



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

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di Confindustria
Auditorium
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LIMITI E PROSPETTIVE DI TRATTAMENTO DELL'IPERTENSIONE POLMONARE SECONDARIA A SCOMPENSO CARDIACO

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Speaker and/or advisor fees from Janssen, MSD, and GSK

PULMONARY HYPERTENSION

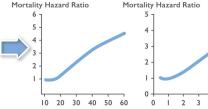
Prevalence



1%
Global population



Pulmonary congestion in post-capillary PH



Mortality Hazard Ratio
mPAP (mmHg)
PVR (Wood units)

Right heart failure

CLINICAL CLASSIFICATION

Pulmonary arterial hypertension (PAH)



- Idiopathic/heritable
- Associated conditions

PH associated with left heart disease



PH associated with lung disease



PH associated with pulmonary artery obstructions



PH with unclear and/or multifactorial mechanisms



- IpcPH
- CpcPH
- Non-severe PH
- Severe PH
- CTEPH
- Other pulmonary obstructions

PREVALENCE

Rare



Very common



Common



Rare



Rare



THERAPEUTIC STRATEGIES

Medical therapy

- PAH drugs
- CCB in responders

Lung transplantation

IpcPH:

- Treatment of LHD^a

CpcPH:

- Treatment of LHD^a
- Potentially: PAH drugs (trials)

PH-lung disease:

- Optimized care of underlying lung disease

Severe PH:

- Potentially: PAH drugs (trials)

Surgical therapy:

- PEA
- Interventional:

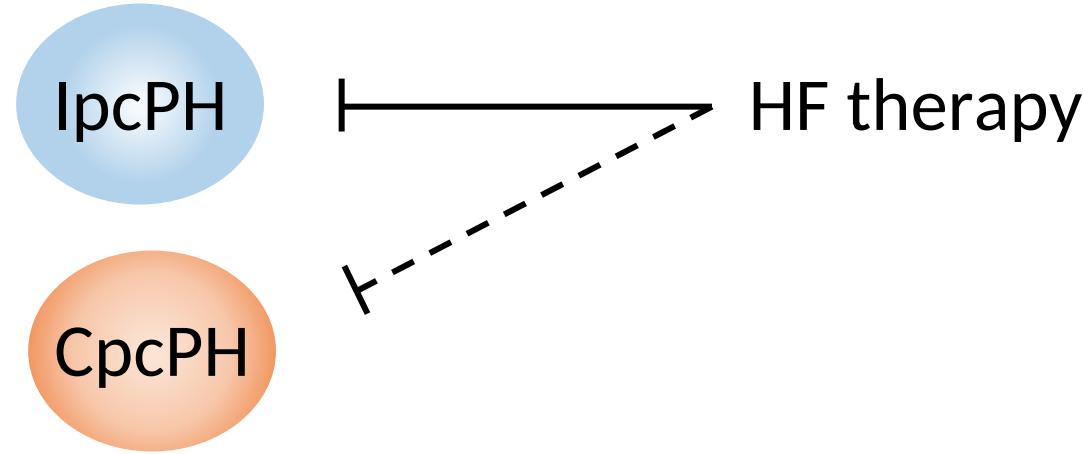
- BPA
- Medical therapy:

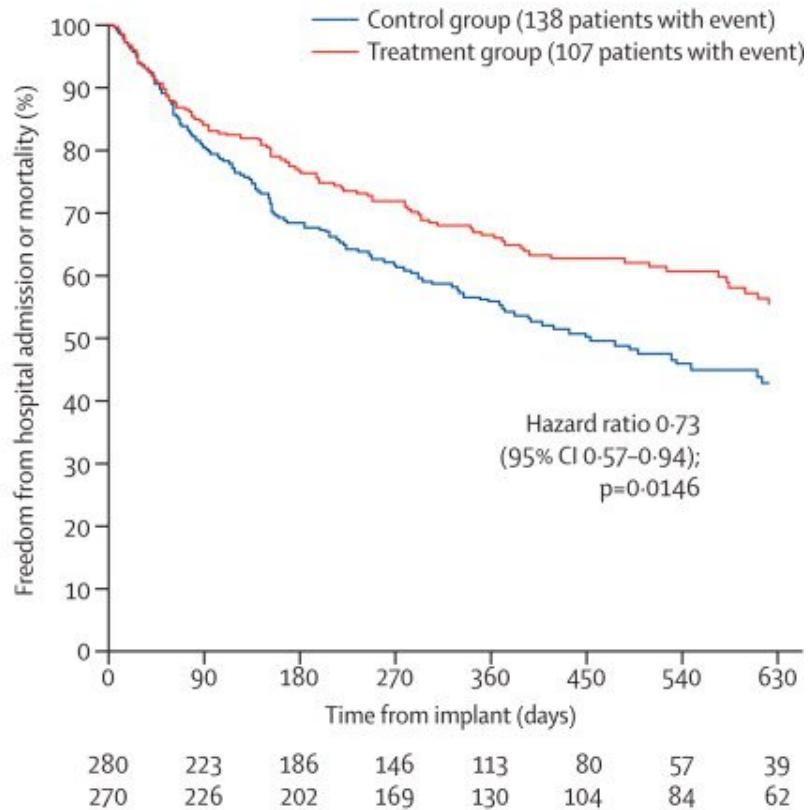
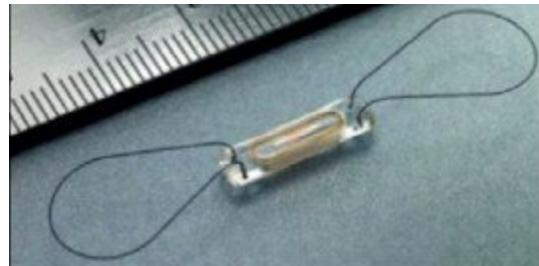
- PH drugs

Optimized treatment of underlying disease

- Potentially: PAH drugs (trials)

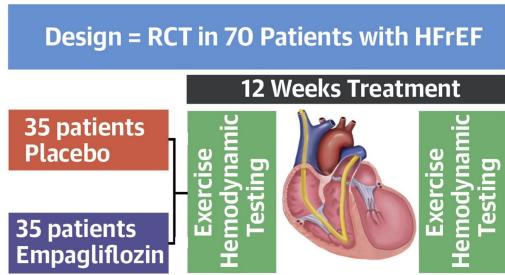




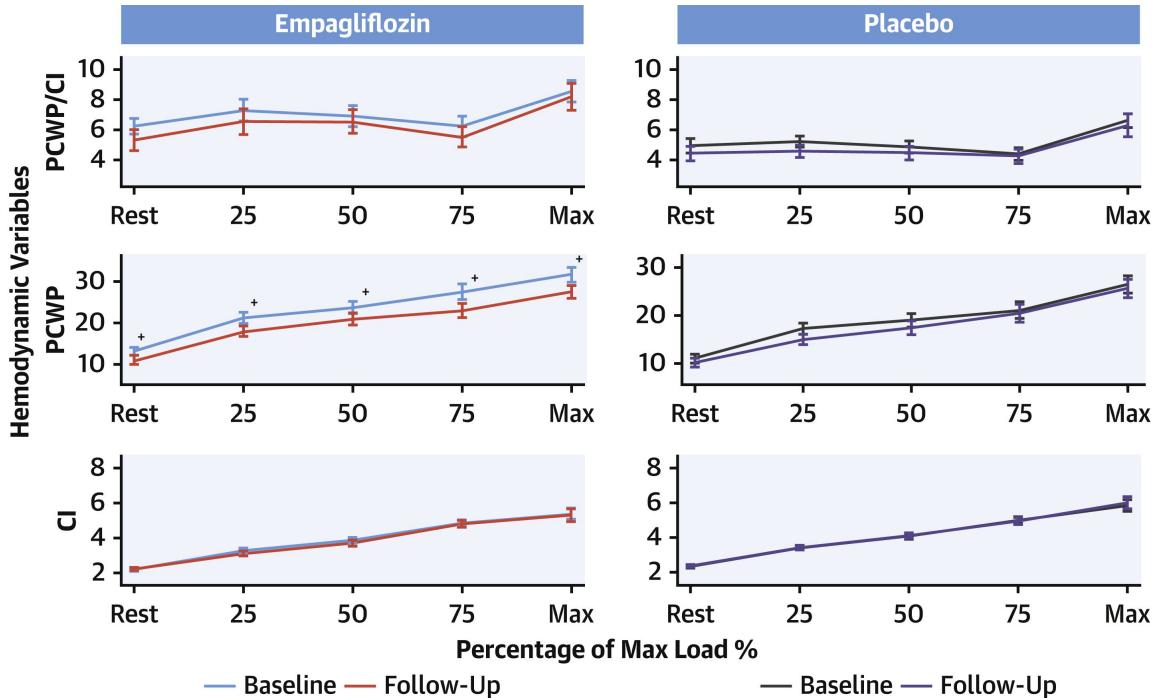


Abraham WT et al. Lancet. 2011;377:658-66

Empire HF



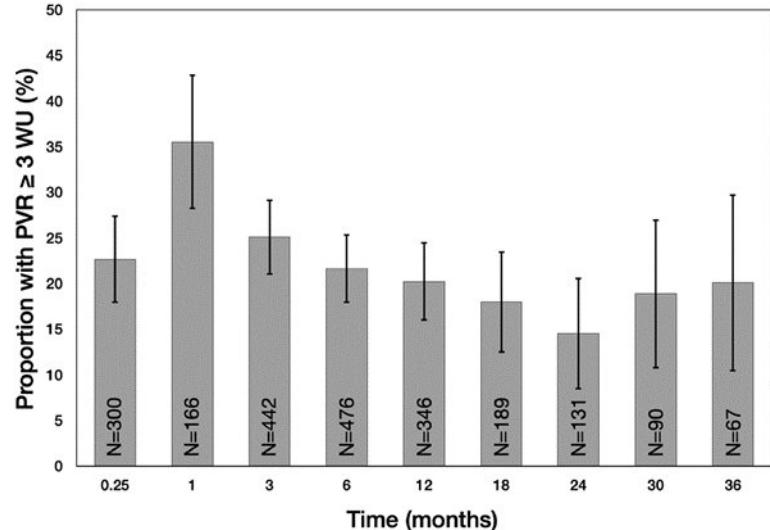
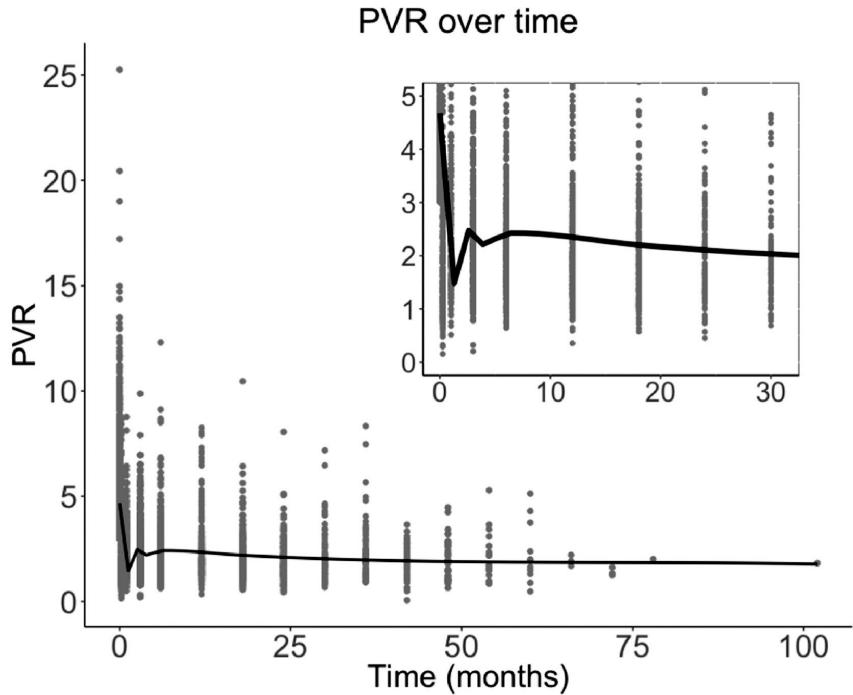
	EMPA	PLACEBO
mPAP, mmHg	20 ± 6	19 ± 7
PCWP, mmHg	13 ± 5	11 ± 6
CI, L/min/m ²	2.2 ± 0.5	2.2 ± 0.4
RAP, mmHg	5 ± 3	5 ± 3



Omar M et al. J Am Coll Cardiol. 2020;76:2740-51

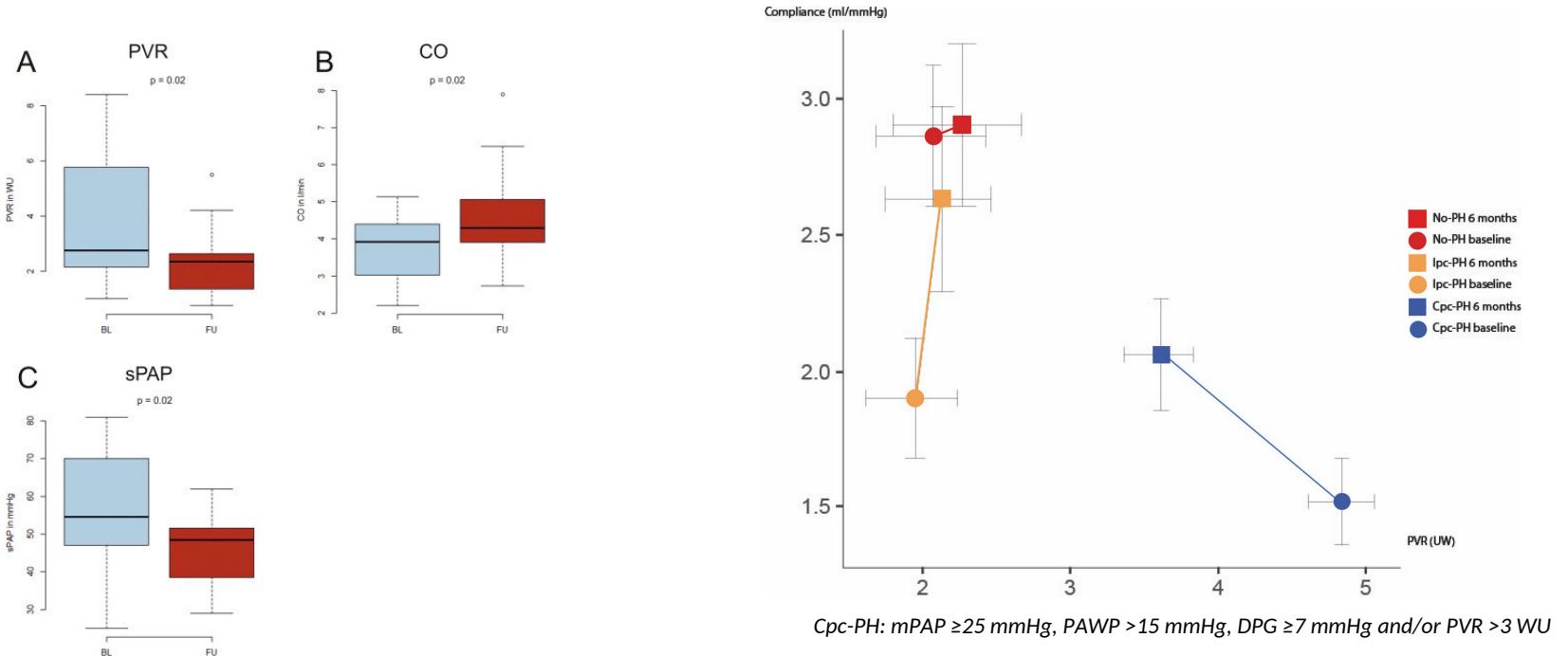
INTERMACS registry

1581 patients with primary continuous-flow LVAD, baseline PVR ≥ 3 WU, and PVR measured at least once postoperatively



Gulati G et al. J Card Fail. 2021;27:552-9

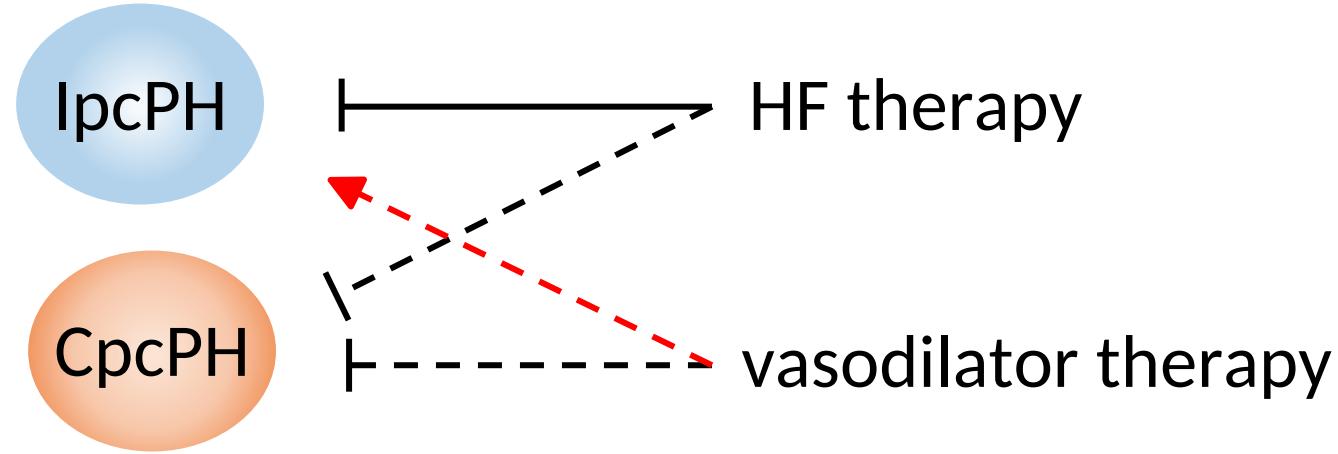
TMVr → LV diastolic unloading, improved CO



Doldi PM et al. Int J Cardiol. 2021;338:72-8

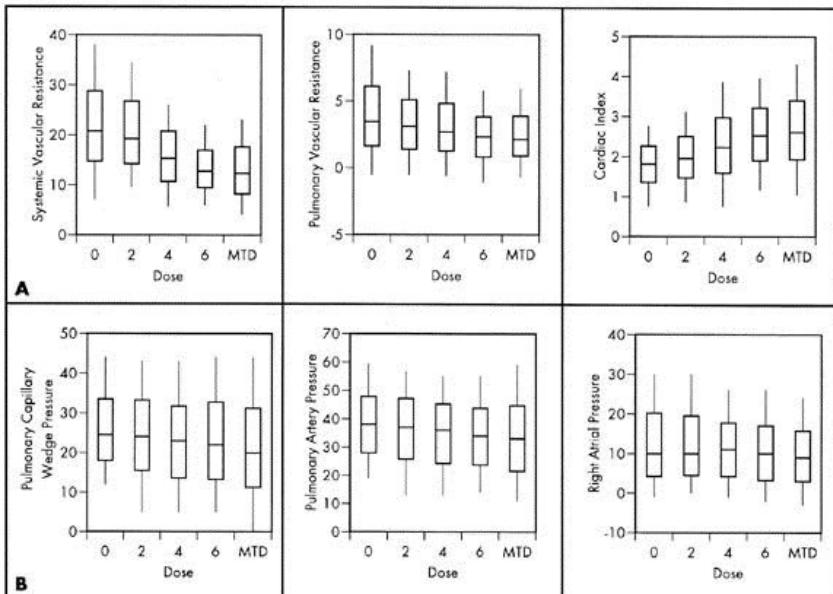
Mandurino-Mirizzi A, Crimi G et al. Eur J Clin Invest. 2021. doi: 10.1111/eji.13676

- ❖ HF therapy
- ❖ Vasodilator therapy (PAH drugs)
- ❖ Improved patient and drug selection
- ❖ Drug discovery

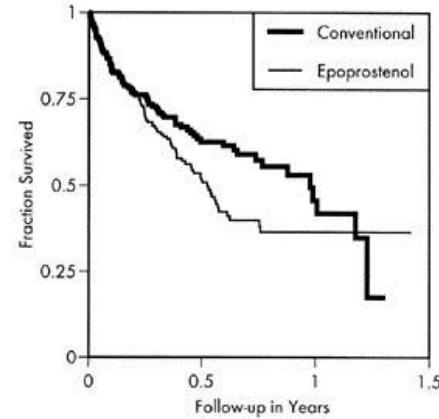


FIRST

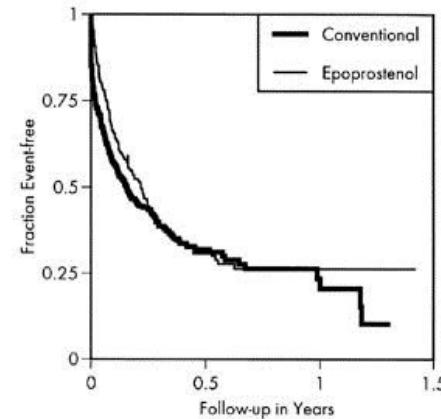
- LVEF <25% or <30% if intravenous inotropic agent
- NYHA IIIB or IV
- CI ≤2.2 L/min/m² and PAWP ≥15 mmHg unless iv vasoactive medications



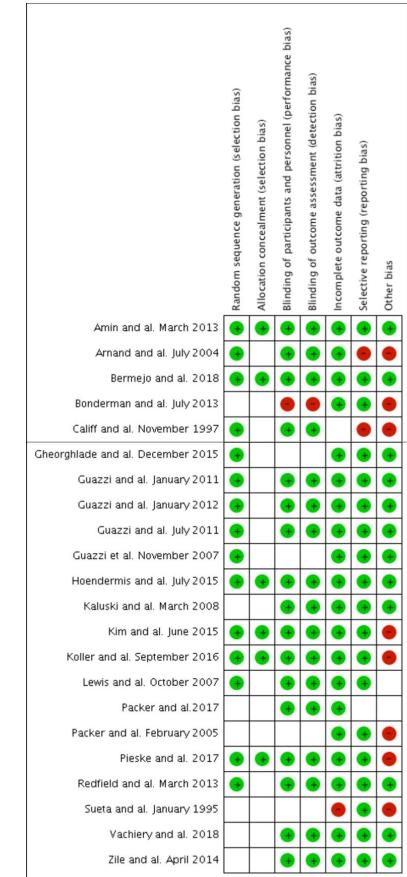
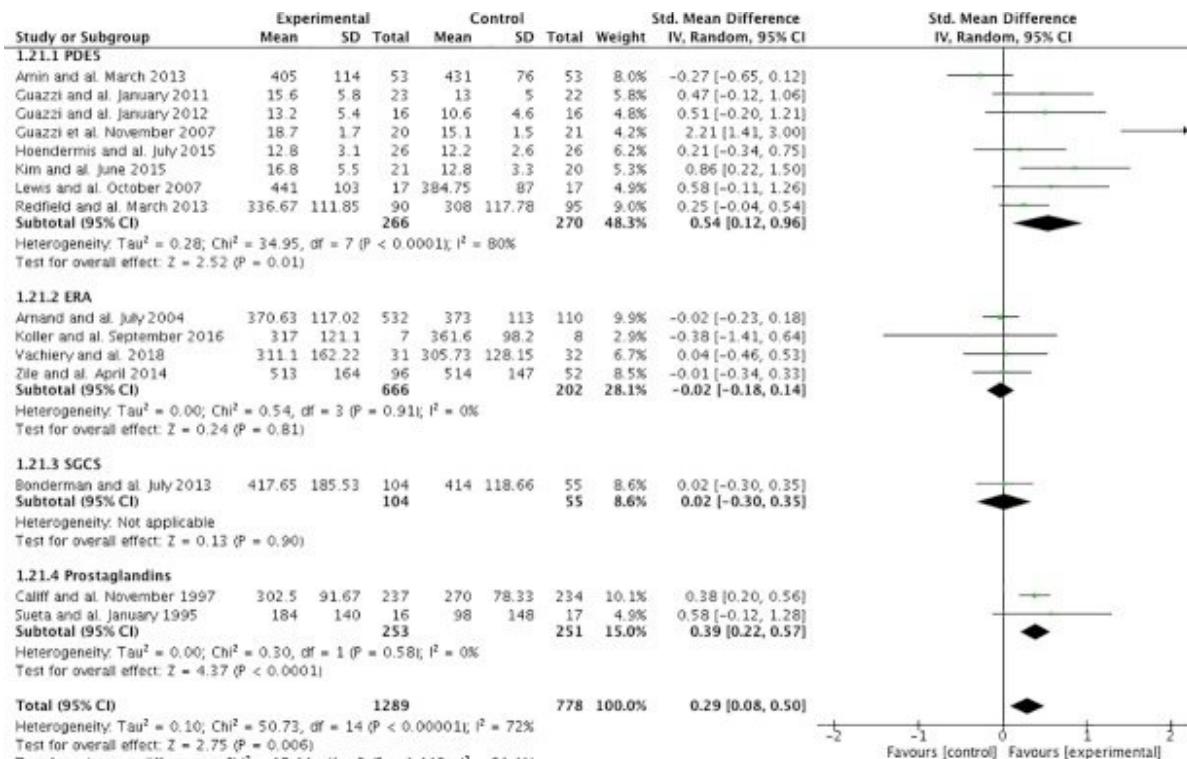
Califf RM et al. Am Heart J. 1997;134:44-54



time to death



time death, HHF, initiation of intravenous inotropes, mechanical assisted circulation, tracheotomy, resuscitation, or MI



Guay CA et al. PLoS One. 2018;13(10):e0204610

Hoendermis ES et al.

Eur Heart J. 2015;36:2565-73



LVEF \geq 45%, mPAP >25 mmHg, PAWP >15 mmHg

Guazzi M et al.

Circulation. 2011;124:164-74



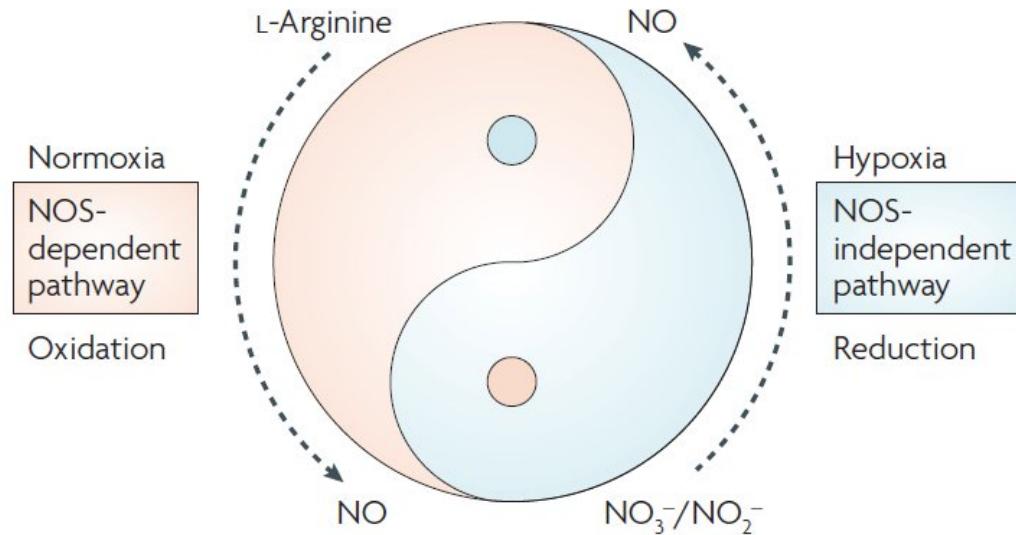
LVEF \geq 50%, estimated sPAP \geq 40 mm Hg;
more male and less diabetic patients, higher BP

	Placebo (n. 26)	Sildenafil (n. 26)	Placebo (n. 22)	Sildenafil (n. 22)
RAP, mmHg	10 (9-12)	9 (7- 11)	23.1 ± 5.5	23.0 ± 4.6
mPAP, mmHg	$35.0 + 7.1$	$35.0 + 9.5$	36.8 ± 5.1	39.0 ± 5.0
PAWP, mmHg	$20.8 + 4.2$	$19.9 + 3.2$	21.9 ± 2.0	22.0 ± 2.5
CI, L/min/m ²	$2.9 + 0.6$	$2.8 + 0.7$	2.3 ± 0.6	2.4 ± 0.6
PVR, WU	2.5 *	2.6 *	3.3 ± 0.9	3.88 ± 1.38
TAPSE, mm	20.1 ± 4.9	18.5 ± 4.1	11.2 ± 2.5	11.3 ± 2.2

* calculated from the published values in dyn·s·cm⁻⁵

- ❖ HF therapy
- ❖ Vasodilator therapy
- ❖ Improved patient and drug selection
- ❖ Drug discovery

Exercise PH in HFrEF

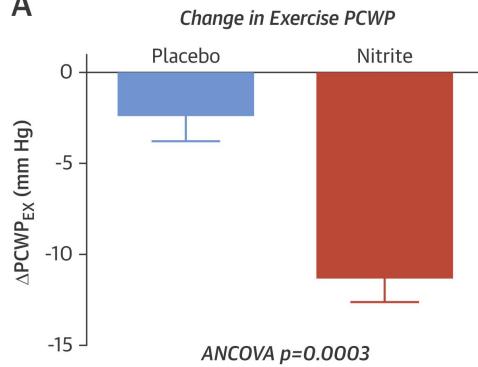


Lundberg JO et al. Nat Rev Drug Discov. 2008;7:156-67

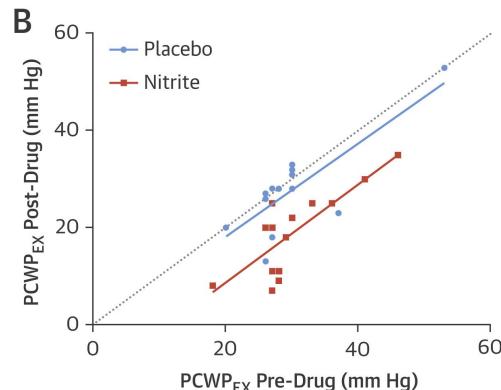
MAYO CLINIC

LVEF $\geq 50\%$, PCWP > 15 mmHg at rest and/or ≥ 25 mmHg with exercise

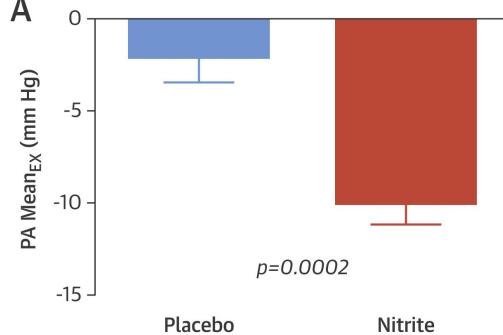
A



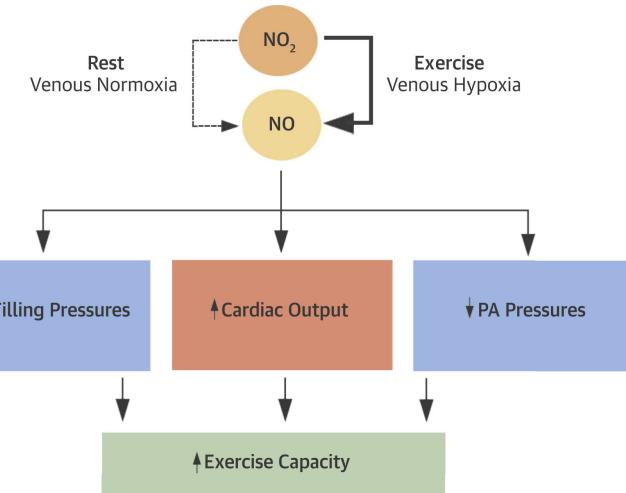
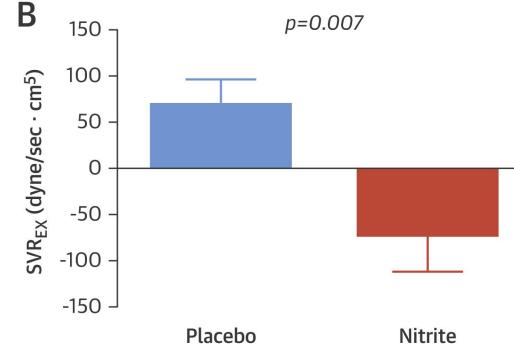
B



A



B

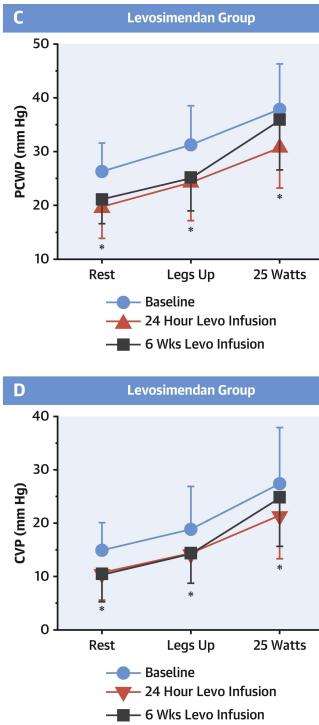
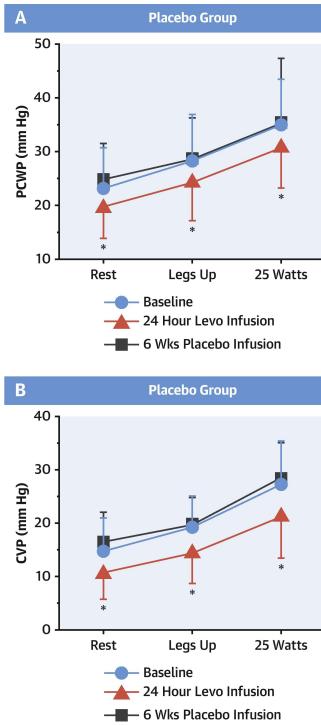


BA Borlaug et al. J Am Coll Cardiol. 2015;66:1672-82

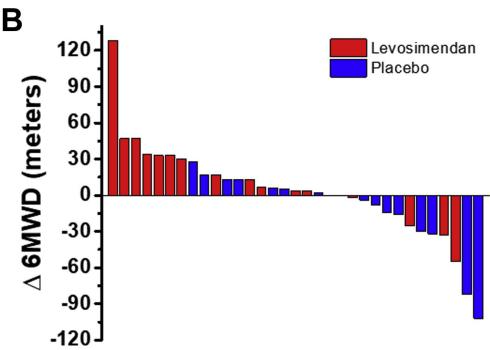
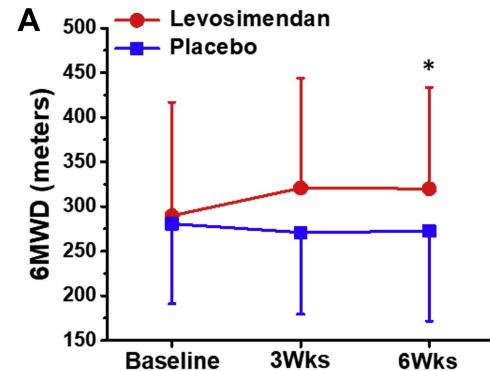
HELP trial

LVEF $\geq 40\%$, mPAP ≥ 35 mmHg and PCWP ≥ 20 mmHg (with legs elevated into pedals of a supine cycle ergometer)

CENTRAL ILLUSTRATION: Effects of Levosimendan on PCWP and CVP



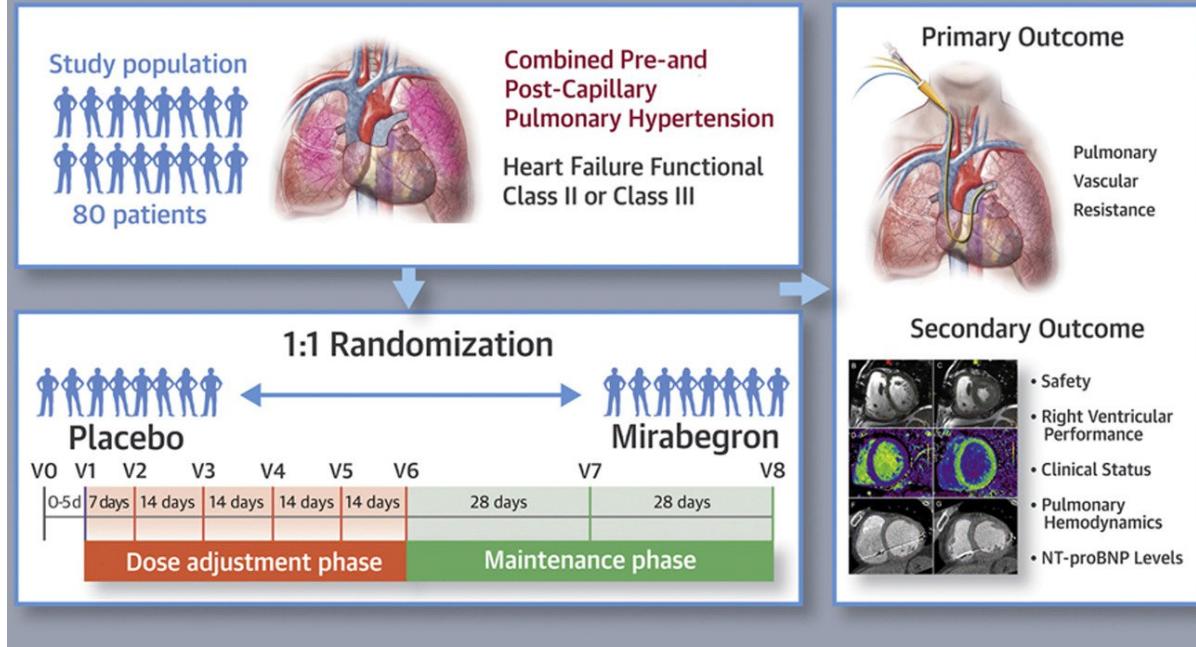
Burkhoff, D. et al. J Am Coll Cardiol HF. 2021;9(5):360-70.



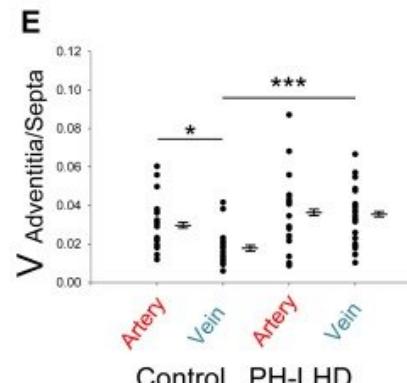
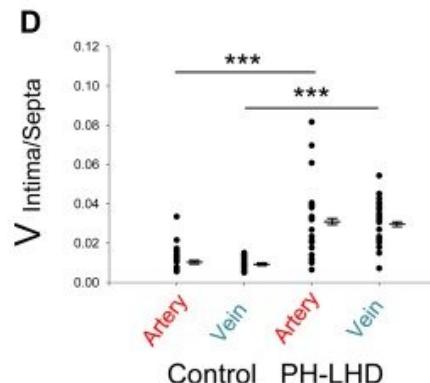
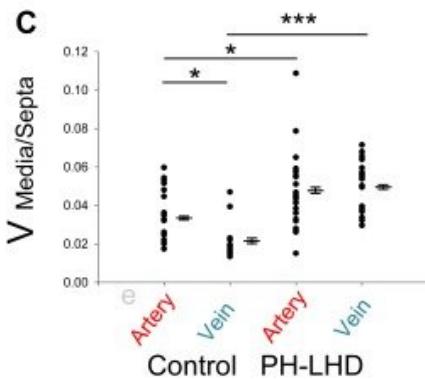
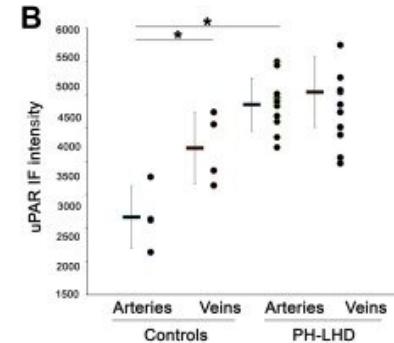
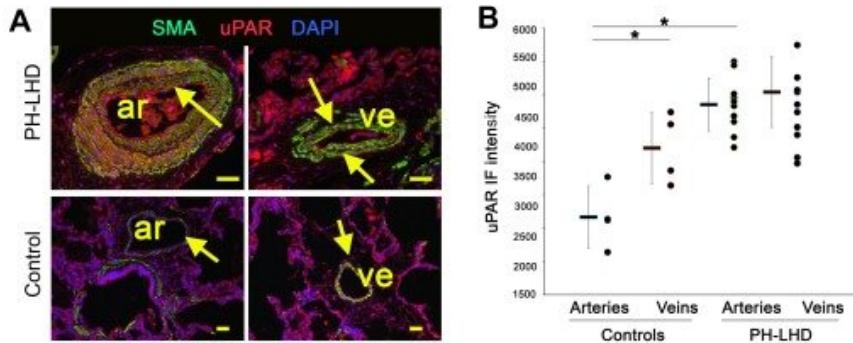
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Design of SPHERE-HF

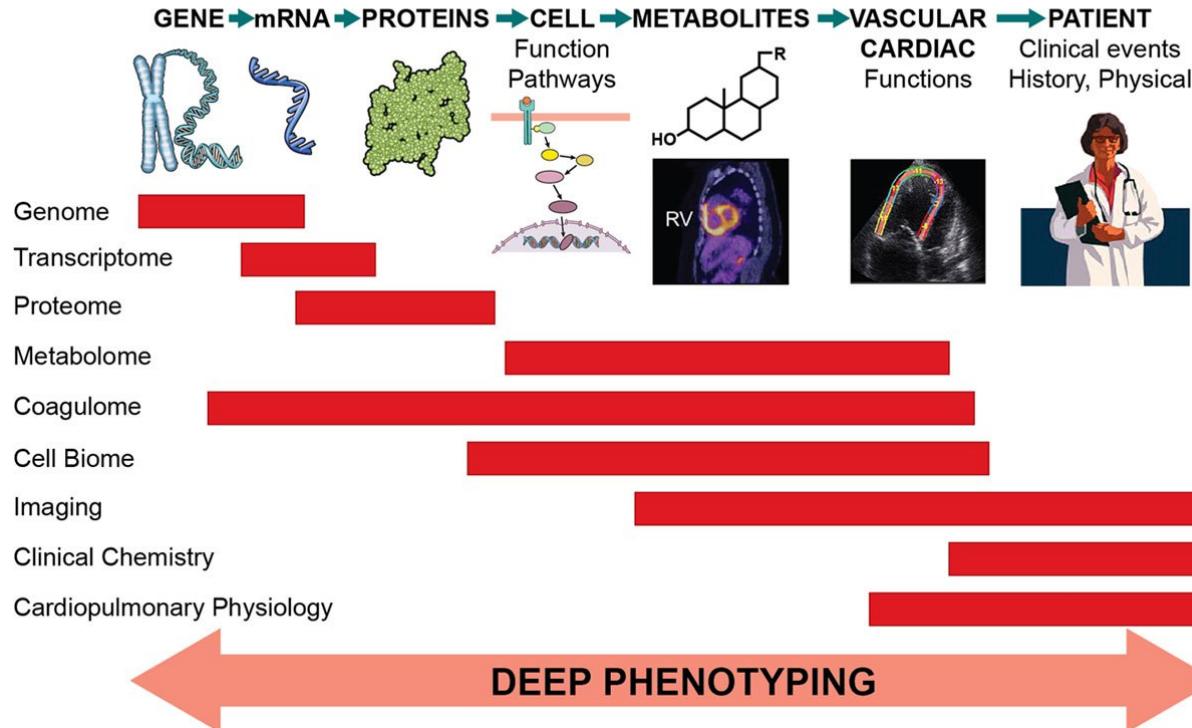
(β_3 adrenergic agonist treatment in chronic Pulmonary Hypertension secondary to Heart Failure trial)



Garcia-Lunar I et al. JACC Basic Transl Sci. 2020;5:317-7



Pathobiology of PH: New Ontology of PH based on Endophenotypes



Hennes AR et al. Circ Res. 2017;121:1136-9

Conclusions

- ❖ At present, there is no approved drug for treatment of PH-HF, which therefore relies on HF therapies
- ❖ Some pulmonary vasodilators, as well as other therapies with different modes of action, may be effective for specific patient subgroups
- ❖ A better understanding of the pathogenesis of PH-HF is expected to lay the foundations for the development of novel therapeutic approaches