

Pulmonary Artery Denervation Interpretation of PADN-5 Clinical Trial Results

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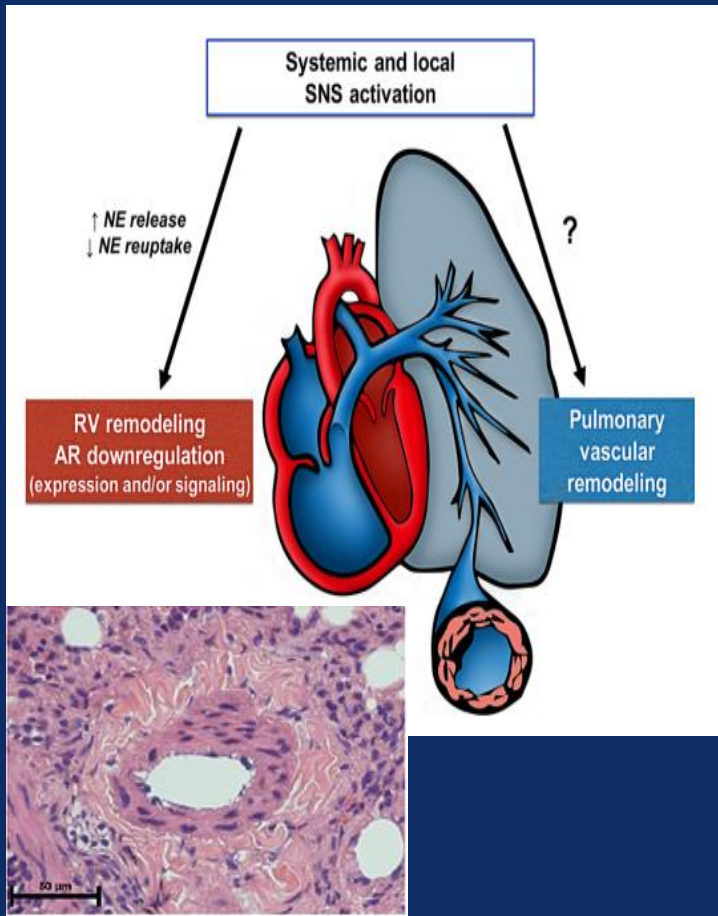
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Disclosure

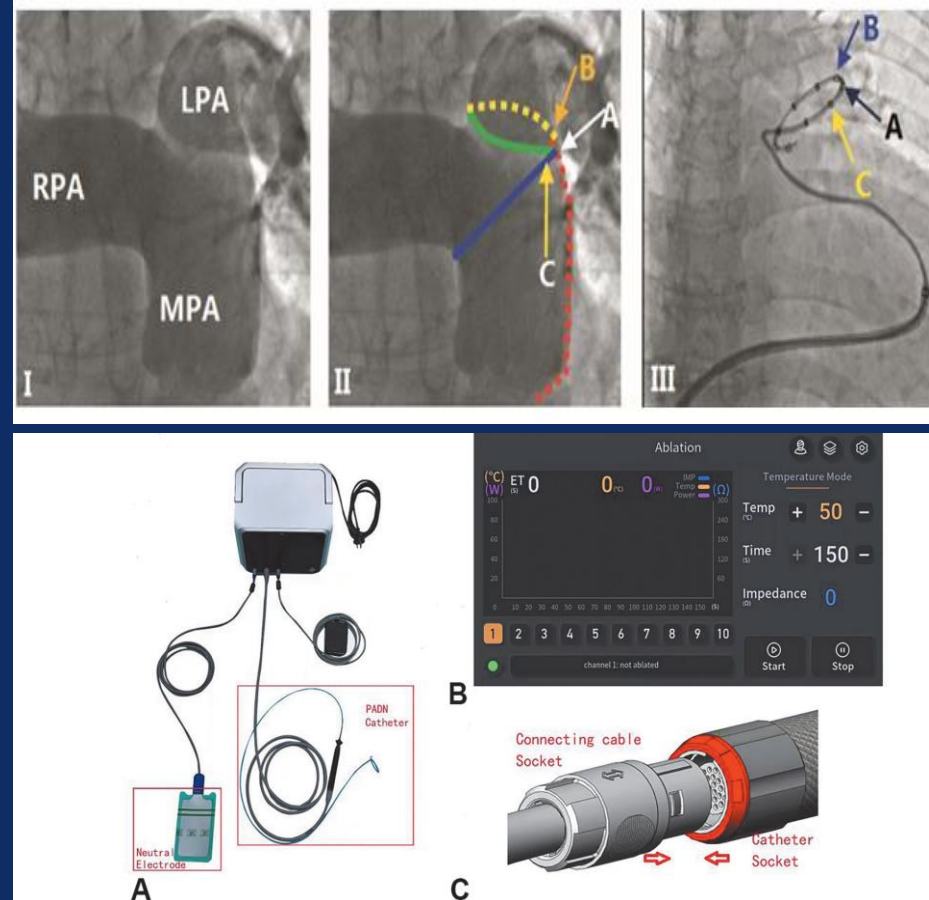
- No conflicts to disclose

PADN for PAH

Pathophysiology

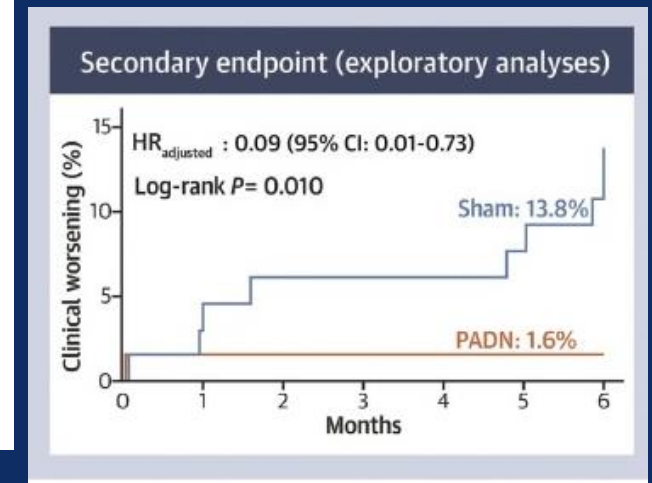


Pulmonary Denervation



Outcomes

Change from baseline to 6 months			
	PADN	Sham	P Value
6MWD (Median)	+61 m	+18 m	0.004
NT-pro BNP	-58.5%	-25.2%	0.018
PVR	-27%	-14.8%	0.003



Building up a Solid Evidence-based Foundation for PADN

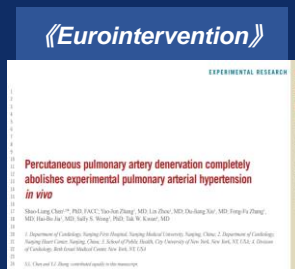
— Over a Decade, from Animal Study to Clinical Trial, >400 Cases

Mechanism exploration

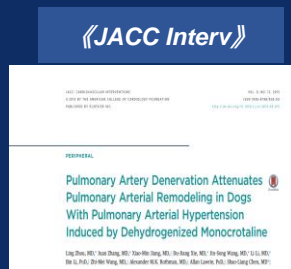
Feasibility study

RCT & regulatory study

Long-term followup



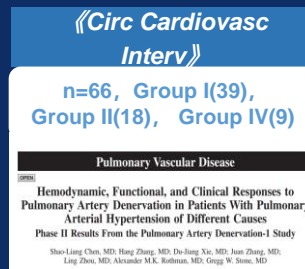
Acute
Animal 1



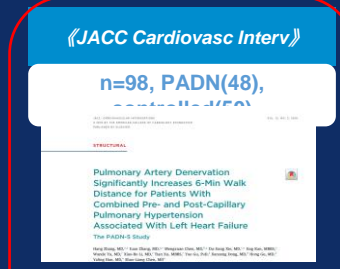
Chronic
Animal 2



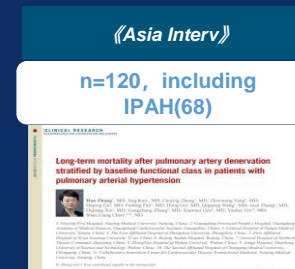
FIM study
PADN-I



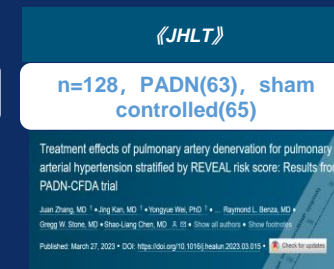
PADN-I
Phase II



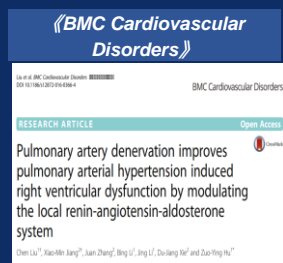
PADN-5
Study



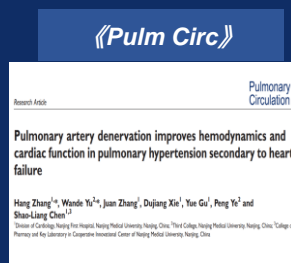
Long-term
Mortality



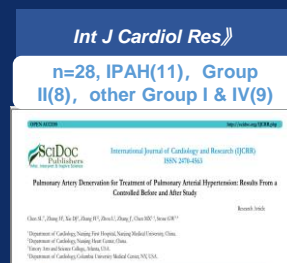
PADN CFDA Stratified
by REVEAL



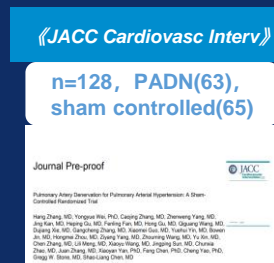
Chronic
Animal 3



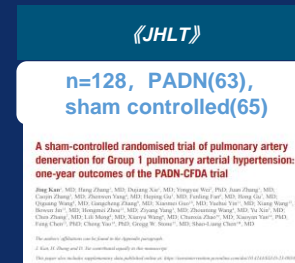
Chronic
Animal 4



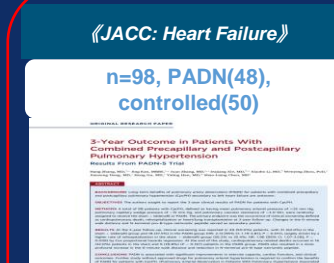
PADN-II



PADN CFDA

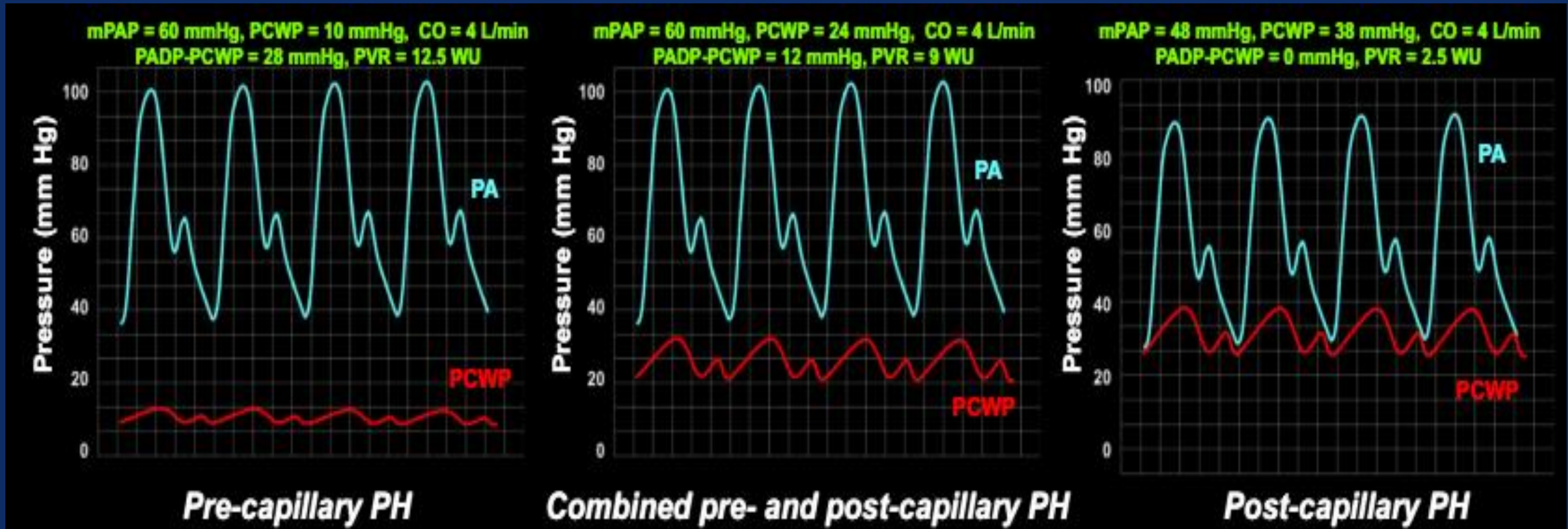


1-year from
PADN CFDA



3-year Outcome
in Group 2 PH

Increases in PAP and PVR are associated with a worse outcome in patients with PH-LHD



mPAP >20mmHg
PAWP ≤15 mmHg
PVR >2 WU

mPAP >20 mmHg
PAWP >15 mmHg
PVR >2 WU

mPAP >20 mmHg
PAWP >15 mmHg
PVR ≤2 WU

PADN -5 Study : Clinical Evidence in Cpc-PH

Study Design

- A prospective, randomized, sham-controlled trial

Intervention

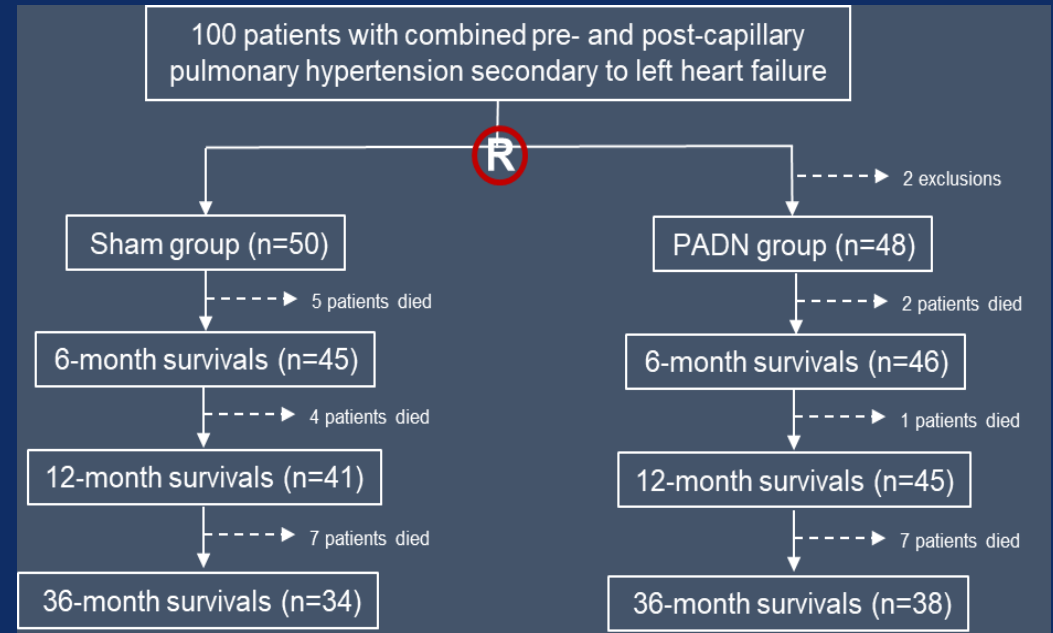
- PADN group: PADN + HF medication
- Sham group: Sham PADN + Sildenafil + HF medication

Primary Endpoint:

Clinical Worsening, including cardiopulmonary death, rehospitalization and heart/lung transplantation.

Major inclusion criteria

- >18 years
- **mPAP \geq 25 mmHg , PCWP $>$ 15 mmHg, PVR $>$ 3.0 WU**
- not received any medications targeting PAH in the 3 months prior to admission



Major exclusion criteria

- WHO-defined Group I PAH, Group III-V PH
- Ccr $<$ 30 mL/min
- Tricuspid or pulmonary valvular stenosis
- Allergic to any drug or metal
- Pregnant

PADN - 5 Study : Baseline Characteristics

	Sham + Sildenafil Group (n = 50)	PADN Group (n = 48)	P Value
Age, y	64 (56.5-71.5)	65.5 (60.0-71.8)	0.771
Male	30 (60.0)	30 (62.5)	0.838
Etiology			
Ischemic cardiomyopathy	8 (16.0)	5 (10.4)	0.554
Previous myocardial infarction	4 (8.0)	4 (8.3)	1.000
Hypertrophic cardiomyopathy	3 (6.0)	3 (6.3)	1.000
Hypertension	33 (66.0)	28 (56.0)	0.275
Diabetes	13 (26.0)	12 (25.5)	0.607
eGFR, mL/min/1.73 m ²	101.5 ± 39.0	108.1 ± 37.1	0.391
eGFR <60 mL/min/1.73 m ²	8 (16.0)	3 (6.2)	0.200
HF			
Duration, ^a y	3.0 (1.1-12.0)	2.5 (1.2-12.1)	0.831
Classification			0.813
HFpEF	19 (38.0)	19 (39.5)	
HFrEF	31 (62.0)	29 (60.5)	
PH duration, ^b y	1.0 (0.4-9.8)	0.85 (0.3-9.5)	0.818
Medications			
Beta-adrenergic receptor blocker	38 (76.0)	33 (68.8)	0.346
Nitrates	5 (10.0)	4 (8.3)	1.000
Diuretics	42 (84.0)	43 (89.6)	0.554
Digoxin	24 (48.0)	17 (35.4)	0.226
ACE inhibitor or ARB	34 (68.0)	31 (64.6)	0.846
NYHA functional class			0.665
Class II or III	40 (80.0)	42 (87.5)	
Class IV	10 (20.0)	6 (12.5)	

	Sham Group (n=50)	PADN Group (n=48)	P Value
HFpEF	19 (38.0)	19 (39.5)	/
HFrEF	31 (62.0)	29 (60.5)	/

	Sham Group (n=50)	PADN Group (n=48)	P Value
HF, yrs	3.0 (1.1-12.0)	2.5 (1.2-12.1)	0.831
PH, yrs	1.0 (0.4-9.8)	0.85 (0.3-9.5)	0.818

PADN - 5 Study : Hemodynamics at 6-month

Sildenafil Group

PADN Group

	Baseline (n=50)	6-Month (n=45)	p Value	Baseline (n=48)	6-Month (n=46)	p Value	p Value*
RA pressure, mm Hg	13.8±5.6	13.1±4.1	0.322	13.8±7.3	11.0±5.1	0.122	0.189
Systolic PAP, mm Hg	56.5±15.2	52.4±11.3	0.196	58.7±19.5	44.6±19.2	<0.001	<0.001
Mean PAP, mm Hg	36.9±10.8	34.4±7.9	0.133	38.8±10.6	28.6±6.5	<0.001	0.037
Cardiac output, l/min	2.56±0.74	2.51±0.72	0.564	2.61±0.76	3.09±0.81	0.021	0.017
Cardiac index, l/min/m ²	1.67±0.79	1.72±0.64	0.089	1.72±0.84	2.52±0.70	0.038	0.035
PVR, Woods units	6.25±3.23	6.09±2.94	0.590	6.38±3.19	4.18±1.51	<0.001	0.001
PCWP, mm Hg	20.9±5.58	19.1±6.1	0.909	22.2±6.6	16.1±6.2	0.013	0.041
TPG, mm Hg	16.1±4.6	15.3±3.8	0.101	16.5±4.7	12.9±3.9	0.001	0.002
>12 mm Hg	29(58.0)	25(55.6)	0.530	35(73.0)	17(38.6)	0.001	0.047
DPG, mm Hg	10.4±3.2	9.86±1.74	0.120	10.9±3.7	6.8±1.2	0.011	0.042
PAC, ml/mm Hg	1.96±0.65	1.95±0.86	0.944	1.92±0.86	3.9±0.96	<0.001	<0.001

PADN - 5 Study : Medications at 3-year

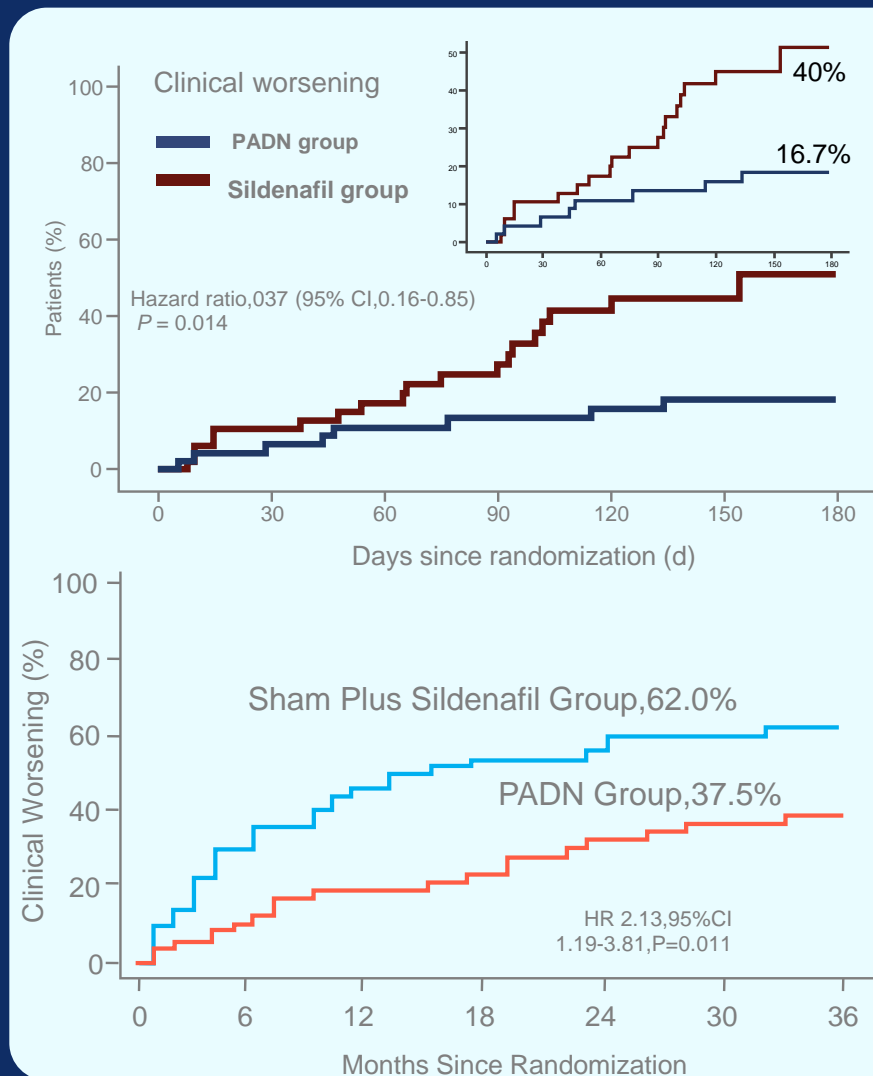
	Sham (N=50)	PADN (N=48)	P-value
Anti-HF medications, n(%)			
Diuretics, n(%)	44(88.0)	35(72.9)	0.140
Combination of 2 or more diuretics	34(68.0)	10(20.8)	0.002
Sacubitril Valsartan (ARNI)	35(70.0)	16(33.3)	0.009
β -adrenergic receptor blocker (β -blocker)	42(84.0)	39(81.3)	0.862
SGLT-2 inhibitor	20(40.0)	12(25.0)	0.074
ACEI or ARB	39(78.0)	31(64.6)	0.225
Combination of ≥ 3 above drugs	33(66.0)	15(31.3)	0.003
PAH-specific drugs between 6 and 36-month			
Sildenafil, n(%)	1(2.0)	1(2.0)	1.000
Prostacyclin analogue*, n(%)	0	0	NS
Endothelin receptor antagonist, n(%)	2(4.0)	2(4.0)	1.000

PADN - 5 Study : NT-proBNP and 6MWD

	Sham (N=50)	PADN (N=48)	P-value
% Reduction in NT-proBNP vs. baseline			
At 6-month	-6.2 (-82~54)	-47.5 (-99~33.1)	0.003
At 3-year	-10.0 (-0.9~89)	-49.2 (-91~67.2)	0.023
6-minute walk distance vs. baseline (m)			
At 6-month	359.4±93.0	434.6±107.6	<0.001
Net increase, median (range)	17.5 (-138.0~+139.0)	80 (-127~+396)	<0.001
At 3-year	352.3±111.0	459.7±133.6	<0.001
Net increase, median (range)	8.0 (-38.0~+124.0)	79.7 (-16~+181.0)	0.004*

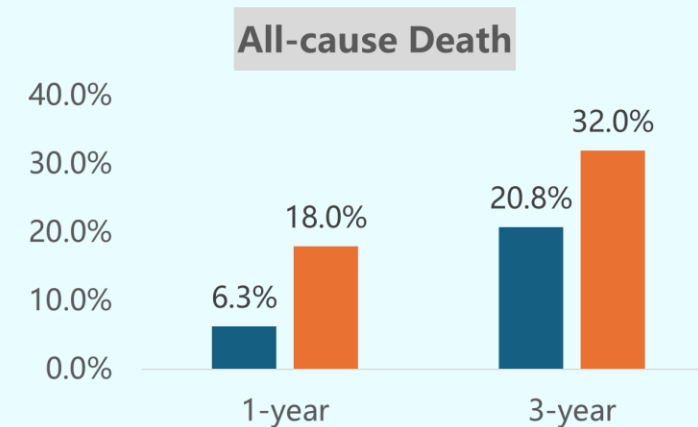
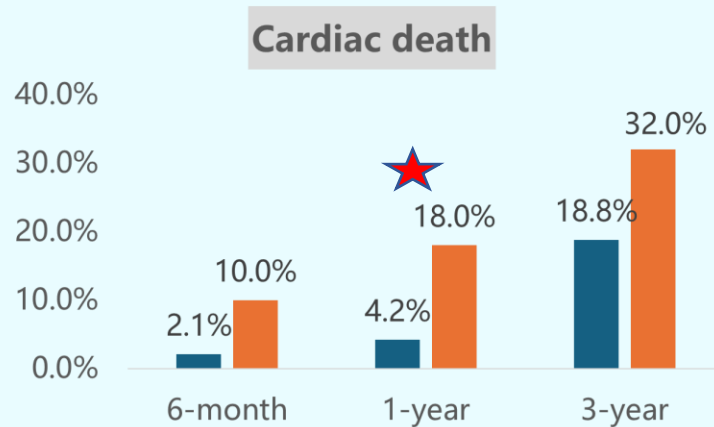
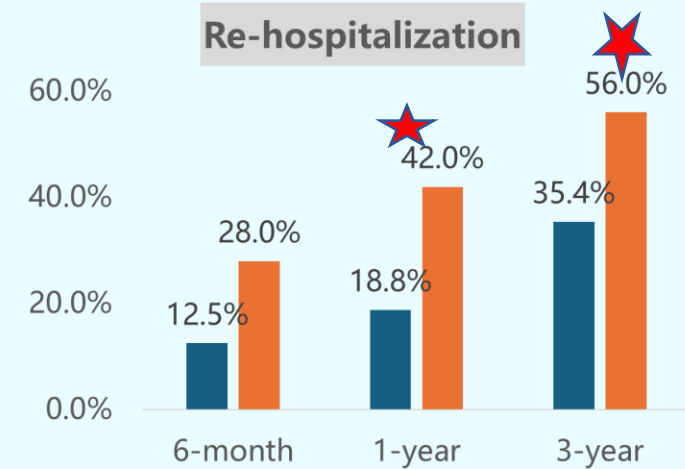
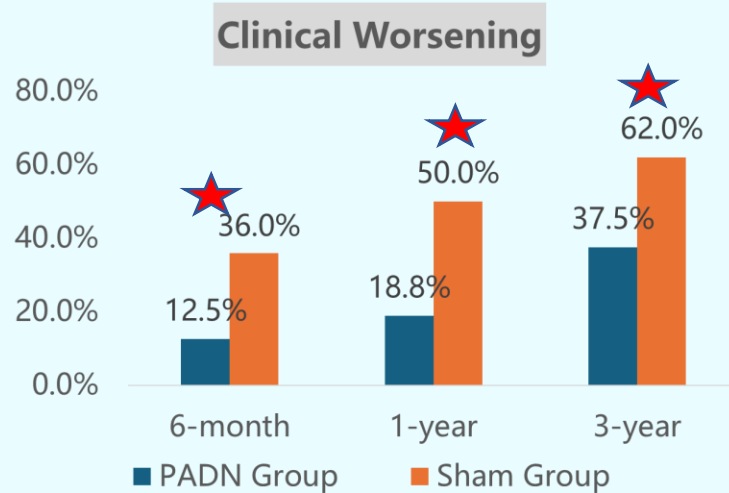
PADN - 5 Study : Clinical Worsening

	Sham + Sildenafil Group (n=50)	PADN Group (n=48)	p Value
At 6-mo follow-up	18(36.0)	6(12.5)	0.009
Cardiopulmonary-related death	5(10.0)	1(2.1)	0.205
Rehospitalization	14(28.0)	6(12.5)	0.052
Heart/lung transplantation	1(2.0)	0	1.000
At 1-y follow-up	25(50.0)	9(18.8)	0.001
Cardiopulmonary-related death	9(18.0)	2(4.2)	0.041
Rehospitalization	21(42.0)	9(18.8)	0.016
Heart/lung transplantation	2(4.0)	0	0.495
At 3-y follow-up	31(62.0)	18(37.5)	0.026
Cardiopulmonary related death	16(32.0)	9(18.8)	0.167
Rehospitalization	28(56.0)	17(35.4)	0.046
Heart/lung transplantation	2(4.0)	0	0.495
All-cause death			
At 1-y follow-up	9(18.0)	3(6.3)	0.122
At 3-y follow-up	16(32.0)	10(20.8)	0.256



PADN - 5 Study : Clinical Worsening

★ $P < 0.05$



A Subgroup Analysis of HFpEF of 3-year Results From the PADN-5 Study

Baseline characteristics

	Total (N=38)	Sham group (N=19)	PADN group (N=19)	P value
Age, yr	67.08±9.58	68.00±9.93	66.16±9.41	0.561
Male, n (%)	15(39.5)	8(42.1)	7(36.8)	1.000
Etiology, n (%)				
Ischemic cardiomyopathy	4(10.5)	3(15.8)	1(5.3)	0.604
Previous myocardial infarction	2(5.3)	1(5.3)	1(5.3)	1.000
Hypertrophic cardiomyopathy	2(5.3)	1(5.3)	1(5.3)	1.000
Hypertension	22(57.9)	15(78.9)	7(36.8)	0.020
Diabetes	11(28.9)	5(26.3)	6(31.6)	1.000
eGFR, ml/min/1.73 m ²	108.59±42.58	110.94±49.21	106.24±35.97	0.739
<60 ml/min/1.73 m ² , n (%)	5(13.2)	4(21.1)	1(5.3)	0.340
PH duration**, yr, median (range)	1.0(0.1-8.0)	1.0(0.1-3.0)	2.0(0.3-4.0)	0.544
Medications, n (%)				
β-adrenergic receptor blocker	17(44.7)	12(63.2)	5(26.3)	0.049
Nitrates	3(7.9)	3(15.8)	0(0.0)	0.230
Diuretics	32(84.2)	13(68.4)	19(100.0)	0.020
Digoxin	7(18.4)	4(21.1)	3(15.8)	1.000
ACEI or ARB or ARNI	17(44.7)	11(57.9)	6(31.6)	0.191
New York Heart Association class				1.000
Class II or III	33(86.8)	16(84.2)	17(89.5)	
Class IV	5(13.2)	3(15.8)	2(10.5)	

Δ NT-proBNP and Δ 6MWD in the PADN group at 6-m and 3-y improved significantly

	Sham group (N=19)	PADN group (N=19)	P-value
NT-pro BNP, pg/ml (median [IQR])			
Prior-to PADN	1154(178-9417)	1489(104-13876)	0.708
At 6-month	980(167-5421)	786(25-4905)	0.471
% of reduction, %	-12(-82-54)	-47(-99-331)	0.023
At 3-year	975(167-5580)	784(50-4655)	0.271
% of reduction, %	-10(-80-95)	-55(-99-38)	0.012
6-minute walk distance, m			
Prior-to PADN	324(153-510)	360(223-504)	0.665
At 6-month	342(161-552)	433(275-580)	0.012
Net increase, median (IQR)	25(-93-106)	77(-9-181)	0.001
Increase, %	7(-29-48)	21(-2-68)	0.001
At 3-year	348(135-435)	450(186-510)	
Net increase, median (IQR)	23 (-98-115)	88(-20-157)	0.001
Increase, %	3.1 (-10.6-27.6)	24.2(-8.9-76.2)	0.001

Clinical worsening in the PADN group was significantly lower than that in the sham group

	Sham group	PADN group	P-value
Anti-HF medications, at 3-year follow-up n (%)			
Diuretics, n (%)	8(42.1)	13(68.4)	0.191
Combination of 2 or more diuretics	0(0.0)	0(0.0)	1.000
β -adrenergic receptor blocker	9(47.4)	3(15.8)	0.079
SGLT-2 inhibitor	2(10.5)	2(10.5)	1.000
ACEI or ARB or ARNI	9(47.3)	7(36.8)	0.737
Combination of ≥ 3 above drugs	4(21.1)	1(5.3)	0.340
Phosphodiesterase 5 inhibitor n (%)	2(10.5)	0(0.0)	1.000
Clinical worsening, n (%)			
At 6-month follow-up, n (%)	5(26.3)	1(5.3)	0.997
Cardio-pulmonary related death	1(5.3)	0(0.0)	1.000
Re-hospitalization	5(26.3)	1(5.3)	0.895
At 3-year follow-up	12(63.2)	6(31.6)	0.006
Cardio-pulmonary related death	4(21.1)	2(10.6)	0.035
Re-hospitalization	12(63.2)	6(31.6)	0.006
Heart/lung transplantation	0 (0.0)	0 (0.0)	1.000

PADN-5: Conclusions



CpcPH patients (N=98)

- mPAP \geq 25 mm Hg
- PCWP > 15 mm Hg
- PVR > 3 WU

Sildenafil + Sham group (N=50)

- Anti-HF medications + Sildenafil + Sham

PADN group (N=48)

- Anti-HF medications + PADN



Day 180

Anti-HF medications + Sildenafil



Anti-HF medications (continuous for 3-year)

3 years

Anti-HF medications

Anti-HF medications (continuous for 3-year)

Conclusions:

- At the 3-year follow-up, clinical worsening was higher in Sham group than the PADN group largely driven by a higher rate of rehospitalization, and more cardiopulmonary-related deaths occurred in Sham group
- PADN also resulted in a more profound increase in the 6MWD and reduction in N-terminal pro-BNP
- PADN is associated with significant improvements in exercise capacity, cardiac function, and clinical outcomes for patients with CpcPH, including HFpEF-CpcPH

6 months follow-up

- **Median 6MWD** increase from baseline:
 - PADN group: increased 80 m
 - Sham group: increased 17.5 m
- **Net reduction of NT-proBNP:**
 - PADN group: decreased by 47.5%
 - Sham group: decreased by 6.2%
- **Clinical worsening**** percentage:
 - PADN group: 12.5%
 - Sham group: 36.0%

3-years follow-up

- **Median 6MWD** increase from baseline:
 - PADN group: increased 79.7 m
 - Sham group: increased 8 m
- **Net reduction of NT-proBNP:**
 - PADN group: decreased by 49.2%
 - Sham group: decreased by 10%
- **Clinical worsening**** percentage:
 - PADN group: 37.5%
 - Sham group: 62.0%

Ongoing PADN for Group 2 PH Clinical Trials

	PADN-5	PADN-HF-PH	PADN-Columbus	PADN-IDE
Study Design	Prospective, multi-center, randomized, sham controlled	Prospective, multicenter, randomized, controlled	Prospective, multicenter, single arm, open label	Prospective, multicenter randomized, sham-controlled
Country	China	China	Portugal, Italy, Switzerland, Singapore, Malaysia, Georgia	US, Europe, Asia
No. of patients	98	264	30	410
Hemodynamic Criteria	mPAP \geq 25mmHg PCWP>15mmHg PVR>3 WU	mPAP>20mmHg PAWP>15mmHg	mPAP>20mmHg PCWP>15mmHg PVR>2 WU	mPAP>20mmHg, PCWP>15mmHg PVR \geq 3 WU
Status	Completed	Enrolment Completed	Ongoing 20 patients enrolled	Plan 2025 Q1 IDE approval

THANKS !

