Pulmonary Denervation: A New Frontier In The Treatment Of Pulmonary Hypertension

VEITH 2024 (15 min)

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Center for Quality, Effectiveness, and Outcomes in Cardiovascular Diseases

Disclosures

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- Specific Disclosures
  - –None
- General Disclosures
  - –None

Current Endpoints

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Acute	Acute Clot management	Restore hemodynamics Prevent Death
Post Acute	Anticoagulation	Facilitate clot resolution Prevent Recurrence
Chronic	Cardio-pulmonary Rehab	Ameliorate Post-PE Syndrome

Post PE Syndrome

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"persistent dyspnea, exercise limitation, and impaired quality of life that persist for longer than 3 months after effective anticoagulation for acute PE. "

50%

Sanders A, Matonhodze M. Post pulmonary embolism syndrome: a common, underdiagnosed complication that is not well recognized. BMJ Case Rep. 2019 Feb 22;12(2):e226674

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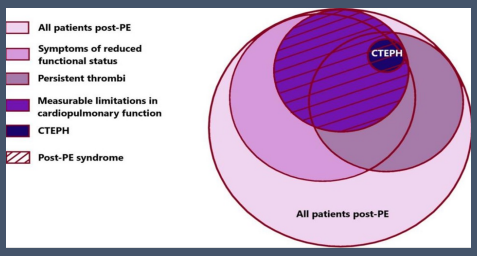

Sanders A, Matonhodze M. Post pulmonary embolism syndrome: a common, underdiagnosed complication that is not well recognized. BMJ Case Rep. 2019 Feb 22;12(2):e226674

Post PE Syndrome

- 25-33% of patients after a PE
  - Incomplete thrombus resolution,
  - Impaired gas exchange,
  - Altered hemodynamics.
- 10-30% of patients
  - Pulmonary artery pressure is elevated,
  - Right ventricular function remains abnormal
- 0.5-4% of patients
  - Chronic thromboembolic pulmonary hypertension (CTEPH)

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ELOPE (Evaluation of Long-term Outcomes after PE) Study

- Predictors of post-PE syndrome
  - male sex,
  - younger age,
  - higher BMI,
  - smoking.
- Cardiopulmonary exercise testing (VO_2 max <80% predicted) or 6-minute walk testing at one month may help to identify patients with a higher risk of post-PE syndrome at one year

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Definition	Characteristics (Based on right heart catheterization)	Clinical group
Precapillary	• *mPAP ≥ 25 mmHg* • *PAWP (or LVEDP) ≤ 15 mmHg*	*I, III, IV, V*
Postcapillary	• *mPAP ≥ 25 mmHg* • *PAWP (or LVEDP) > 15 mmHg* ○ *Post-capillary PH: TPG ≤ 12 mmHg or DPG < 7 mmHg* ○ *Combined post & pre-capillary PH: TPG > 12 mmHg or DPG ≥ 7 mmHg*	*II*

TPG (Trans-pulmonary gradient) = mPAP – PAWP
DPG (Diastolic pulmonary gradient) = dPAP – PAWP

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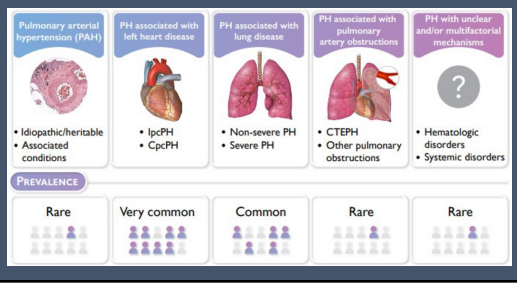

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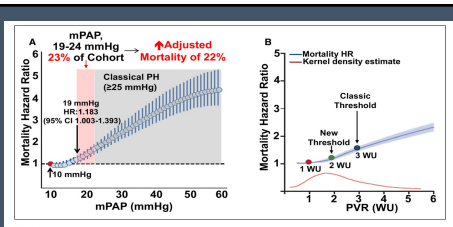

Figure 3. The relationship between pulmonary hypertension (PH) hemodynamic parameters and all-cause mortality.
In a national cohort of patients referred for right heart catheterization, mean pulmonary artery pressure (mPAP) (N=21 727) (**A**) and pulmonary vascular resistance (PVR) restricted to patients with mPAP ≥19 mm Hg (N=32 725) (**B**) were modeled continuously, and the association with all-cause mortality risk is shown. These results converge with normative data,[18, 19] suggesting that the upper limits of normal for mPAP and PVR are ≈20 mm Hg and 2 WU, respectively. Taken together, these data establish an evidence-based framework for the new hemodynamic definition of PH. The red disc represents the referent group. Adapted with permission from Maron BA, et al[16] © 2016, American Heart Association, Inc (**A**); and Maron BA, et al[17] © 2020, Elsevier Ltd (**B**). HR indicates hazard ratio; and WU, Wood units.

Risk assessment and stratifications REVEAL Lite 2

- Parameters
  - New York Heart Association (NYHA)
  - WHO functional class (FC)
  - Vital signs (systolic BP [SBP]and heart rate)
  - 6MWD - walking
  - Brain Natriuretic Peptide(BNP)/N-terminal prohormone of brain natriuretic peptide(NT-proBNP)
  - Renal insufficiency: eGFR<60mL/min/1.73m^2
- Risk Stratification
  - 1 – 5 low
  - 6 – 7 intermediate
  - > 8 high-risk

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Risk nd Outcomes

- .
- Risk Stratification and 1-year mortality
  - Low (<5%),
  - Intermediate (5-10%)
  - High-risk (>10%)

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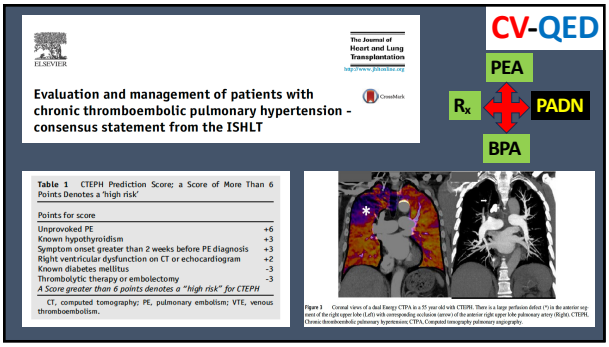
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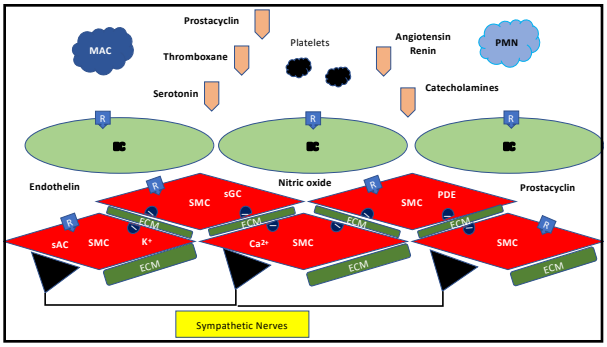
PEA
Rx
PADN
BPA
Evaluation and management of patients with chronic thromboembolic pulmonary hypertension - consensus statement from the ISHLT
The Journal of Heart and Lung Transplantation
Table 1 CTEPH Prediction Score; a Score of More Than 6 Points Denotes a 'high risk'
Points for score
Unprovoked PE +6
Known hypothyroidism +3
Symptom onset greater than 2 weeks before PE diagnosis +3
Right ventricular dysfunction on CT or echocardiogram +2
Known diabetes mellitus -3
Thrombolytic therapy or embolectomy -3
A Score greater than 6 points denotes a "high risk" for CTEPH
CT, computed tomography; PE, pulmonary embolism; VTE, venous thromboembolism.


MAC
Prostacyclin
Thromboxane
Platelets
Angiotensin
Renin
PMN
Serotonin
Catecholamines
Endothelin
Nitric oxide
Prostacyclin
SMC
sGC
PDE
sAC
K+
Ca2+
ECM
Sympathetic Nerves

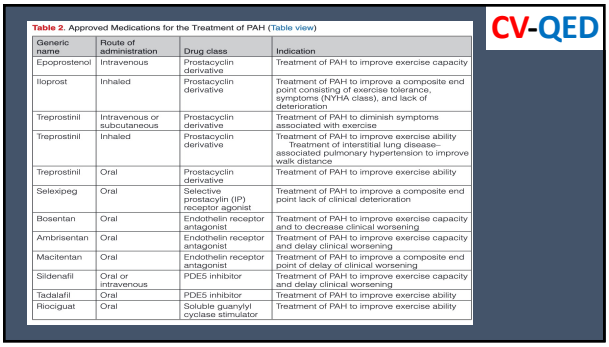

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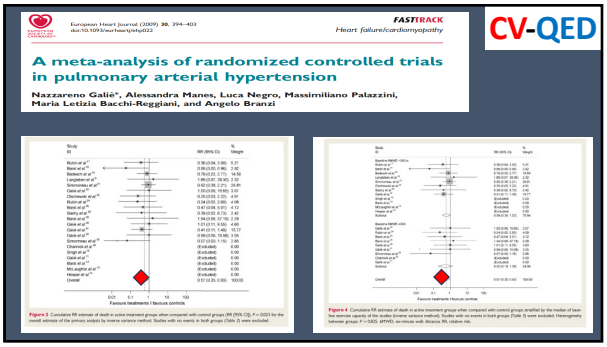
Table 2. Approved Medications for the Treatment of PAH (Table view)
Generic name | Route of administration | Drug class | Indication
Epoprostenol | Intravenous | Prostacyclin derivative | Treatment of PAH to improve exercise capacity
Iloprost | Inhaled | Prostacyclin derivative | Treatment of PAH to improve a composite end point consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration
Treprostinil | Intravenous or subcutaneous | Prostacyclin derivative | Treatment of PAH to diminish symptoms associated with exercise
Treprostinil | Inhaled | Prostacyclin derivative | Treatment of PAH to improve exercise ability Treatment of interstitial lung disease–associated pulmonary hypertension to improve walk distance
Treprostinil | Oral | Prostacyclin derivative | Treatment of PAH to improve exercise ability
Selexipeg | Oral | Selective prostacylin (IP) receptor agonist | Treatment of PAH to improve a composite end point lack of clinical deterioration
Bosentan | Oral | Endothelin receptor antagonist | Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan | Oral | Endothelin receptor antagonist | Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan | Oral | Endothelin receptor antagonist | Treatment of PAH to improve a composite end point of delay of clinical worsening
Sildenafil | Oral or intravenous | PDE5 inhibitor | Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil | Oral | PDE5 inhibitor | Treatment of PAH to improve exercise ability
Riociguat | Oral | Soluble guanylyl cyclase stimulator | Treatment of PAH to improve exercise ability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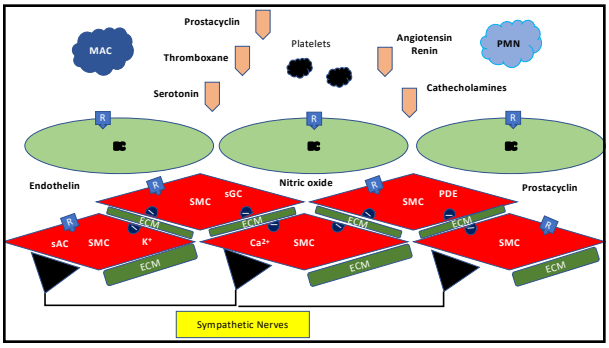
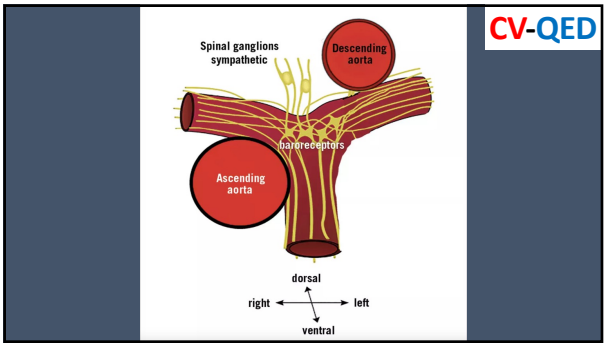
European Heart Journal (2009) 30, 394–403
FASTTRACK
Heart failure/cardiomyopathy
A meta-analysis of randomized controlled trials in pulmonary arterial hypertension
Nazzareno Galiè*, Alessandra Manes, Luca Negro, Massimiliano Palazzini, Maria Letizia Bacchi-Reggiani, and Angelo Branzi


MAC
Prostacyclin
Thromboxane
Platelets
Angiotensin
Renin
PMN
Serotonin
Cathecholamines
Endothelin
Nitric oxide
Prostacyclin
SMC
sGC
PDE
sAC
K+
Ca2+
ECM
Sympathetic Nerves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Spinal ganglions sympathetic
Descending aorta
baroreceptors
Ascending aorta
dorsal
right
left
ventral

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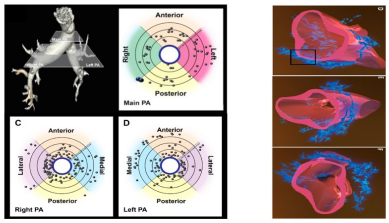
Pulmonary Artery Innervation



Rothman et al. Circ Cardiovasc Interv. 2015;8:e002569. DOI: 10.1161/CIRCINTERVENTIONS.115.002569.
Zhou L. et al. J Am Coll Cardiol Intv. 2015; DOI: 10.1016/j.jcin.2015.09.015

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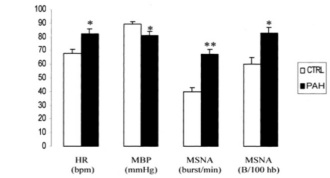
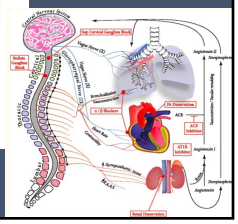
Pulmonary Arterial Hypertension:
Sympathetic Activation



Velez-Roa et al. Circulation. 2004; 110:1308–1312.



Experimental studies of PADN

						Outcome			
Author	Ref	Year	Species	Model	Technique	PAP	PVR	Histological	Humoral
Juratsch	5	1980	Canine	balloon inflation in main PA	Surgical and chemical PADN	benefit	benefit		
Chen	28	2013	Canine	left pulmonary distal basal trunk or interlobar artery occlusion	Radiofrequency PADN	benefit	benefit		
Zhou	33	2015	Canine	intra-atrial N-dimethylacetamide or DMACT	RadiofrequencyPADN			benefit	
Rothman	39	2015	Porcine	TnA 2 challenge pre- and post-PADN	RadiofrequencyPADN			benefit	benefit
Liu	27	2016	Canine	IV monocrotaline	PADN				benefit
Zhang	28	2018	Rat	supracoronary aortic banding	Surgical and chemical PADN	benefit		benefit	
Huang	29	2019	Rat	IV monocrotaline	Radiofrequency PADN	benefit	benefit	benefit	benefit
Garcia-Lunar	30	2019	Porcine	pulmonary vein banding	Surgical and Radiofrequency PADN	no effect	no effect		
Rothman	34	2019	Porcine	TnA 2 challenge pre- and post-PADN	PADN	benefit		benefit	

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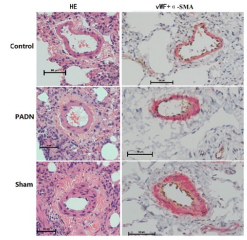
Remodelling of Pulmonary Vessels



Zhou L. et al. J Am Coll Cardiol Intv. 2015; DOI: 10.1016/j.jcin.2015.09.015

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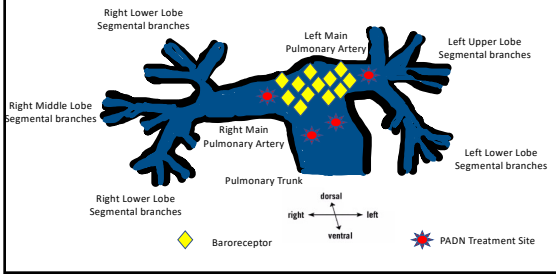
Pulmonary Disorders

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)

Shao-Liang Chen, MD,*† Feng-Fu Zhang, MD,* Jing Xu, MD,* Du-Jiang Xie, MD,* Ling Zhou, MD,* Thach Nguyen, MD,‡ Gregg W. Stone, MD§
Nanjing, China; Hobart, Indiana; and New York, New York



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The following ablation parameters were applied at each spot: temperature >50°C, energy = 10 W, and time = 120 s.

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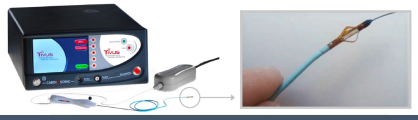
SoniVie Technology - TIVUS™ System

Non Focused Ultrasound for intra-vascular denervation



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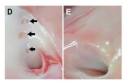
Pulmonary cryoablation – new turn in advanced ablation technologies



Cryoablation temperature – 70 C
Duration at each spot – 2 min
Average number of cryoablation spots at each ostium – 6 to 7

Human Studies

				Study characteristics						Outcomes								
Study type	Author	Ref	Year	Modality	n	Therapy Group	Control Group	Follow up (months)	Lost to follow up	6-minute walking distance	Mean pulmonary artery pressure	Pulmonary vascular resistance	Left ventricular end-systolic diameter	Cardiac output	Mortality	Morbidity	Cardiac function	Readmission rate	Lung Transplantation Free Mortality
Case Series	Chen	20	2014	PADN	21	13	8	3	0	1	1								
Case Series	Chen	20	2015	PADN	66	66	0	12	0	1	1	2	2	2	2		2	2	
Case report	Kiuchi	9	2015	PADN	1	1	0	6	0	1	2	2	2	2					
Case report	Zhang	8	2016	PADN	1	1	0	12	0	1	1								
Randomized	Karaskov	21	2017	Surgery +DN	30	30	15	15	0		2	2							
Randomized	Zhang	22	2019	PADN	98	48	50	6	0	1	1	2	2	2	2		2	2	2
Case Series	Trofimov	26	2019	Surgery +DN	140	55	69	2	0	2			2						
Randomized	Romanov	27	2020	PADN	50	25	25	12	0	2	2	2		2					
Case Series	Rothman	23	2020	PADN	23	23	0	6	0	2	2	2			2	1			
Case report	Ganshanna	24	2020	PADN	3	3	0	12	0	1	1	1							
Case Series	Witkowski	16	2020	PADN	10	10	0	6	0	1	2	2							
Case Series	Zhang	17	2022	PADN	120	120	0	46	0	2									1

PADN Catheter Pulmonary artery denervation
Surgery and DN Mitral and/or left atrial surgery with Pulmonary artery denervation
1 Well defined primary endpoint
2 Secondary endpoint

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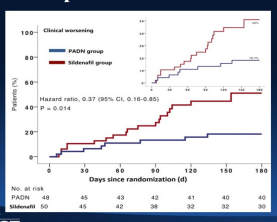
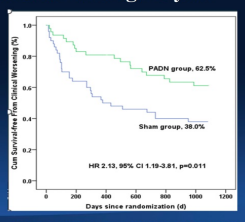
Improvement in clinical outcome through 3-year





TCT Chen, et al. JACC-Cardiovasc Interv 2017 Zhang J...Chen SL, et al. JACC-Heart Failure 2023

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Clinical trials

Inclusion criteria

- 18 years and older
- mPAP ≥25mmHg,
- PCWP <15mmHg
- PVR >3.0 WU
- WHO pulmonary hypertensive class 1

Exclusion criteria

- estimated life expectancy < 12 months
- pregnant or breast feeding
- WHO pulmonary hypertensive classes 2, 3, 4, 5
- Creatinine clearance <30 ml/min,
- Abnormal platelet count <100,000/L.
- Autoimmune diseases. malignancy,
- Tricuspid valve stenosis
- Supra-pulmonary valve stenosis

Class 1 Loss and obstructive remodeling of the pulmonary vascular bed	Class 4 CTEPH

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A Meta-analysis of the efficacy of pulmonary artery denervation in the treatment of pulmonary hypertension

Zhenzhen Zheng[a,1], Riken Chen[b,1], Xishi Sun[a,c,1], Jianmin Liu[a], Donghao Wang[a], Haimin Liu[a], Minshan Chen[b,d], Huimin Chen[b,e,*], Cheng Hong[b,e]

5 Trials

The literature quality evaluations were all Level B

PADN treatment

- **Significant effect**
  - Improved 6-minute walking distance
  - Reduced mean pulmonary artery pressure (mPAP),
  - Reduced pulmonary vascular resistance (PVR)
  - Improved cardiac output
- **No significant effect**
  - Left ventricular end-systolic diameter
  - Mortality rate
  - Cardiac function

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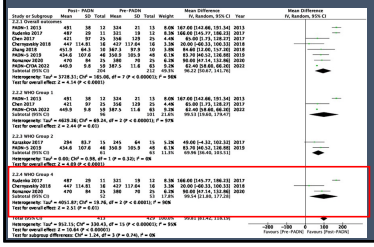
Pulmonary Artery Denervation as a New Therapeutic Option for Pulmonary Hypertension: A Systematic Review and Meta-Analysis

Adolfo Martinez Salazar, MD[a,*], Khalid Saeed Al-Asad, MD[a], Rohan M. Prasad, DO[b], Gabriel Panama, MD[a], Sandeep Banga, MD[a], and Matthew Wilcox, DO[a]

6 Trials



"PADN improves hemodynamics in patients with PH by a significant reduction in mPAP and PVR while having a significant increase in cardiac output……..

PADN improved functional capacity with a marked increase in 6MWD and better quality of life."

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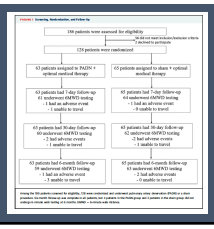
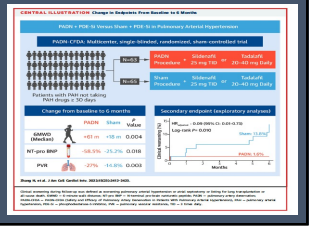
Pulmonary Artery Denervation for Pulmonary Arterial Hypertension

A Sham-Controlled Randomized PADN-CFDA Trial

Hang Zhang, MD,[a,1] Yongxue Wei, PhD,[a,1] Caojin Zhang, MD,[a,*] Zhenwen Yang, MD,[a,*] Jing Kan, MD,[a,1] Heping Gu, MD,[a] Fenling Fan, MD,[a] Xiaomei Gao, MD,[a] Yunhui Yin, MD,[a] Bowen Jin, MD,[a] Hongmei Zhou, MD,[a] Zhang Yang, MD,[a] Zhouming Wang, MD,[a] Yu Xin, MD,[a] Chen Zhang, MD,[a] Liqi Meng, MD,[a] Xiaoyu Wang, MD,[a] Jingting Sun, MD,[a] Chunxia Zhao, MD,[a] Juan Zhang, MD,[a] Xiaoyan Yan, PhD,[b] Feng Chen, PhD,[c] Cheng Yan, PhD,[c] Gregg W. Stone, MD,[d] Shao-Liang Chen, MD[a]



"In patients with WHO group 1 PAH, PADN improved exercise capacity, hemodynamic status, and clinical outcomes during 6-month follow-up"



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Treatment effects of pulmonary artery denervation for pulmonary arterial hypertension stratified by REVEAL risk score: Results from PADN-CFDA trial

Juan Zhang, MD,[a,1] Jing Kan, MD,[a,1] Yongxue Wei, PhD,[b,1] Caojin Zhang, MD,[a,*] Zhenwen Yang, MD,[a] Heping Gu, MD,[a] Fenling Fan, MD,[a] Xiaomei Gao, MD,[a] Yunhui Yin, MD,[a] Bowen Jin, MD,[a] Hongmei Zhou, MD,[a] Zhang Yang, MD,[a] Zhouming Wang, MD,[a] Yu Xin, MD,[a] Chen Zhang, MD,[a] Liqi Meng, MD,[a] Xiaoyu Wang, MD,[a] Chunxia Zhao, MD,[a] Hang Zhang, MD,[a,1] Xiaoyan Yan, PhD,[c,*] Feng Chen, PhD,[c] Cheng Yan, PhD,[c] Raymond L. Benza, MD,[d] Gregg W. Stone, MD,[e] and Shao-Liang Chen, MD[a,*]

REVEAL = The Registry to Evaluate Early and Long-Term PAH Disease Management risk calculator

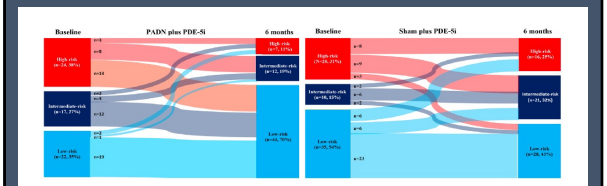

Figure 3 Graphical abstract. Abbreviations: PADN, pulmonary artery denervation; PDE-5i, phosphodiesterase 5 inhibitors.

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Aggressive Thrombus Removal

Balloon Pulmonary Angioplasty/PEA

Pulmonary Artery Denervation — OPEN / PERCUTANEOUS

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Center for Quality, Effectiveness, and Outcomes in Cardiovascular Diseases