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PADN-5 Trial

Pulmonary artery denervation significantly increases 6-minute walk distance for patients with CpcPH: The PADN-5 Study

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Disclosure Statement of Financial Interest

I, (Shao-Liang Chen) DO NOT have a financial interest or 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.

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Background

- The backward transmission of increased LV filling pressure results in elevated pulmonary venous pressure (IpcPH)

- Long lasting of IpcPH leads to CpcPH (12%-13%)—overactivation of sympathetic nervous activity

- Medications targeting PAH are not recommended for CpcPH

- Pulmonary artery denervation (PADN) has never been studied for CpcPH in a randomized study using sham-control

CpcPH was defined as mPAP≥25mmHg, PCWP>15mmHg, PVR>3WU

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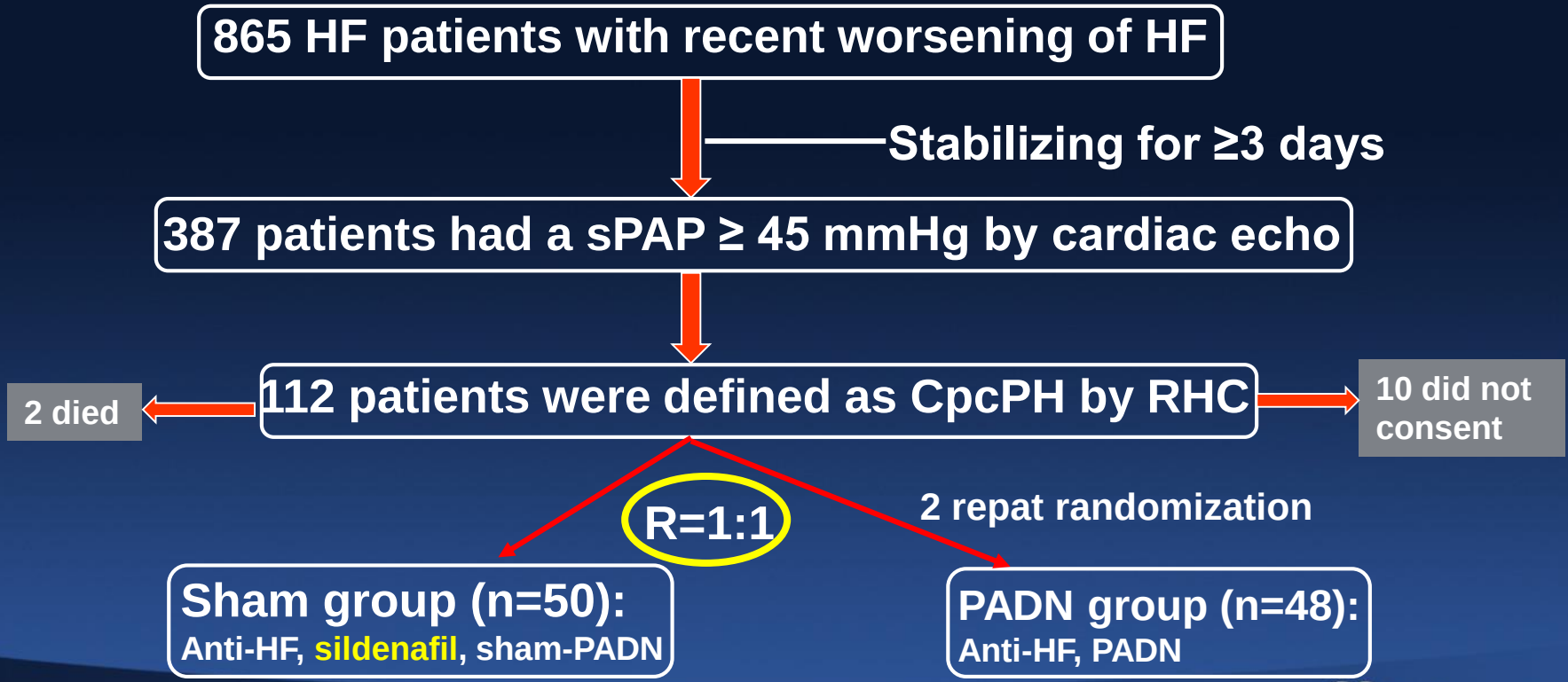
Study design



Sildenafil dosage: (20 mg, tid x 1-week; 40 mg, tid x 6 months)

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Major inclusion criteria

- >18 years
- mPAP ≥ 25 mmHg
- PCWP >15 mmHg
- PVR >3.0 WU
- no targeting PAH drug 3-m prior to admission

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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
- Women who were pregnant

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Protocol procedures

- At 6 months after treatment
  - --- Transthoracic echocardiography
  - --- Right heart catheterization
  - -- NT-pro BNP
- Warfarin for patients with AF, 1 month
- DAPT for patients without AF, 1 month

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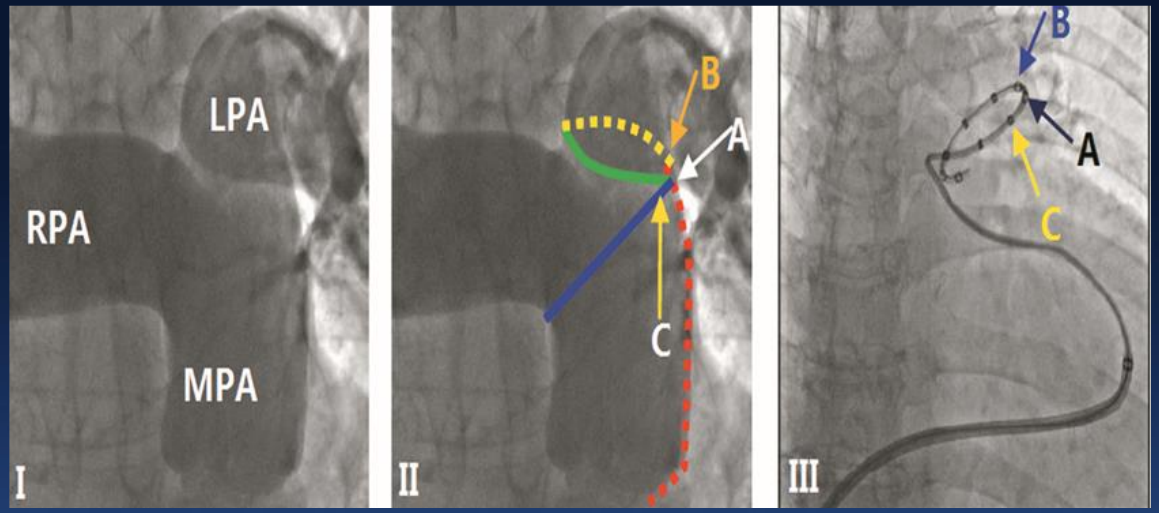
PADN procedure



The following ablation parameters were programmed at each point: temperature ≥ 45°C, energy ≤ 20 W, and time 120 seconds.

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

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Endpoints

Endpoints	R	G
Primary endpoint:		
6-minute walk distance	6 months	Superiority
Secondary endpoints:		
PVR by RHC	6 months	-
Clinical worsening	6 months	-
Safety endpoint:		
Suspected/fatal PE	6 months	-

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Sample size calculation

Difference in the increase of 6MWD between 2 groups: SD=85 m, Mean value=60 m [6]

↓

80% power with a 2-sided alpha of 0.025
82 patients (41pts/per group)

↓

20% lost = total 100 pts

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Study organization

Principal Investigator: Shao-Liang Chen

Executive Committee: PIs plus Hang Zhang, Dujiang Xie, Yaling Han, Juan Zhang

Statistical Committee: Feng Chen (Chair, Nanjing Medical University)

Site management and data monitoring: Wen Teng, Ling Lin, Hai-Mei Xu

Data management: Rod Byrne Information Technology Co. (China)

Clinical Endpoints Committee: Bao-Xiang Duan (Director), Mingfan Cha

Cardiac Echo Core Lab: Jing ping Sun (Chinese University of Hong Kong)

RHC Core Lab: Key Lab, Cardiovascular Institute, Nanjing Medical Univeristy

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Baseline Data (i)

	Sildenafil n = 50	PADN n = 48	*P* Value
Age (yrs)	63.0±12.3	63.7±11.8	0.77
Ischemia cardiomyopathy, n (%)	8(16.0)	5(10.4)	0.55
Hypertrophic cardiomyopathy*, n (%)	3(6.0)	3(6.3)	1.0
Hypertension, n (%)	33(66.0)	28(56.0)	0.28
Diabetes, n (%)	13(26.0)	12(25.5)	0.61
HF duration, yrs, median(range)	3(1-12.0)	2.5(1.2-12.1)	0.83
HFpEF#, n (%)	19(38.0)	19(39.5)	0.83
HFrEF, n (%)	31(62.0)	29(60.5)	0.80

* After PTSMA; # defined as LVEF≥50%

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Baseline Data (ii)

	Sildenafil n = 50	PADN n = 48	*P* Value
PH duration, yrs, median (range)	1.0(0.4-9.8)	0.85(0.3-9.5)	0.82
Medications prior-to recruitment, n(%)			
-β-adrenergic receptor blocker	38 (76.0)	33 (68.8)	0.35
-Nitrates	5 (10.0)	4 (8.3)	1.0
-Diuretics	42 (84.0)	43 (89.6)	0.55
-Digoxin	24 (48.0)	17 (35.4)	0.23
-ACEI or ARB	34 (68.0)	31 (64.6)	0.85
NYHA class III/IV	48 (96.0)	46 (95.8)	0.67

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Echocardiographic Data

	Sildenafil group		PADN group		*P*
	Baseline	6-month	Baseline	6-month	
sPAP, mmHg	57.7±7.7	58.3±7.0	58.3±7.9	52.2±7.5	0.017
LAd, mm	53.1±9.3	55.4±9.8	52.6±9.2	50.5±9.6	0.004
LVDd, mm	59.8±12.3	60.7±12.3	58.4±13.1	57.1±13.0	0.019
LVEF, %	44.5±16.5	42.3±15.7	43.2±15.4	47.9±14.3	0.050
Increase, %	No	-4.8	No	+10.4	0.031
E/E' ratio	17.7±6.8	17.9±6.0	18.0±7.3	10.6±3.17	0.011
TAPSE, mm	15.3±4.9	15.1±2.7	15.8±3.6	19.7±2.8	0.017
RV Tei, %	0.44±0.12	0.45±0.10	0.49±0.17	0.38±0.11	0.016
RAd, mm	60.4±12.4	59.6±10.7	59.7±13.5	58.2±11.2	0.561

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Hemodynamic Data via RHC

	Sildenafil		PADN group		*P* value
	Baseline	6-month	Baseline	6-month	
RAP, mmHg	**13.8±5.6**	**13.1±4.1**	**13.8±7.3**	**11.0±5.1**	**0.189**
sPAP, mmHg	56.5±15.2	52.4±11.3	58.7±19.5	44.6±19.2	<0.001
mPAP, mmHg	36.9±10.8	34.4±7.9	38.8±10.6	28.6±6.5	0.037
CO, L/min	2.56±0.74	2.51±0.72	2.61±0.76	3.09±0.81	0.017
CI, L/min/m^2	1.67±0.79	1.72±0.64	1.72±0.84	2.52±0.70	0.035
PVR, WU	6.25±3.23	6.09±2.94	6.38±3.19	4.18±1.51	0.001
PCWP, mmHg	20.9±5.58	19.1±6.1	22.2±6.6	16.1±6.2	0.041
PAC, ml/mmHg	1.96±0.65	1.95±0.86	1.92±0.86	3.9±0.96	<0.001

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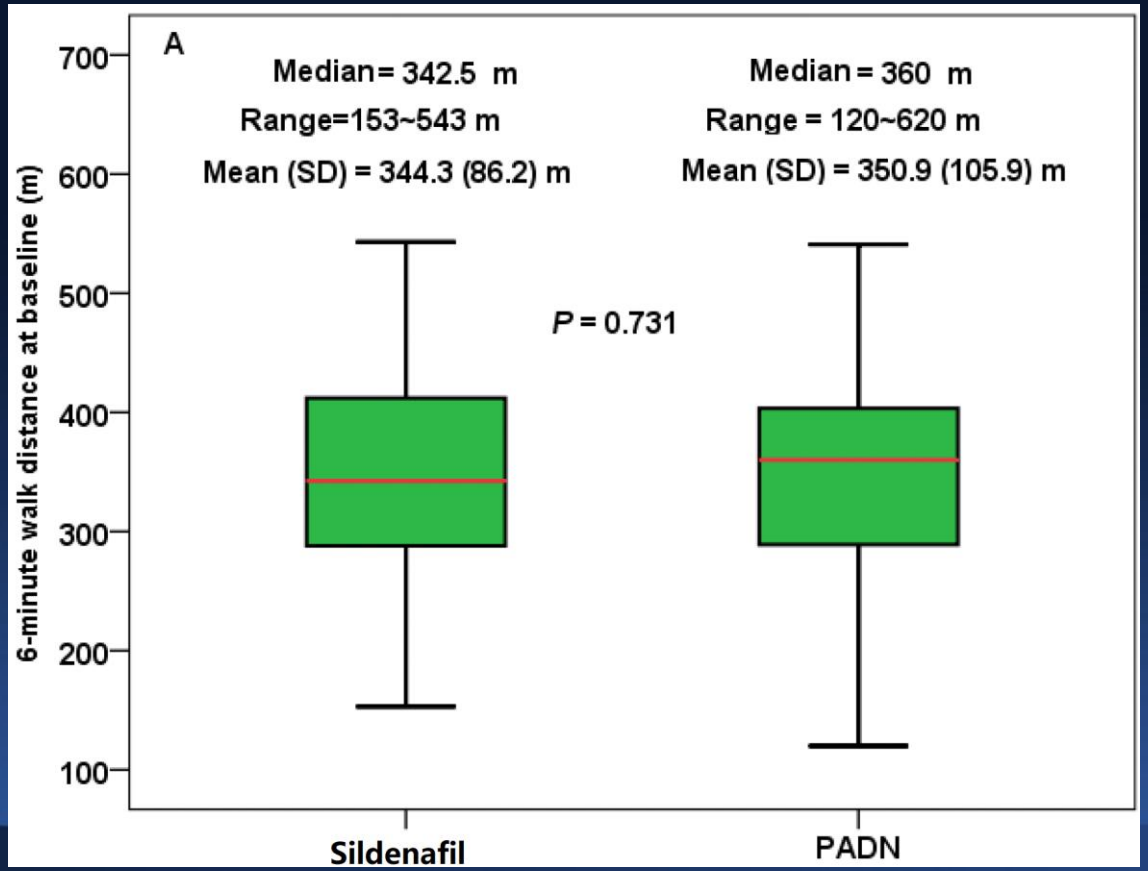
Baseline 6MWD



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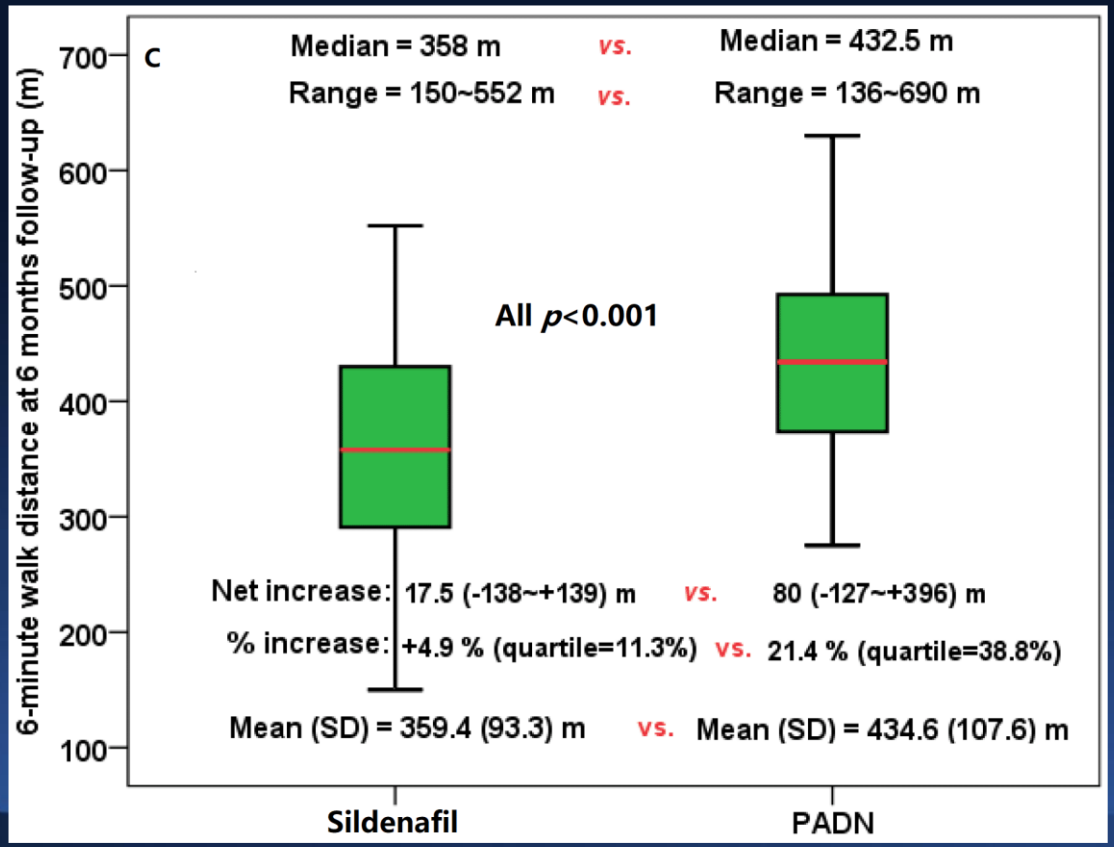
Change of 6MWD



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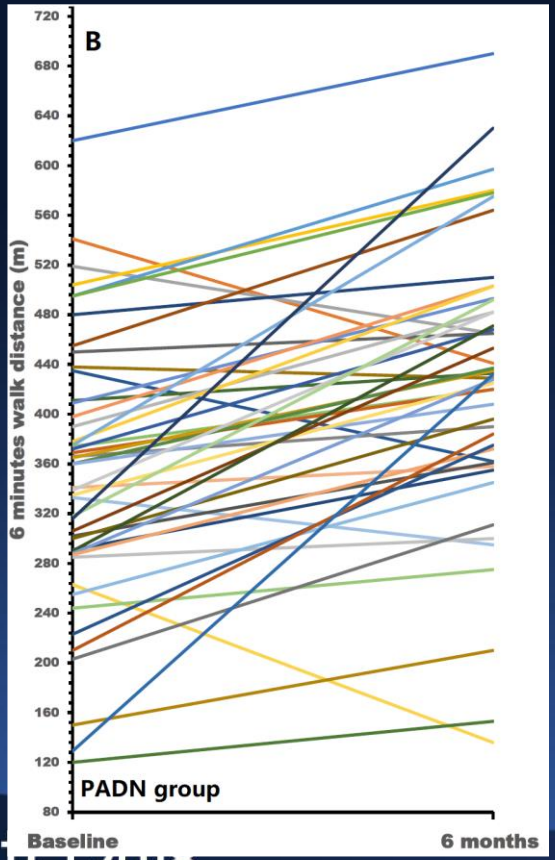
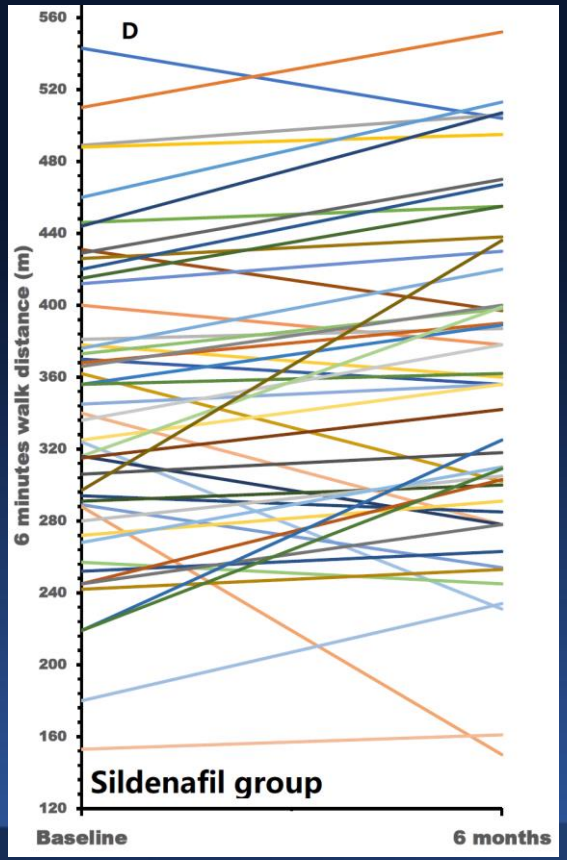
Comparison of 6MWD change in individual





6MWD reduction:

-- 12 (26.7%) in sildenafil

-- 6 (12.5%) in PADN

6MWD reduction >15%:

-- 7 (14.0%) in sildenafil

-- 3 (6.3%) in PADN

-- HR=2.947

95%CI=1.152-4.501

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Adjusted Prediction of 1-SD decrease in 6MWD for clinical events

	Hazard ratio	95% C.I	*P*
Clinical worsening	3.023	1.052-8.742	0.040
Worsening of HF	2.550	0.875-7.431	0.086
All-cause death	36.730	0.045-29703.3	0.291
Re-hospitalization	1.880	0.628-5.623	0.259

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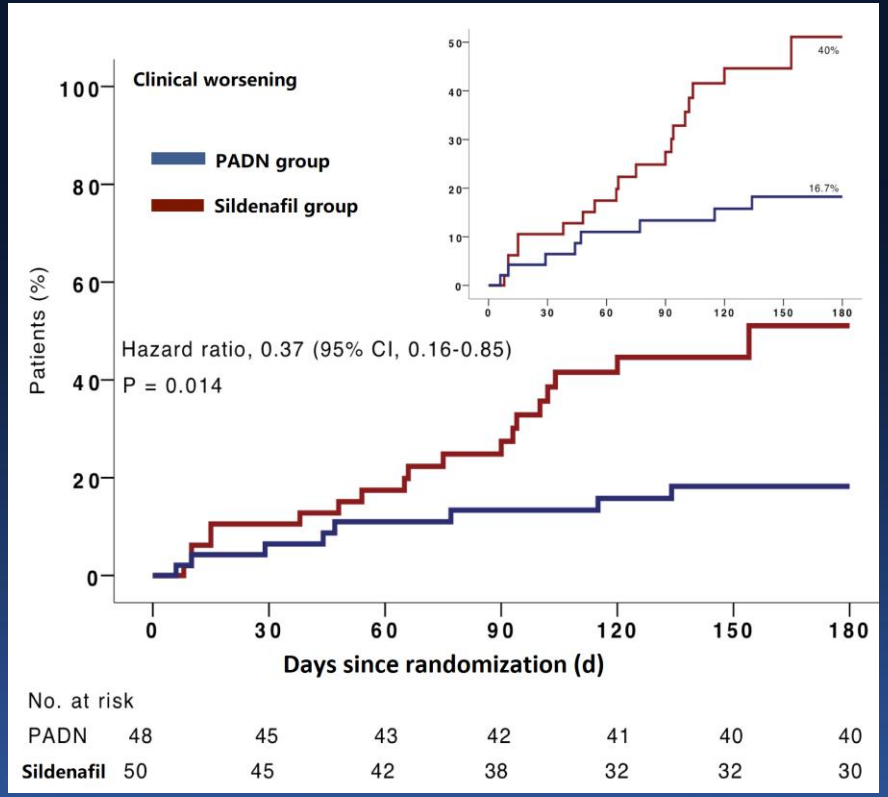
Kaplan-Meier Survival



All-cause death:

--5 in sildenafil

--2 in PADN

Limitations

- Both HFrEF and HFpEF were included
- 6MWD may be different day by day
- Sildenafil was used in Sham group

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Conclusions

. PADN-5 trial demonstrates the benefits of PADN for patients with CpcPH

. Both HFpEF and HFrEF equally benefit from PADN

. No sign showing the harm of sildenafil to CpcPH

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Thanks for your attention!

JACC Cardiovascular Interventions

Pulmonary Artery Denervation Significantly Increases 6-minute Walk Distance for Patients with Combined Pre- and Post-capillary Pulmonary Hypertension Associated with the Left Heart Failure: PADN-5 Study

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