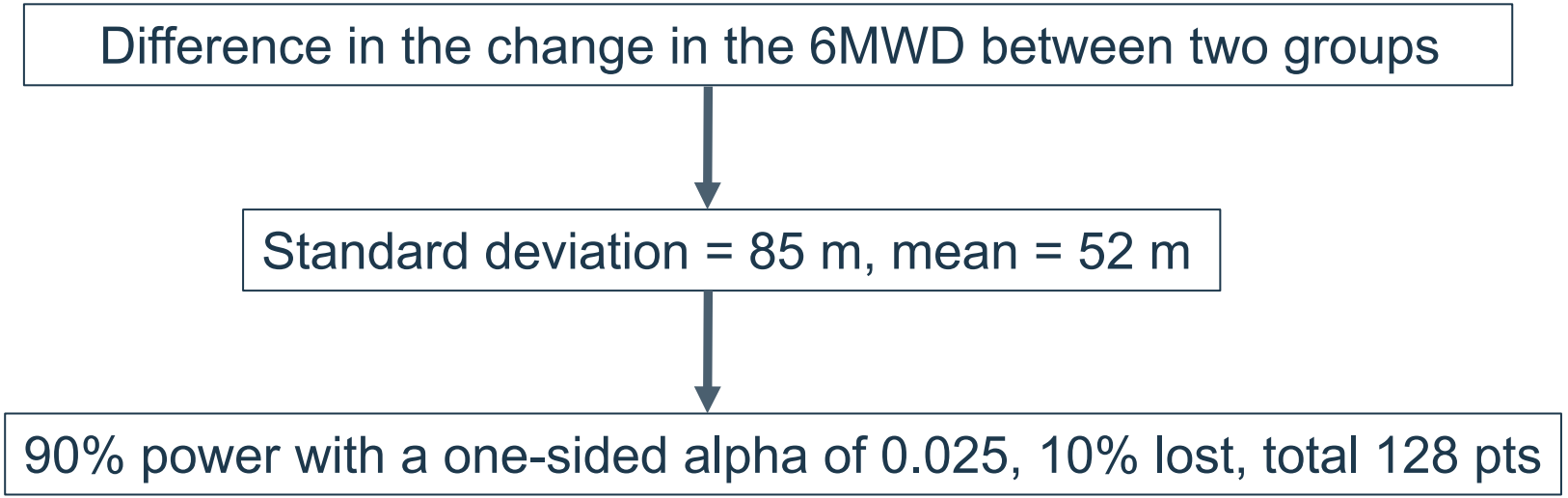
Responder was defined as reduction of sPAP or mPAP ≥10% post-PADN

Endpoints

Outcome	Time point	Powered	Blinded
Primary endpoint			
-- Difference in the change in the 6MWD (m)	6 months	Superiority	Yes
Secondary endpoints			
-- PVR via RHC (Wood units)	6 months	--	Yes
-- NT-proBNP (pg/ml)	6 months	--	Site report
-- Clinical worsening (%)	6 months	--	Yes
-- Satisfactory clinical response (%)	6 months	--	Yes
-- Cardiac function via cardiac echo	6 months	--	Yes

- PVR = pulmonary vascular resistance
- RHC = right heart catheterization

Assumptions and Statistical Analysis



- The between-group change in the 6MWD and sensitivity were analyzed using mixed-model repeated measures (*MMRM*)
- Sensitivity analysis was performed using MMRM and Markov Chain Monte Carlo (*MCMC*)

Baseline Data

	PADN n = 63	Sham n = 65
Age, years	41.2 ± 11.9	39.5 ± 11.5
Female, n (%)	57 (90.5)	49 (75.4)
Idiopathic PAH, n (%)	36 (57.1)	34 (52.3)
CTD-related PAH, n (%)	14 (22.2)	17 (26.2)
Associated with CHD, n (%)	9 (14.3)	13 (20.0)
WHO functional class III/IV, n (%)	35 (55.6)	29 (34.6)
6-minute walk distance, m	387.5 ± 91.7	414.3 ± 91.5
NT-proBNP, pg/ml	2679 ± 3358	2015 ± 2928
PVR, Woods Unit	11.7 ± 5.6	10.3 ± 4.5

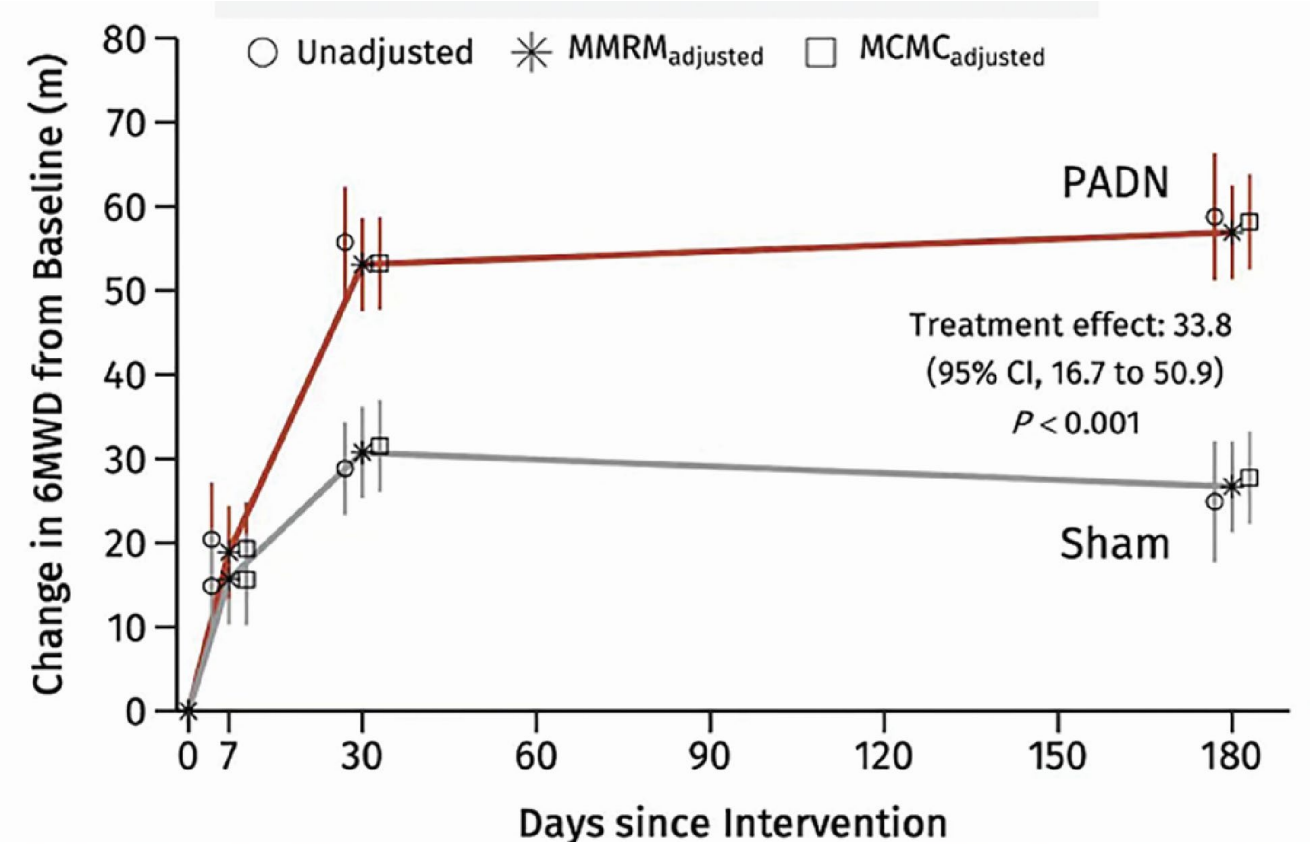
PAH=pulmonary arterial hypertension; CTD=connective tissue disease; CHD=congenital heart disease; PVR=pulmonary vascular resistance

Medications During Follow-up

	PADN n = 63	Sham n = 65	
PDE-5i therapy, n (%)			
-- at 1-month	58 (92.1)	59 (90.8)	1.3 (-10.4 to 12.9)
-- at 6-month	57/61 (93.4)	58/64 (90.6)	2.8 (-8.8 to 14.3)
Combination therapy, n (%)	**N = 61**	**N=64**	-1.5 (-11.1 to 8.3)
-- at 1-month	2 (3.2)	3 (4.7)	-6.0 (-17.5 to 5.4)
-- at 6-month	3 (4.9)	7 (10.9)	
Diuretics, n (%)	**N = 61**	**N = 64**	
-- at 1-month	13 (20.6)	41 (63.1)	-42.5 (-56.8 to -24.5)
2 or more diuretics	3 (4.8)	21 (32.3)	-27.5 (-40.9 to -13.3)
-- at 6-month	17 (27.9)	45 (70.3)	-42.4 (-57.2 to -24.0)
2 or more diuretics	5 (8.2)	25 (39.1)	-30.9 (-44.9 to -15.1)

Between-group differenced were estimated using the *Newcombe-Wilson test*

Change in the 6-Minute Walk Distance



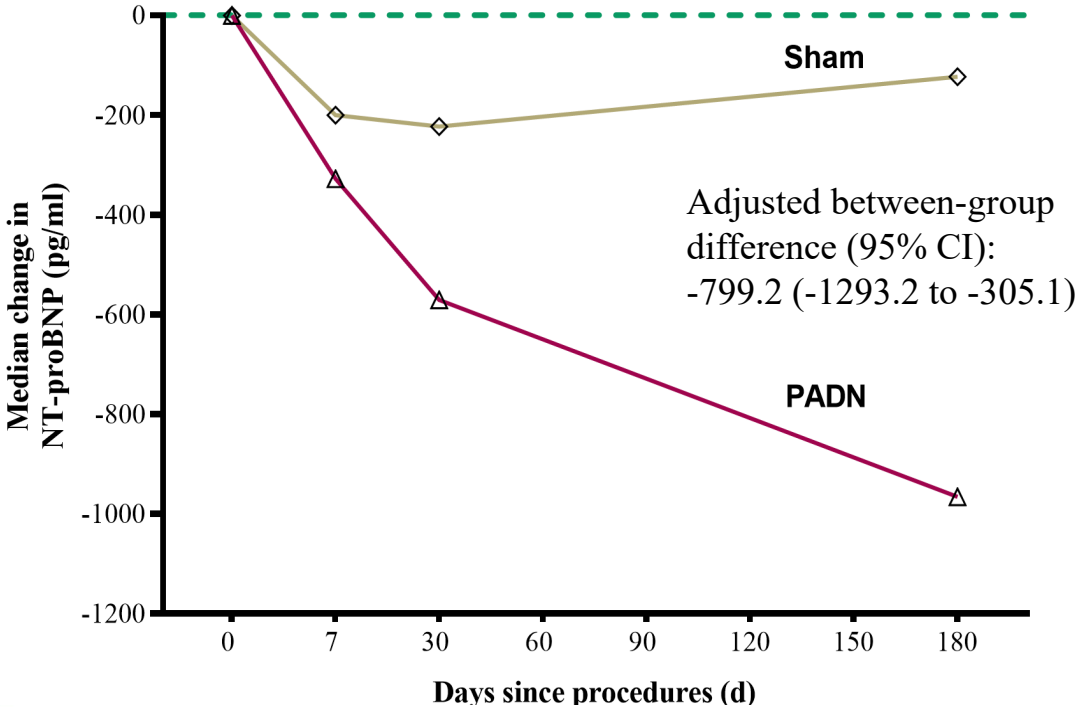
Adjusted Change in 6-Minute Walk Distance

	PADN n = 63	Sham n = 65	LSM Difference (95% CI)
Primary endpoint			
--Change in 6MWD to 6 months, m	57.0 ± 5.5 (n = 59)	26.7 ± 5.3 (n = 63)	34.0 (16.8 to 51.1)
Secondary endpoints			
--Change in 6MWD to 7 days, m	19.0 ± 5.4 (n = 61)	15.7 ± 5.3 (n = 64)	7.0 (-13.5 to 27.4)
--Change in 6MWD to 30 days, m	57.0 ± 5.5 (n = 60)	30.8 ± 5.4 (n = 62)	25.9 (6.2 to 45.7)

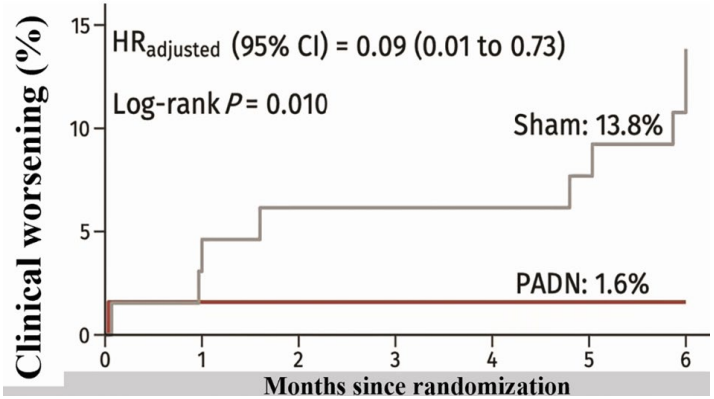
Differences of least squares means between the groups were estimated using MMRM with adjustment for age, sex, and body mass index

LSM=least square mean

Changes in the NT-proBNP, PVR and clinical worsening



Change from baseline to 6 months	PADN group	Sham arm	p value
NT-pro BNP	-58.5%	-25.2%	0.018
PVR	-27%	-14.8%	0.003



Clinical worsening was defined as all-cause death, rehospitalization and worsening of PAH

6-Month Changes in Cardiac Function and Hemodynamics

	PADN n = 63	Sham n = 65	LSM difference (95% CI)
Echocardiography			
-- Right atrial pressure, mmHg	-1.7 ± 0.3	0.4 ± 0.3	-2.0 (-2.8 to -1.3)
-- RV fractional area change, (%)	10.4 ± 0.9	-0.6 ± 0.9	11.0 (8.5 to 13.5)
-- TAPSE, mm	4.3 ± 0.3	-0.1 ± 0.3	4.4 (3.5 to 5.3)
-- RV global longitudinal strain, %	-2.9 ± 0.3	-0.1 ± 0.3	-2.8 (-3.7 to -2.0)
Right heart catheterization			
-- Mean PAP, mmHg	-7.8 ± 1.0	-3.5 ± 0.9	-4.3 (-6.9 to -1.6)
-- Cardiac output, L/min	0.96 ± 0.14	0.32 ± 0.13	0.64 (0.33 to 0.78)
-- PA compliance, ml/mmHg	0.51 ± 0.57	0.16 ± 0.88	0.34 (0.15 to 0.52)

PAP=pulmonary arterial pressure; RV=right ventricular; TAPSE=tricuspid annular plane systolic excursion

LSM=least square mean

Conclusions

- Treatment with PADN plus a PDE-5i was safe and resulted in *improved exercise capacity* at 6 months compared with PDE-5i treatment alone.

- In addition, treatment with PADN reduced PVR and PAP, improved right ventricular function, reduced tricuspid regurgitation and NT-proBNP levels, and improved clinical outcomes during 6-month follow-up.

Thank you for your attention!

PADN-CFDA trial was simultaneously published in

JACC: Cardiovascular Interventions