Exercise PVR: A Key Predictor of Benefit of Atrial Shunt Therapy in HFpEF?

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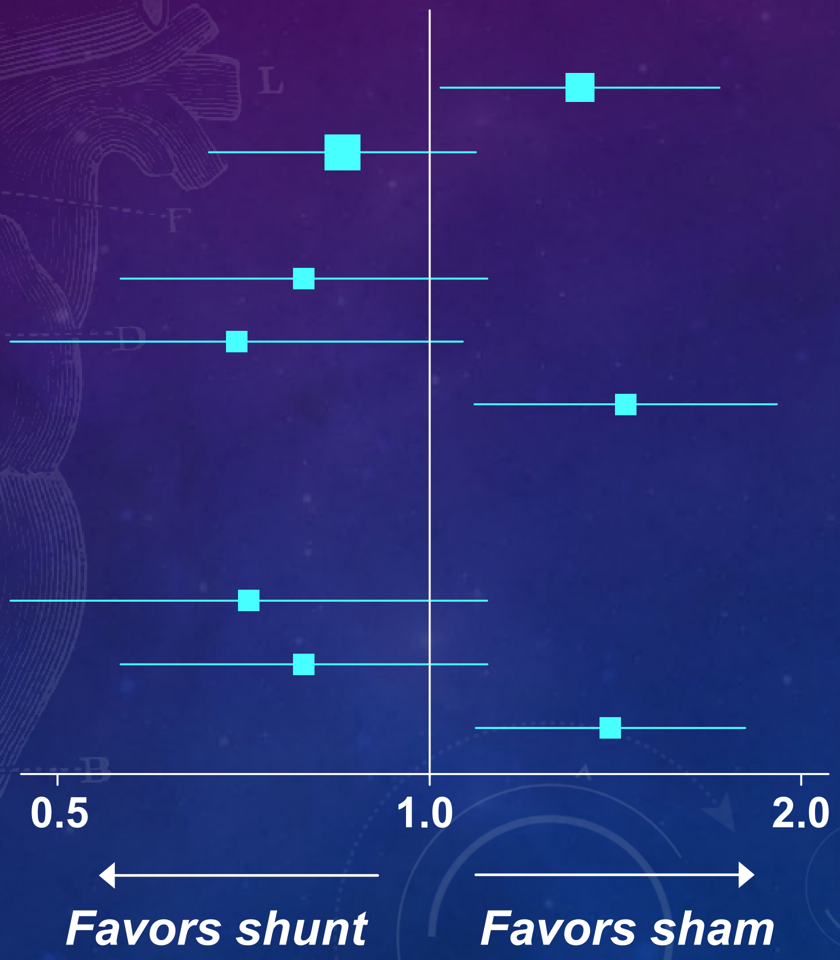
Pre-specified subgroup analyses

Subgroup	N	IRR (95% CI)	$P_{interaction}$
Sex			0.020
• **Male**	**239**	**1.32 (1.01-1.71)**	
• Female	382	0.85 (0.55-1.09)	
RA volume index			0.012
• Tertile 1	167	0.79 (0.57-1.11)	
• Tertile 2	168	0.70 (0.46-1.07)	
• **Tertile 3**	**168**	**1.43 (1.08-1.90)**	
PA systolic pressure at 20W			0.002
• Tertile 1	192	0.71 (0.46-1.11)	
• Tertile 2	202	0.80 (0.57-1.12)	
• **Tertile 3**	**202**	**1.40 (1.10-1.79)**	



Statistical significance threshold: interaction p-value <0.05

Shah SJ, et al. *Lancet* 2022

Responder analysis

$$PA\ pressure = \boxed{PVR} \times CO + PCWP$$

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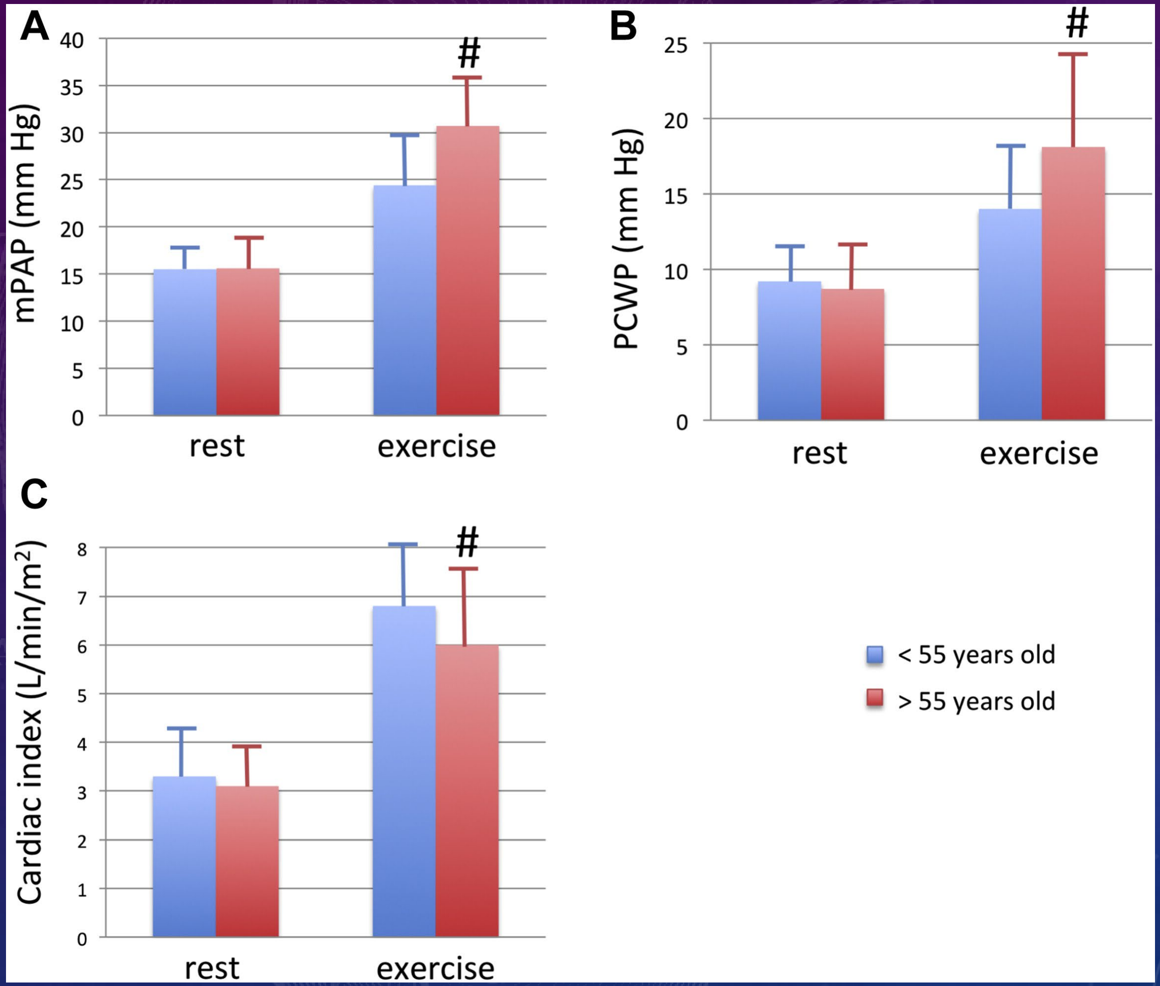
- **Markers of pulmonary vascular disease**
  - ✓ **PVR at rest, peak**
  - ✓ PASP at rest, legs up, 20W, peak
  - ✓ TPR (mPAP/CO) at rest, peak
  - ✓ PA compliance at rest/peak
  - ✓ PASP/SV at rest, peak
- **Hemodynamic markers of RV dysfunction**
  - ✓ PCWP-CVP at rest, legs up, 20W, peak
  - ✓ TAPSE/PASP ratio

- **Time to first HF event**
- **Total (first and recurrent) HF events**
- **Change in KCCQ, baseline to 12 months**

What is a normal peak exercise PVR?

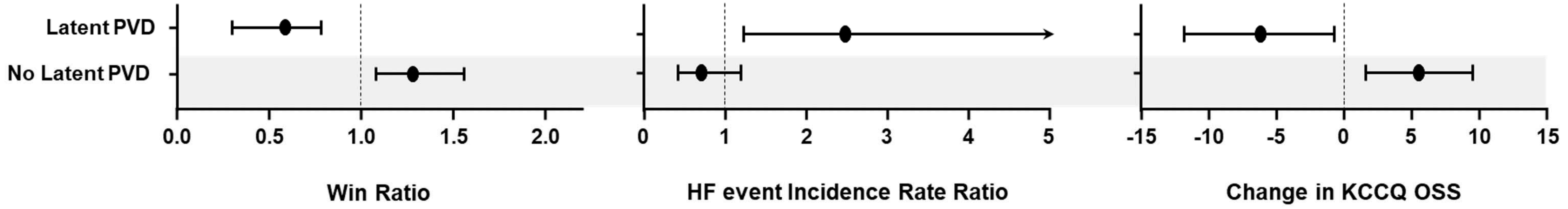


- **Study of 55 healthy participants**
- **Right heart catheterization**
- **Mean age 50, 36% age >55**
- **Similar resting hemodynamics in both age groups (<55 and >55 yrs)**
- **Older healthy individuals have ↑PA pressure and ↑PCWP, ↓CI during exercise**
- **Mean peak PVR = 1.0, SD = 0.4 WU**
- ***Peak exercise PVR upper limit of normal (mean+2SD): 1.8 WU***

Van Empel V, et al.
Am J Cardiol 2014

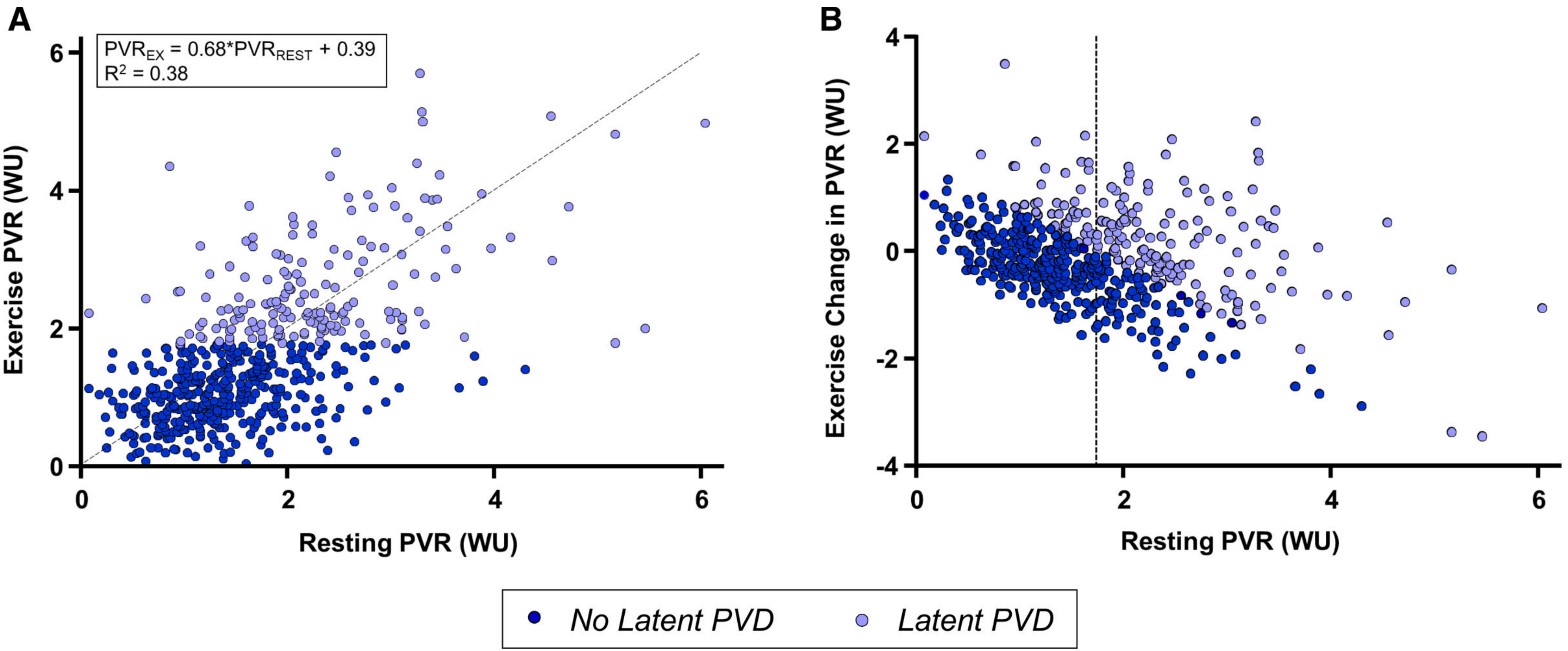
Latent PVD: worse outcomes with IASD

Latent PVD = peak exercise PVR ≥1.74 WU (highest tertile)



Borlaug BA…Shah SJ.
Circulation 2022

Resting vs. exercise PVR in REDUCE II



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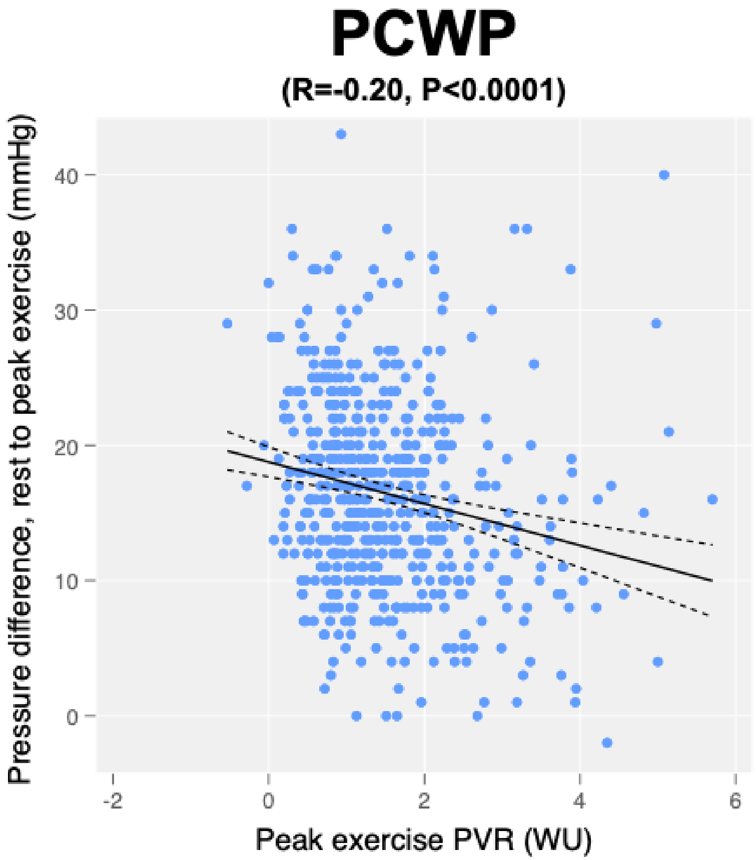
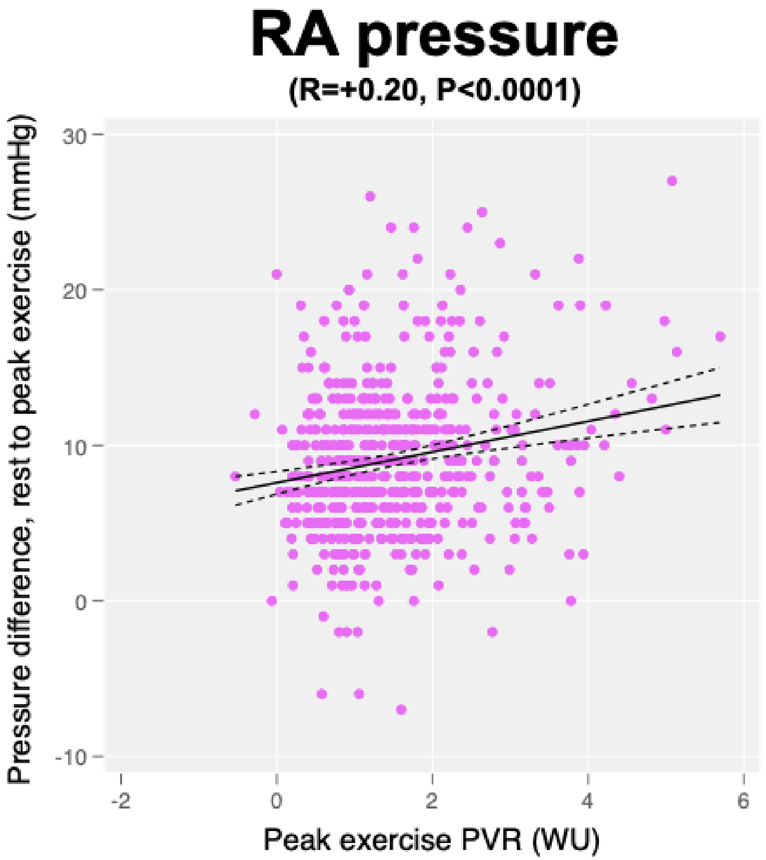
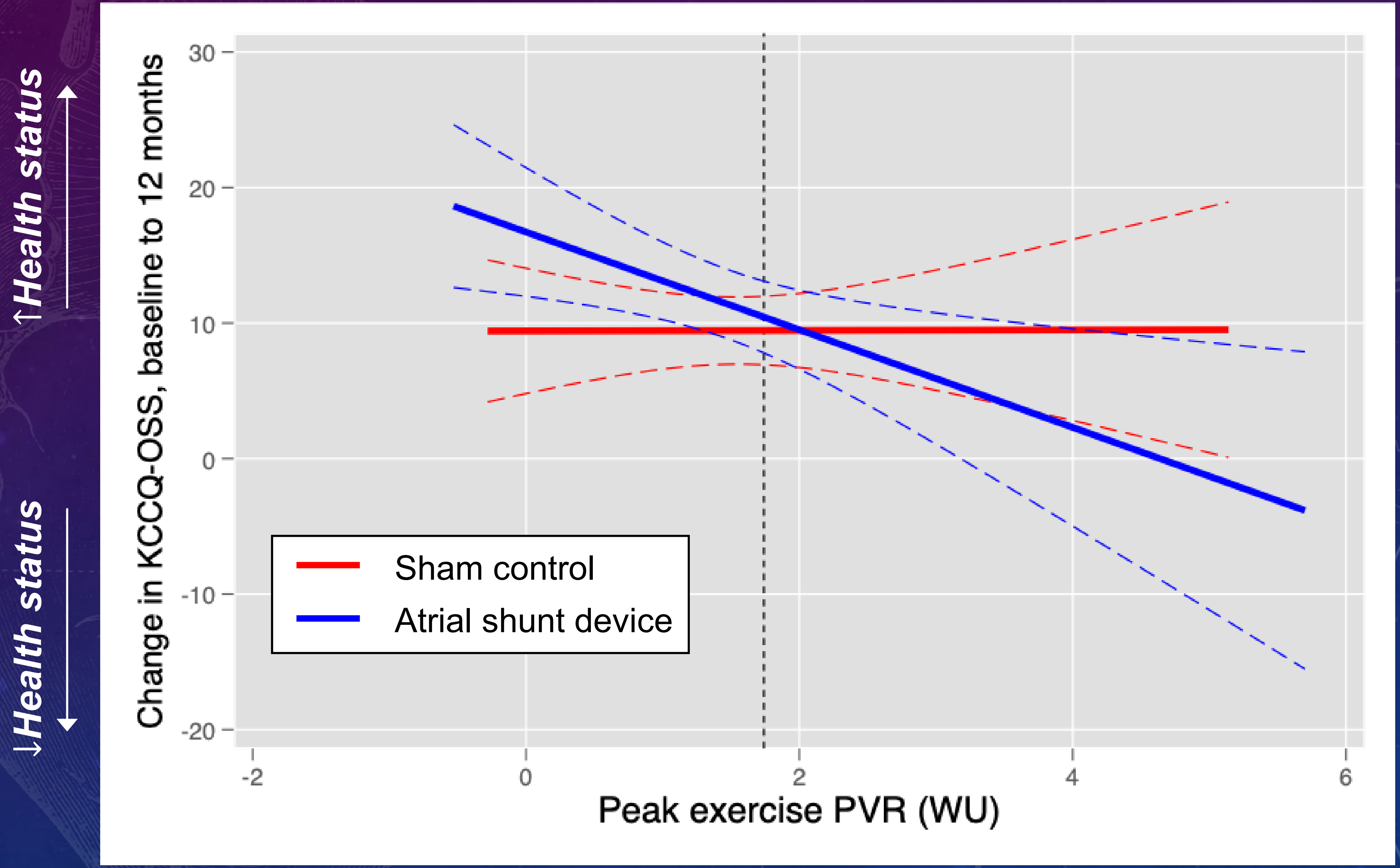
Peak exercise PVR vs. delta PCWP, RAP





Effect of shunt on KCCQ by peak exercise PVR



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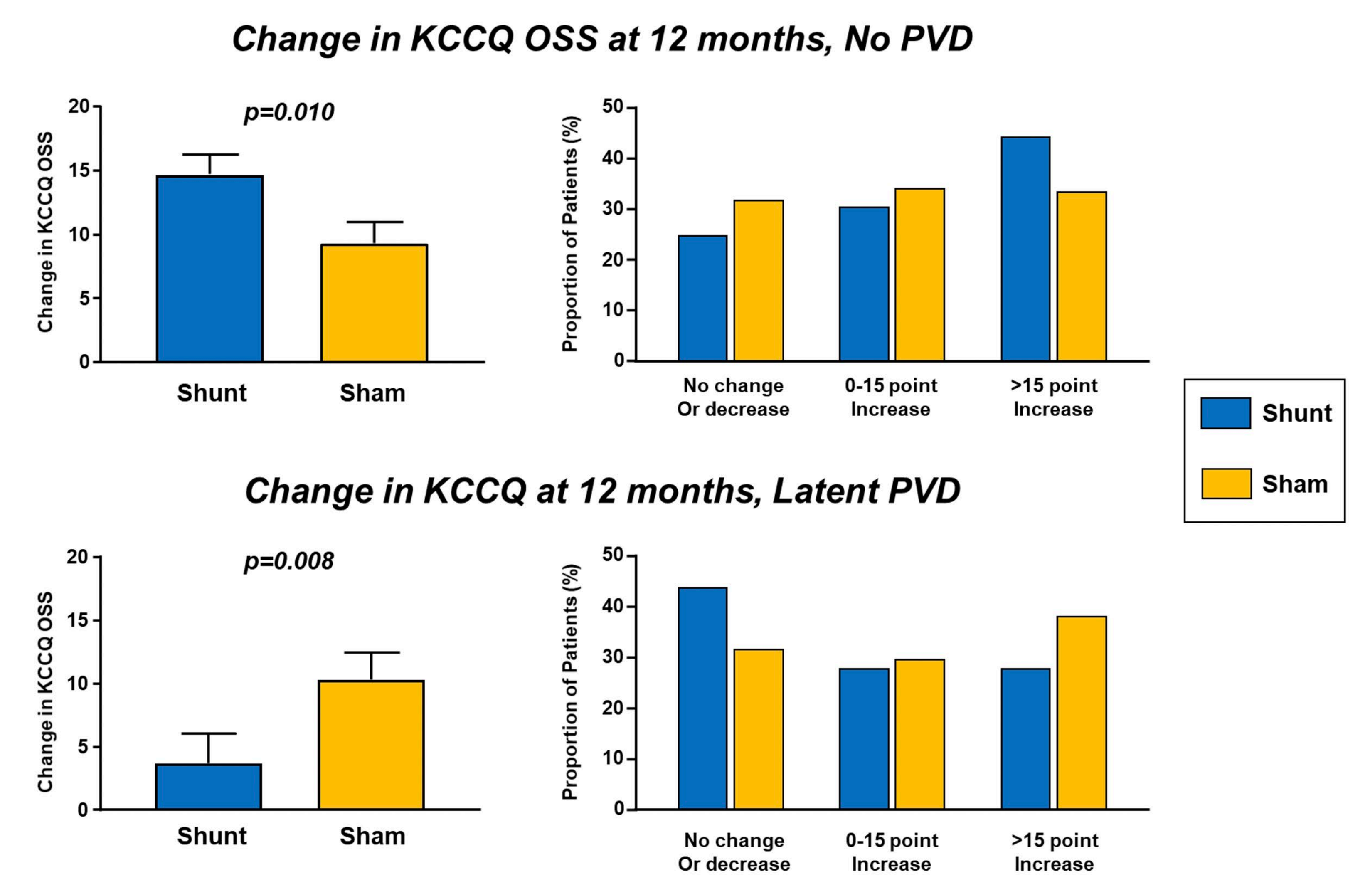
Effect of shunt on KCCQ by ± latent PVD



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Effect of shunt on echo by ± latent PVD

No latent PVD (peak exercise PVR <1.74 WU)

Echo change variable (baseline to 12 months)	Shunt device	Sham control	P-value
RA volume	↑	↔	<0.001
RV end-diastolic volume	↑	↔	<0.001
TAPSE	↔	↔	0.25
TR severity	↑	↔	<0.001
LA volume	↔	↔	0.90
LV end-diastolic volume	↔	↔	0.16
LVEF	↔	↔	0.97

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Effect of shunt on echo by ± latent PVD

Latent PVD (peak exercise PVR ≥1.74 WU)

Echo change variable (baseline to 12 months)	Shunt device	Sham control	P-value
RA volume	↑	↑	0.227
RV end-diastolic volume	↑	↑	0.367
TAPSE	↔	↔	0.366
TR severity	↑	↑	0.956
LA volume	↔	↔	0.383
LV end-diastolic volume	↓	↔	0.008
LVEF	↔	↔	0.481

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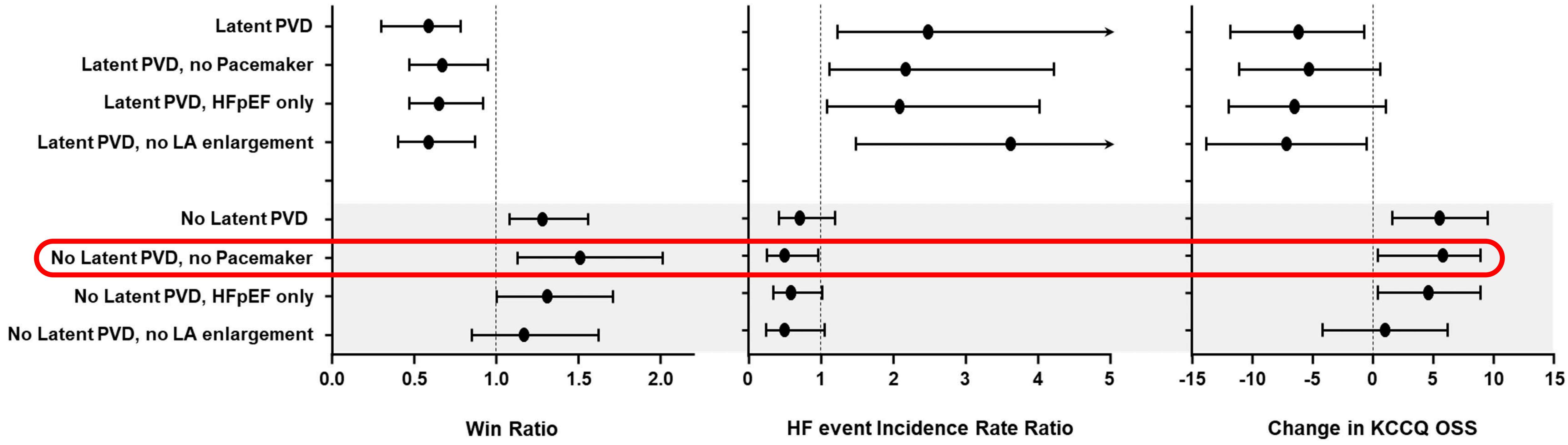
Responder analysis

Latent PVD = peak exercise PVR ≥1.74 WU



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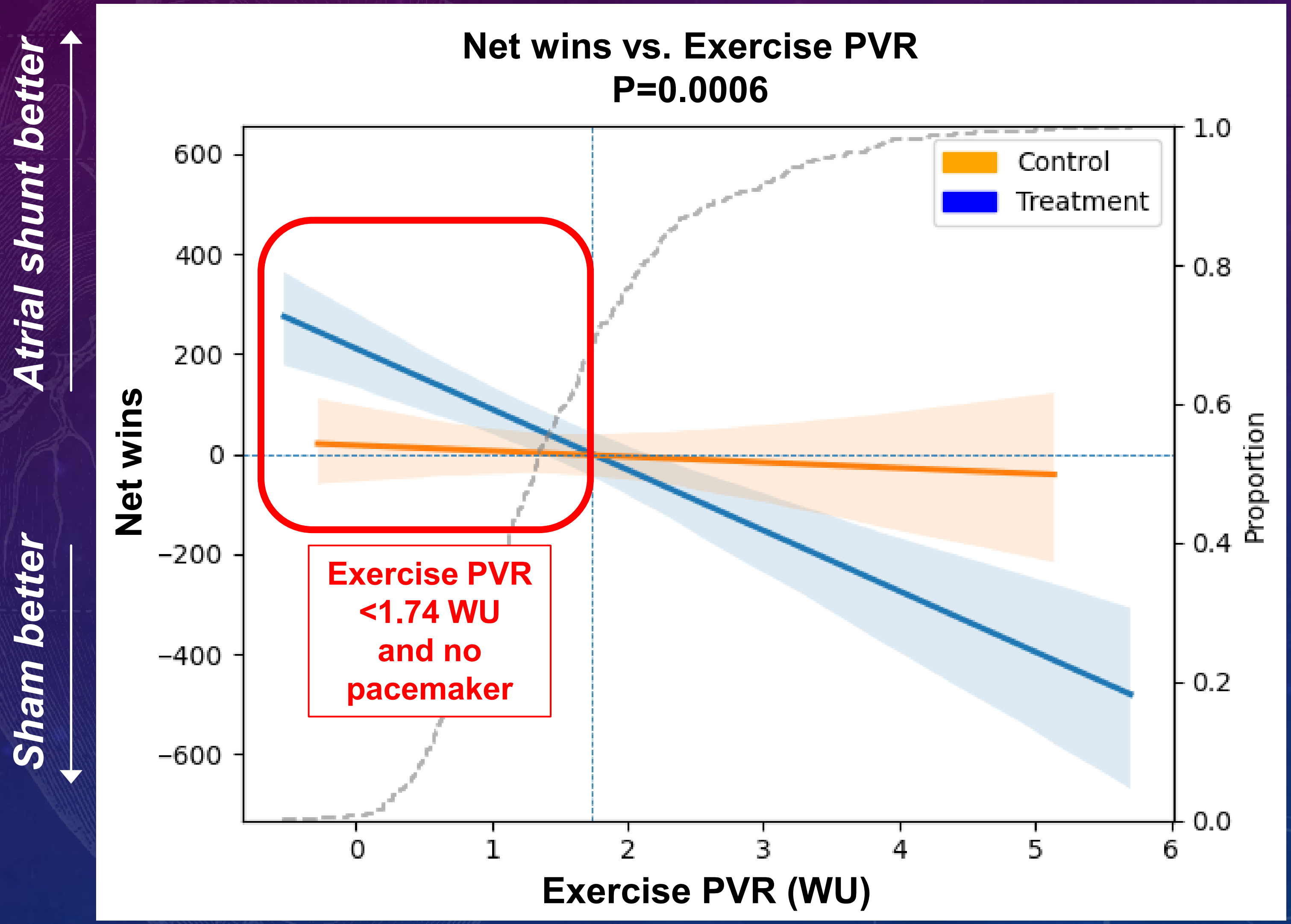
Overall efficacy of shunt by peak exercise PVR



- ~50% of patients had exercise PVR <1.74 and no pacemaker
- These patients had more "wins" when treated with atrial shunt device (↓HF hospitalizations and ↑health status)
- Opposite was true in those with exercise PVR ≥1.74 or pacemaker

Future directions: ↑Precision medicine

ALL suspected HFpEF → **Most major pharma trials**

Definite HFpEF (exercise PCWP ≥25 mmHg)

Excluding RV dysfunction, ≥2+ TR, resting PVR >3.5 WU

→ **REDUCE LAP-HF II trial**

Excluding PVD during *exercise* *and* *PM* → **Large potential responder group for future trials of interatrial shunt devices (~50% of patients enrolled)**

*PVD = pulmonary vascular disease, defined as abnormal ↑PVR during exercise (~1.8 WU or higher)
PM = pacemaker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