Clinical and Translational Research in HFpEF

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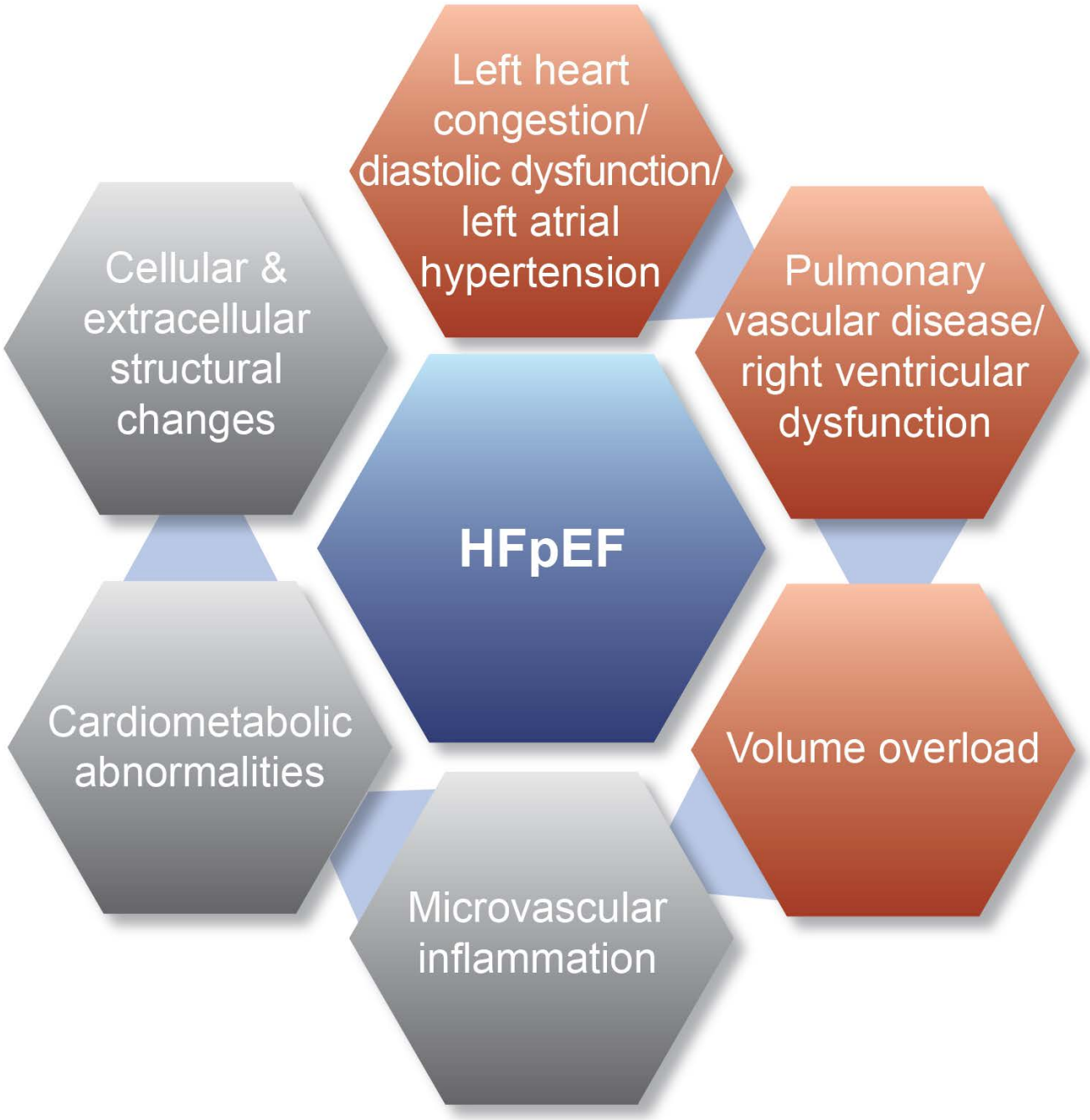
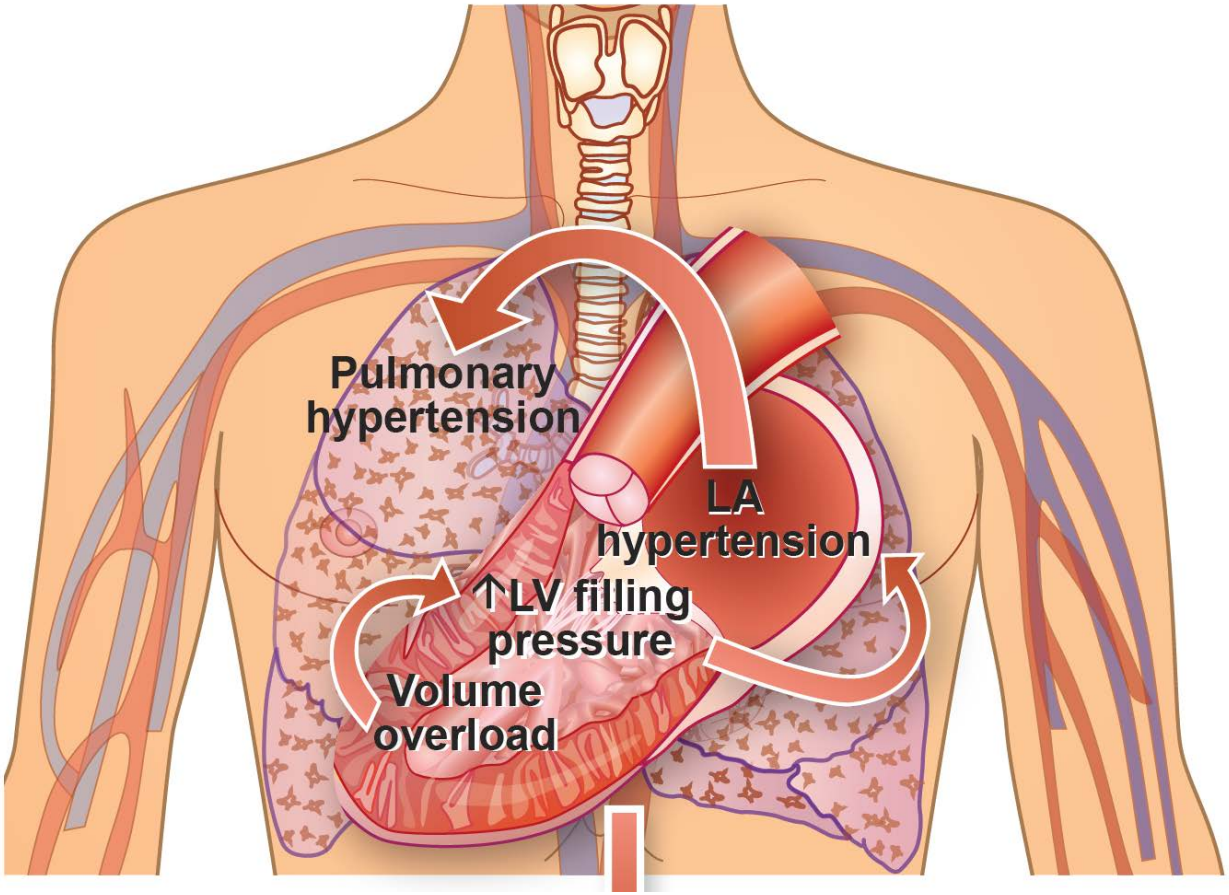
Director, Clinical & Translational Research Office at NHCS
Affiliate Member, SingHealth Duke-NUS Institute of Precision Medicine (PRISM)
Scientific Advisor to the Clinical Trials Coordinating Centre (CTCC) at SingHealth



Lam, Voors, de Boer, Solomon, van Veldhuisen Eur Heart J 2018

Potential targets in HFpEF

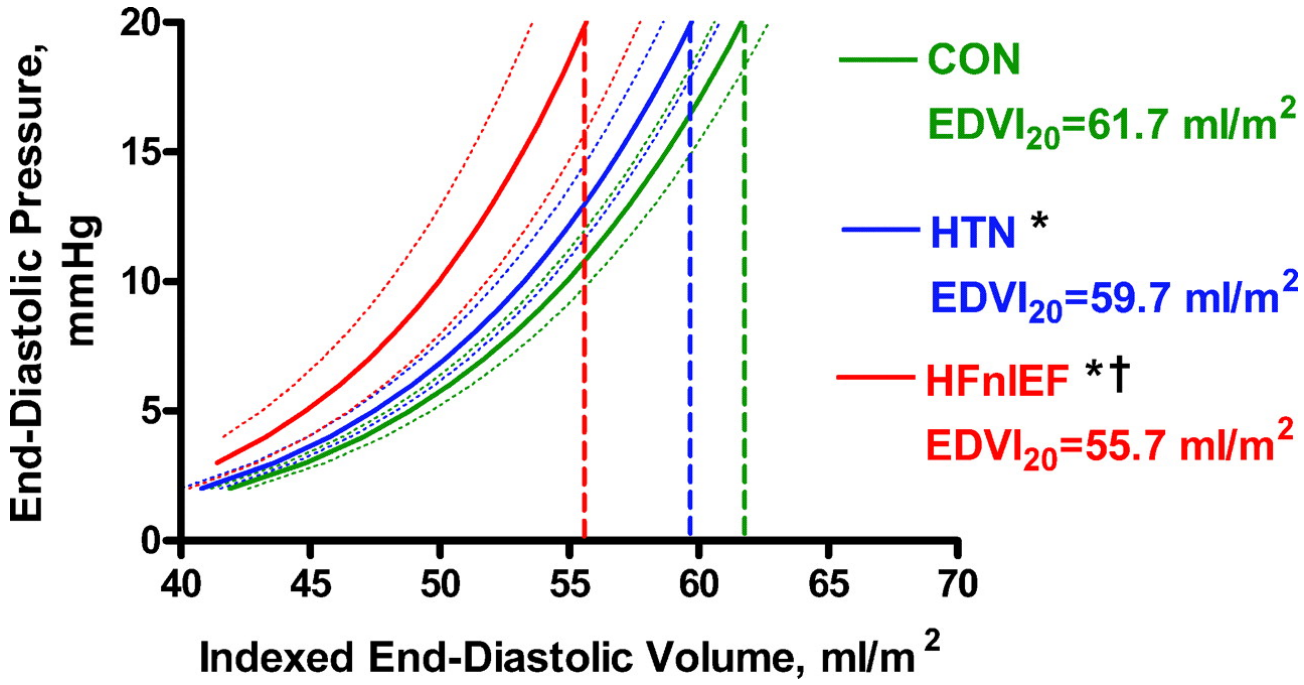
1. Hemodynamic targets

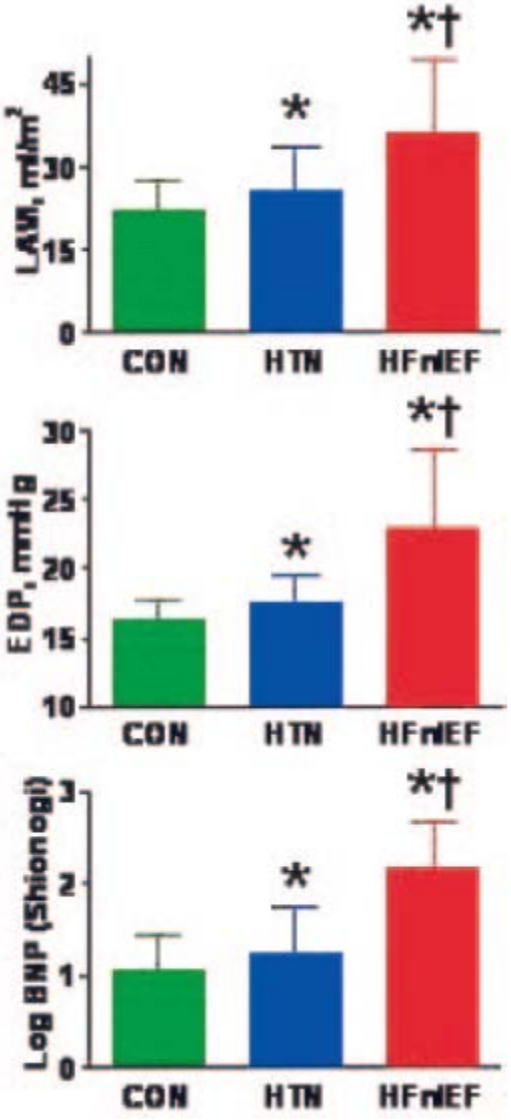


Lam, Voors, de Boer, Solomon, van Veldhuisen Eur Heart J 2018

LV diastolic dysfunction

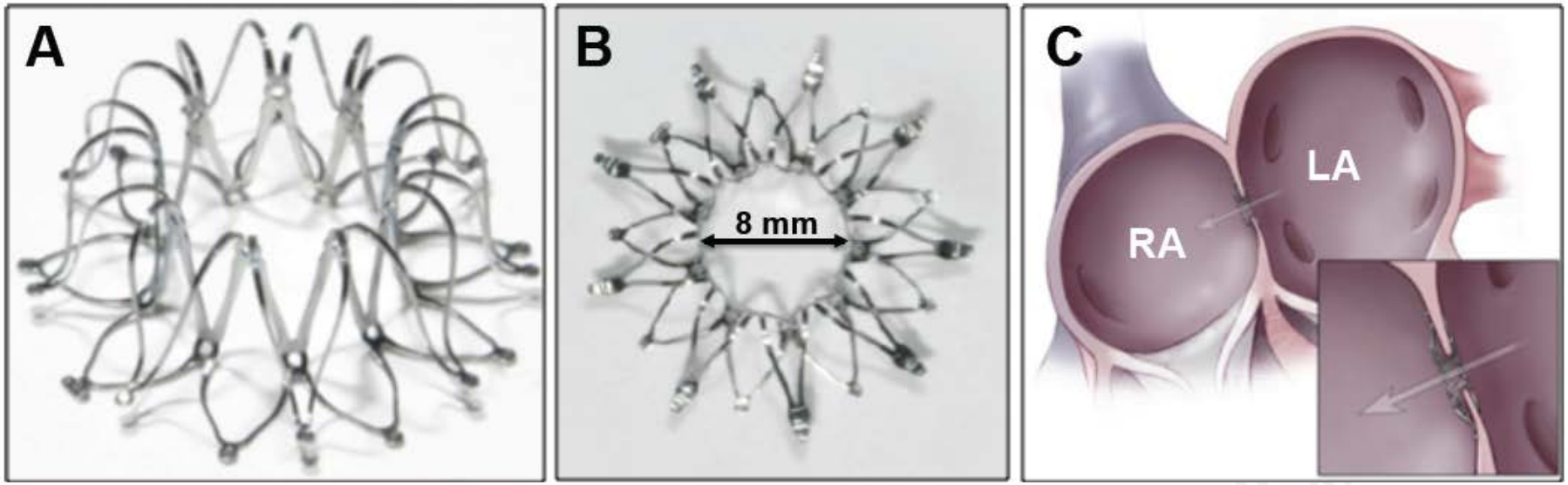
Population-based age-, sex-, body size- adjusted

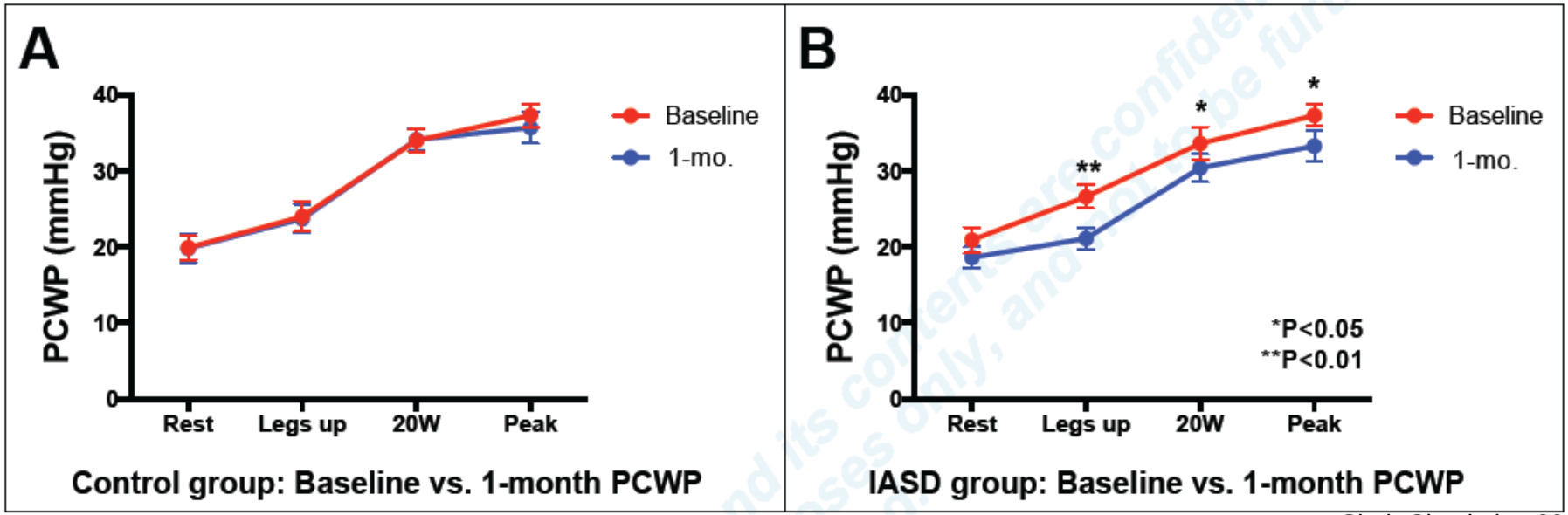




Lam Circulation 2007

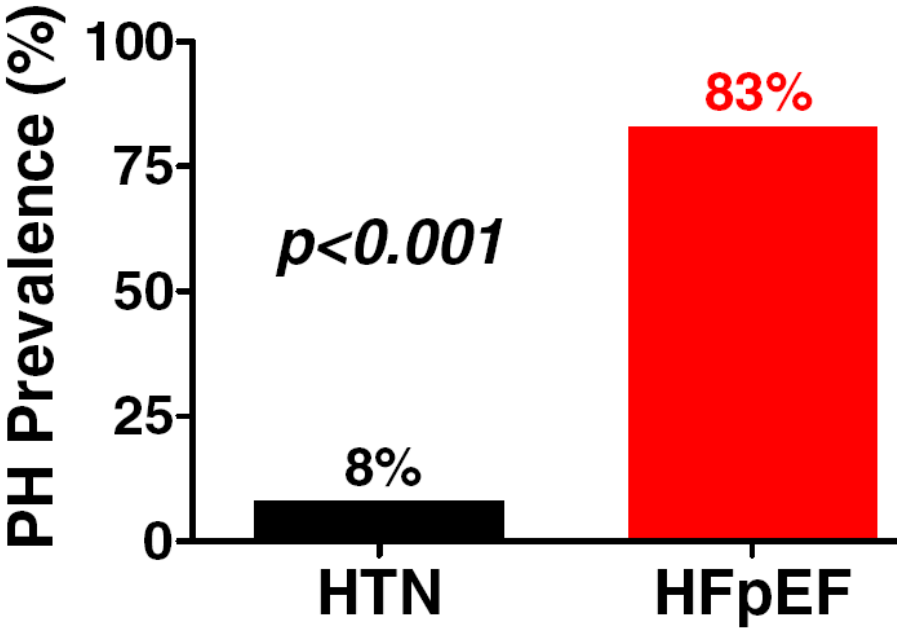
Left atrial hypertension: REDUCE-LAP HF I (Phase 2)

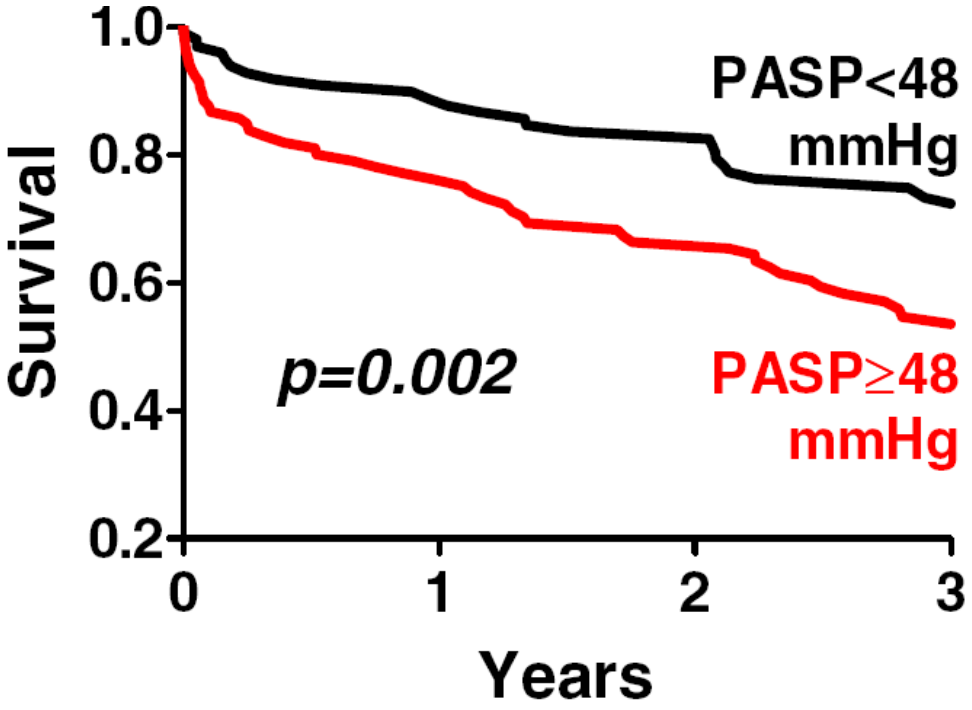




Shah Circulation 2017

Pulmonary Hypertension

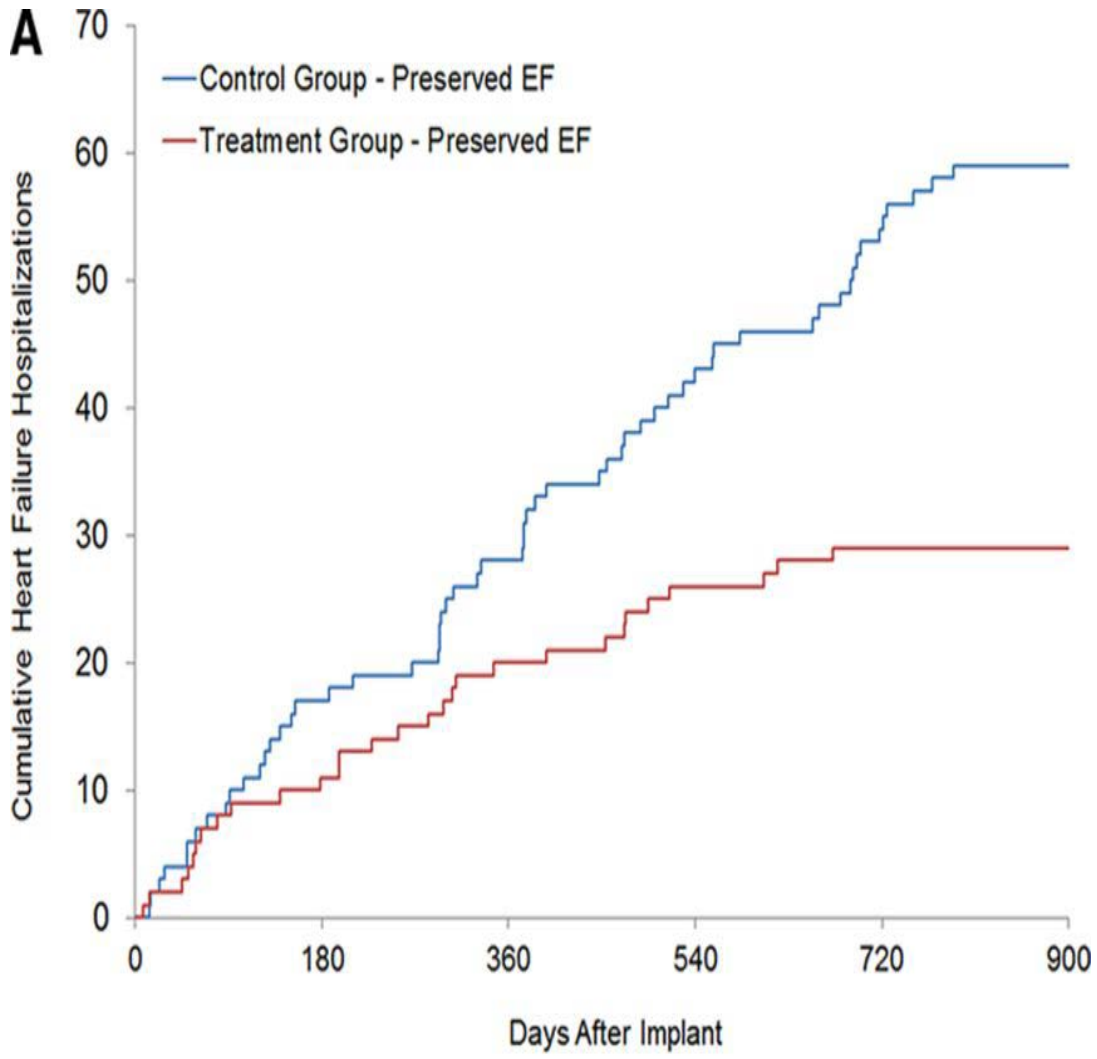




High prevalence & prognostic impact of PH in HFpEF suggest an important pathophysiologic role

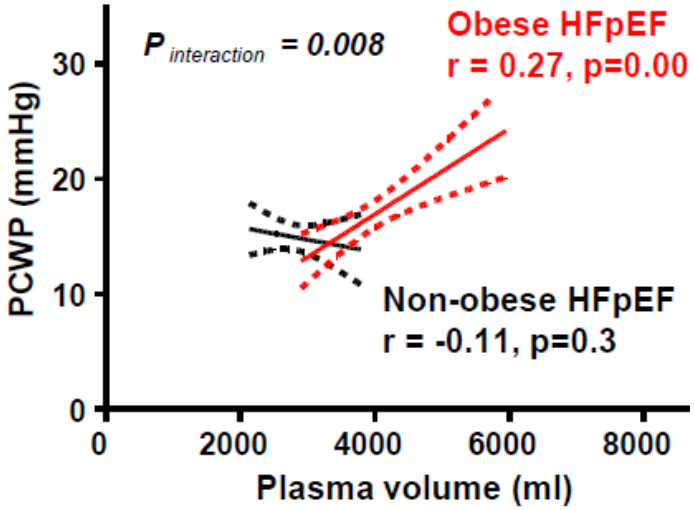
Lam C.S. et al J Am Coll Cardiol. 2009;53:1119-26

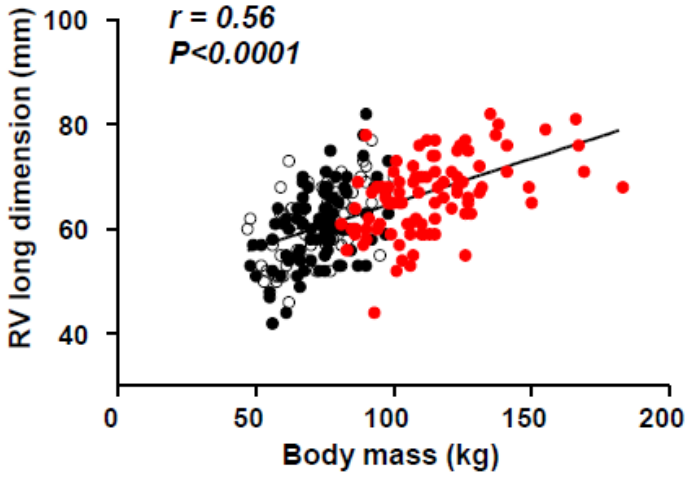
Pulmonary hypertension: CHAMPION

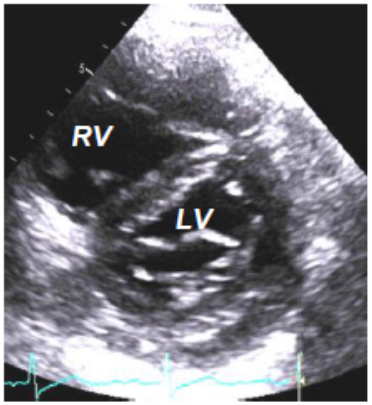


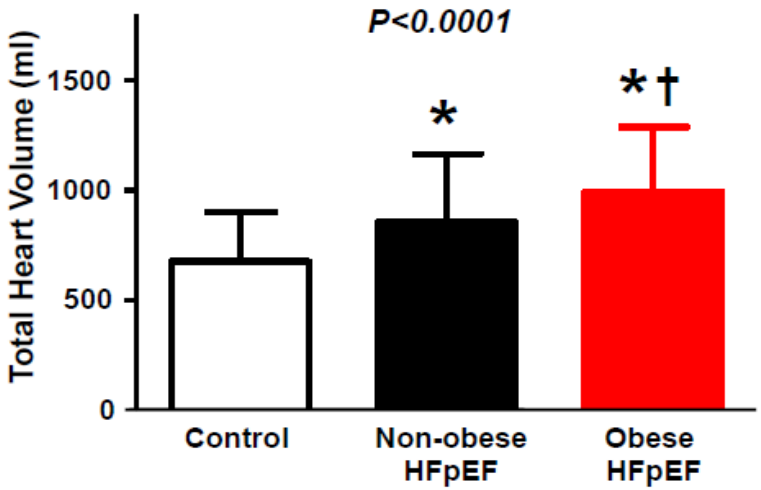
Philip B. Adamson et al. Circ Heart Fail. 2014

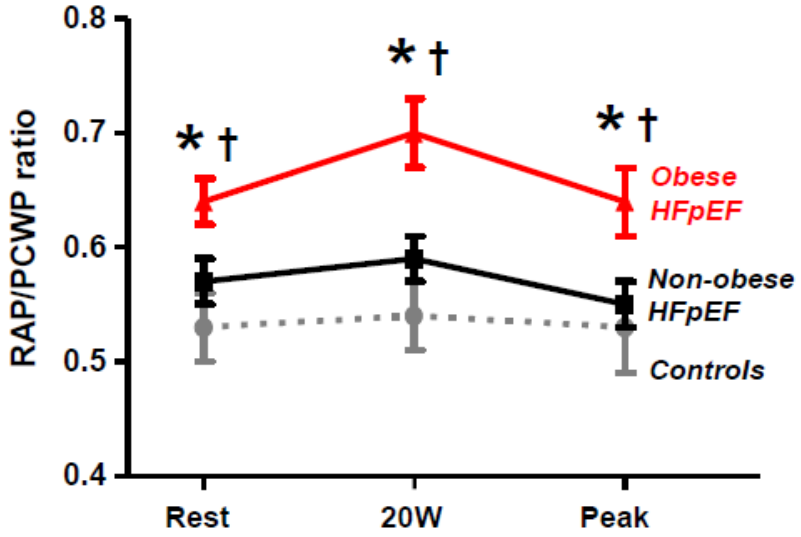
Volume overload: Obese HFpEF









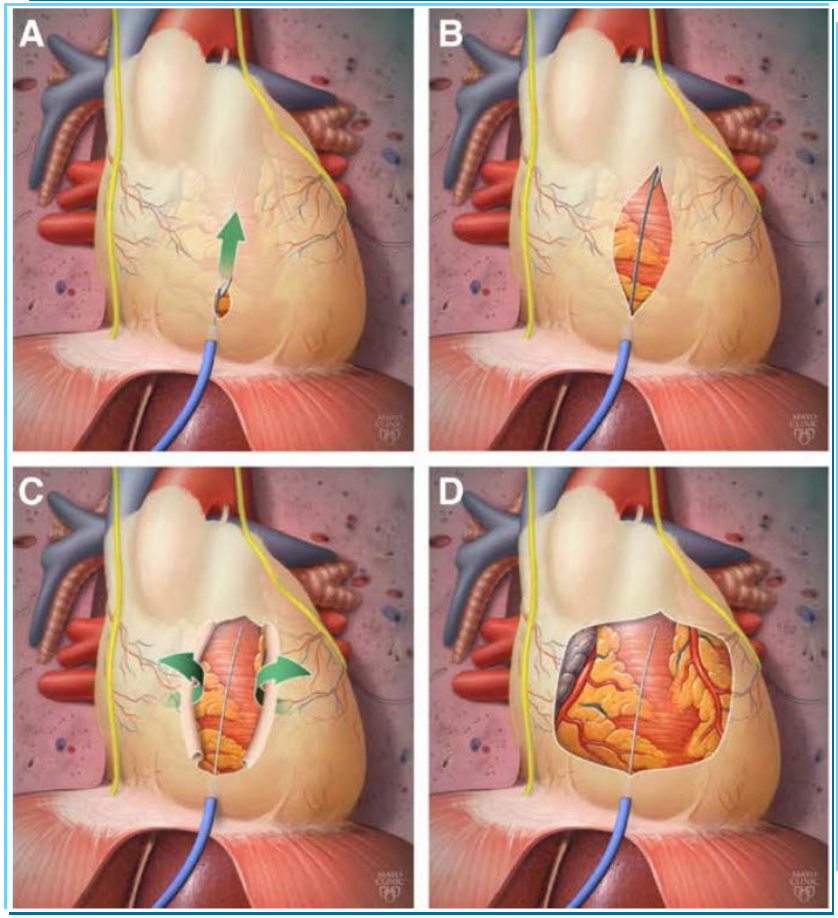


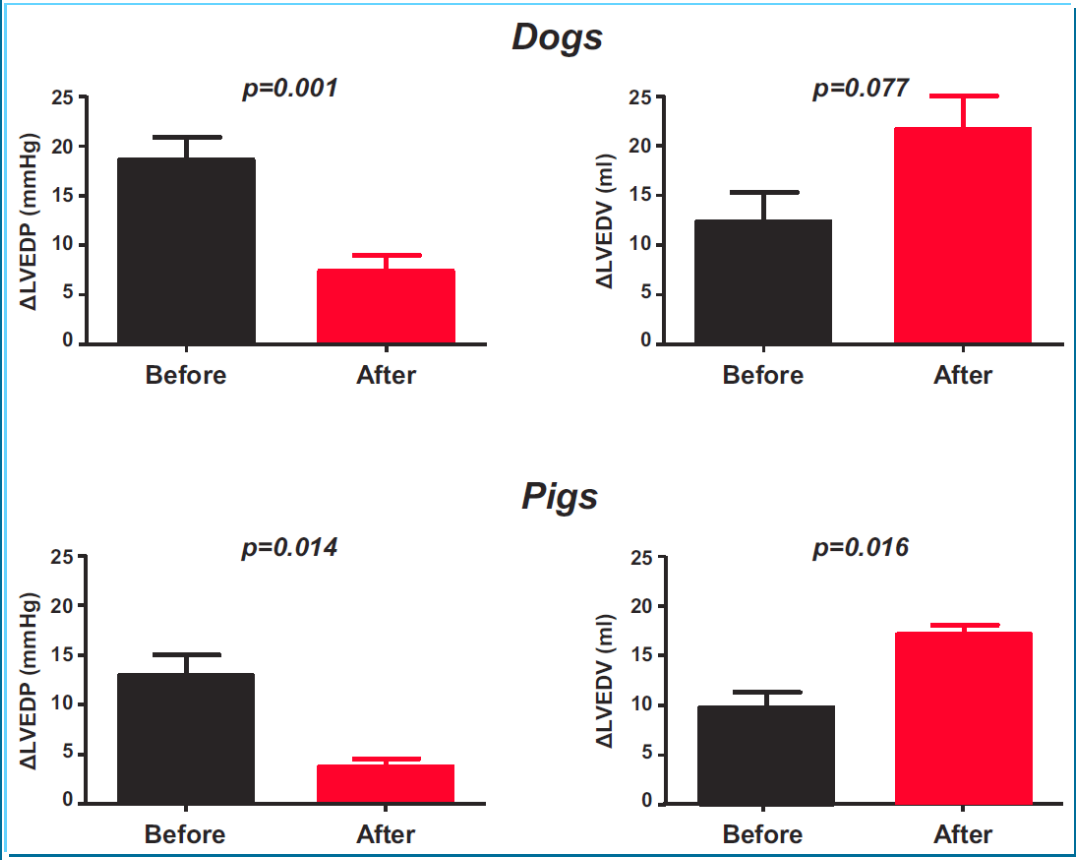
Masaru-Obokata Circulation 2017

Percutaneous Pericardial Resection

A Novel Potential Treatment for Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD; Rickey E. Carter, PhD; Vojtech Melenovsky, MD, PhD; Christopher V. DeSimone, MD, PhD; Prakriti Gaba, BS; Ammar Killu, MBBS; Niyada Naksuk, MD; Lilach Lerman, MD, PhD; Samuel J. Asirvatham, MD





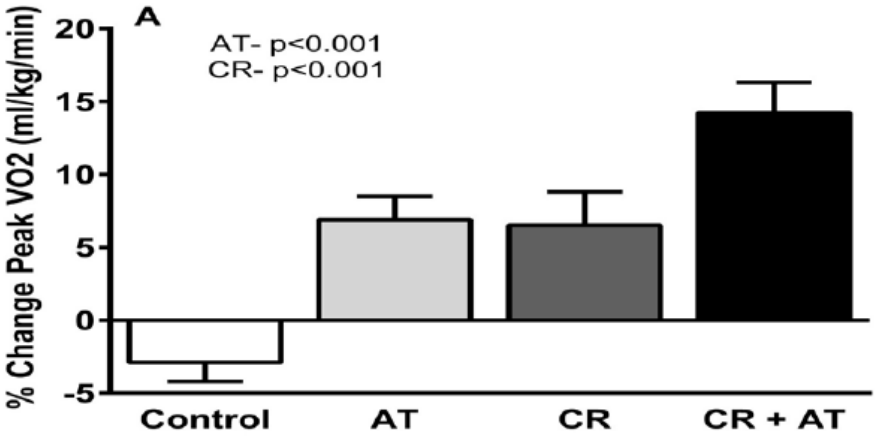
Borlaug Circ HF 2017

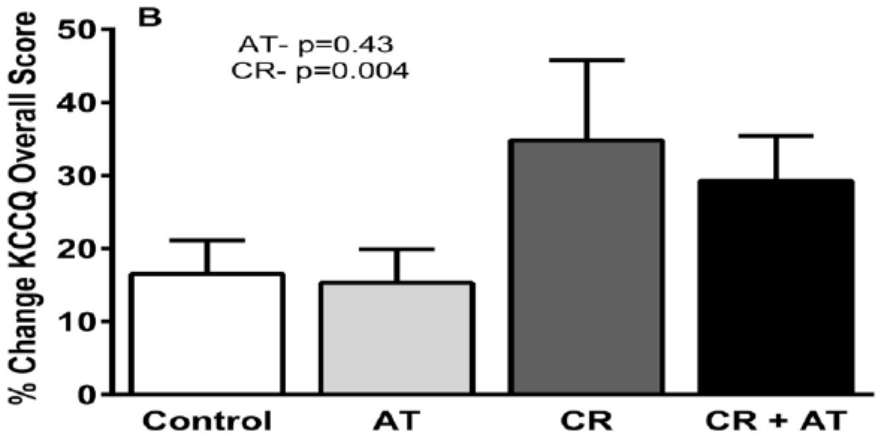
Original Investigation

Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction

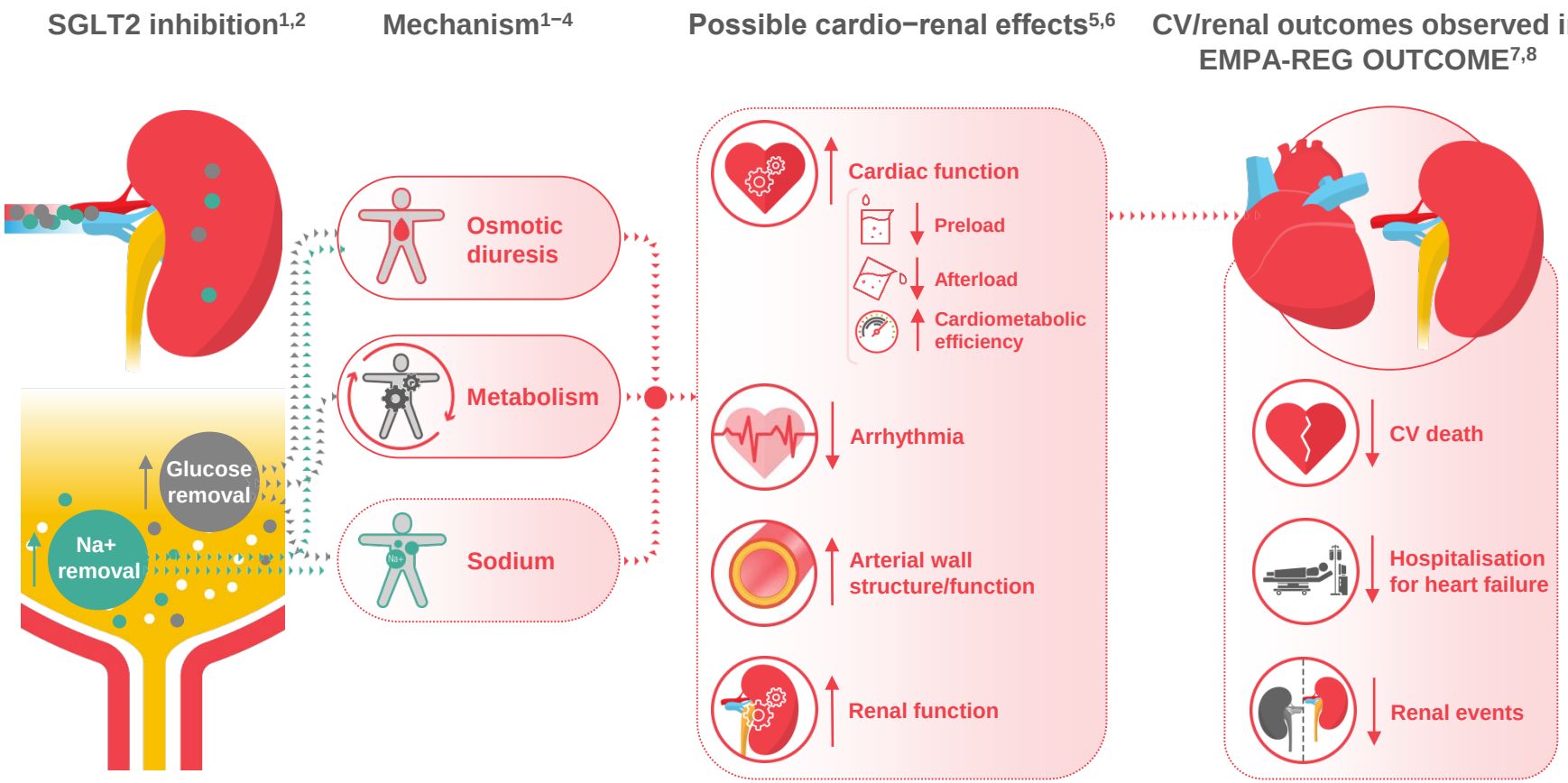
A Randomized Clinical Trial

Dalane W. Kitzman, MD; Peter Brubaker, PhD; Timothy Morgan, PhD; Mark Haykowsky, PhD; Gregory Hundley, MD; William E. Kraus, MD; Joel Eggebeen, MS; Barbara J. Nicklas, PhD





Role for SGLT2i: EMPEROR-Preserved



SGLT2, sodium-glucose co-transporter-2

1. Heise T *et al. Diabetes Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Zinman B *et al. N Engl J Med* 2015;373:2117; 8. Wanner C *et al. N Engl J Med* 2016;375:323

Empagliflozin is not indicated for the treatment of heart failure or renal disease; empagliflozin is not indicated in all countries for CV risk reduction.

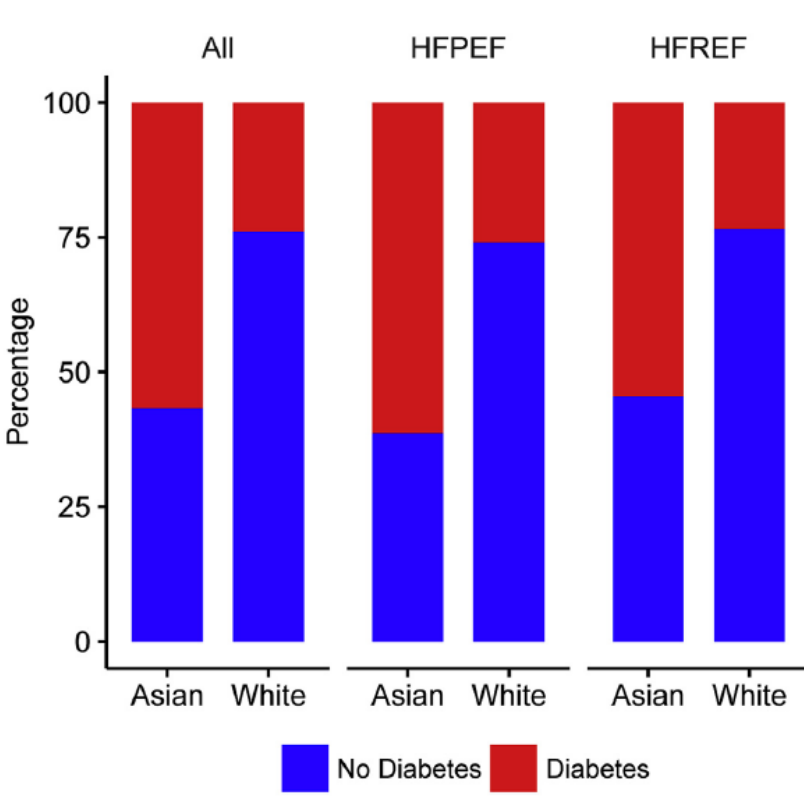
The pathways shown represent not yet proven hypotheses and may not apply to individual patients

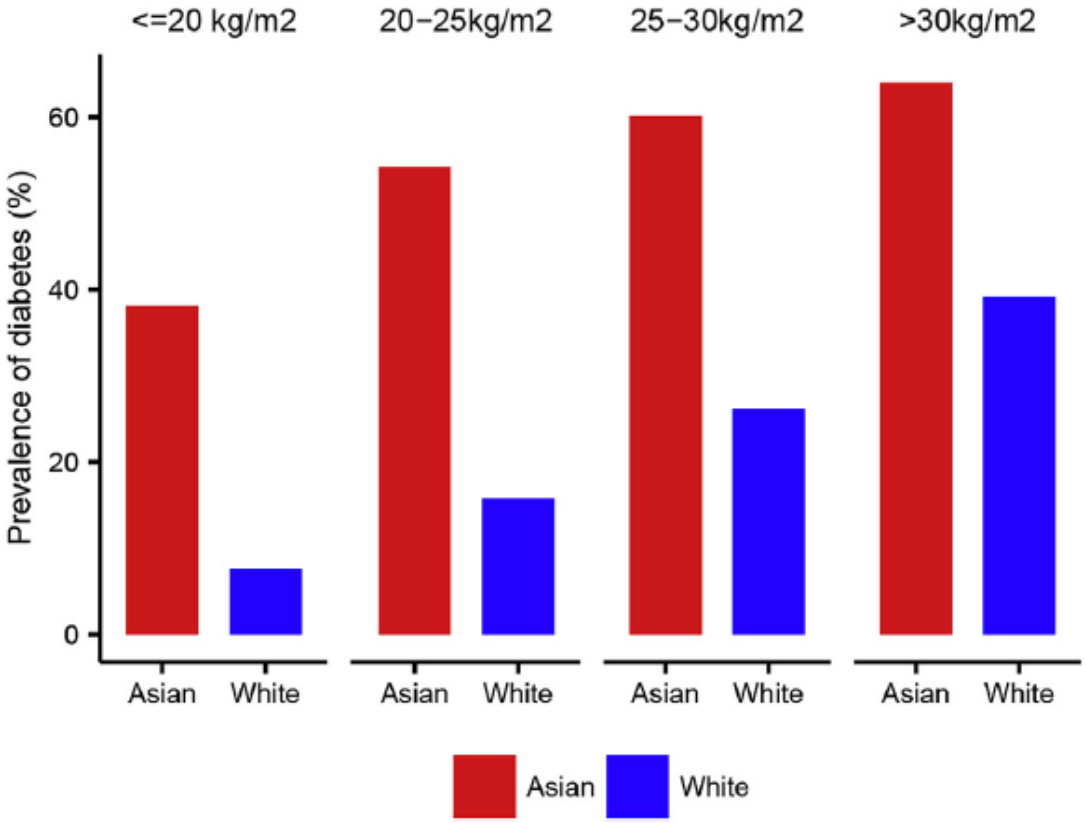
The effects shown for renal function is based on the long-term results of empagliflozin versus placebo in EMPA-REG OUTCOME[8]

EMPEROR HEART FAILURE STUDIES

Asian vs White HF

Singapore Asians vs Swedish whites

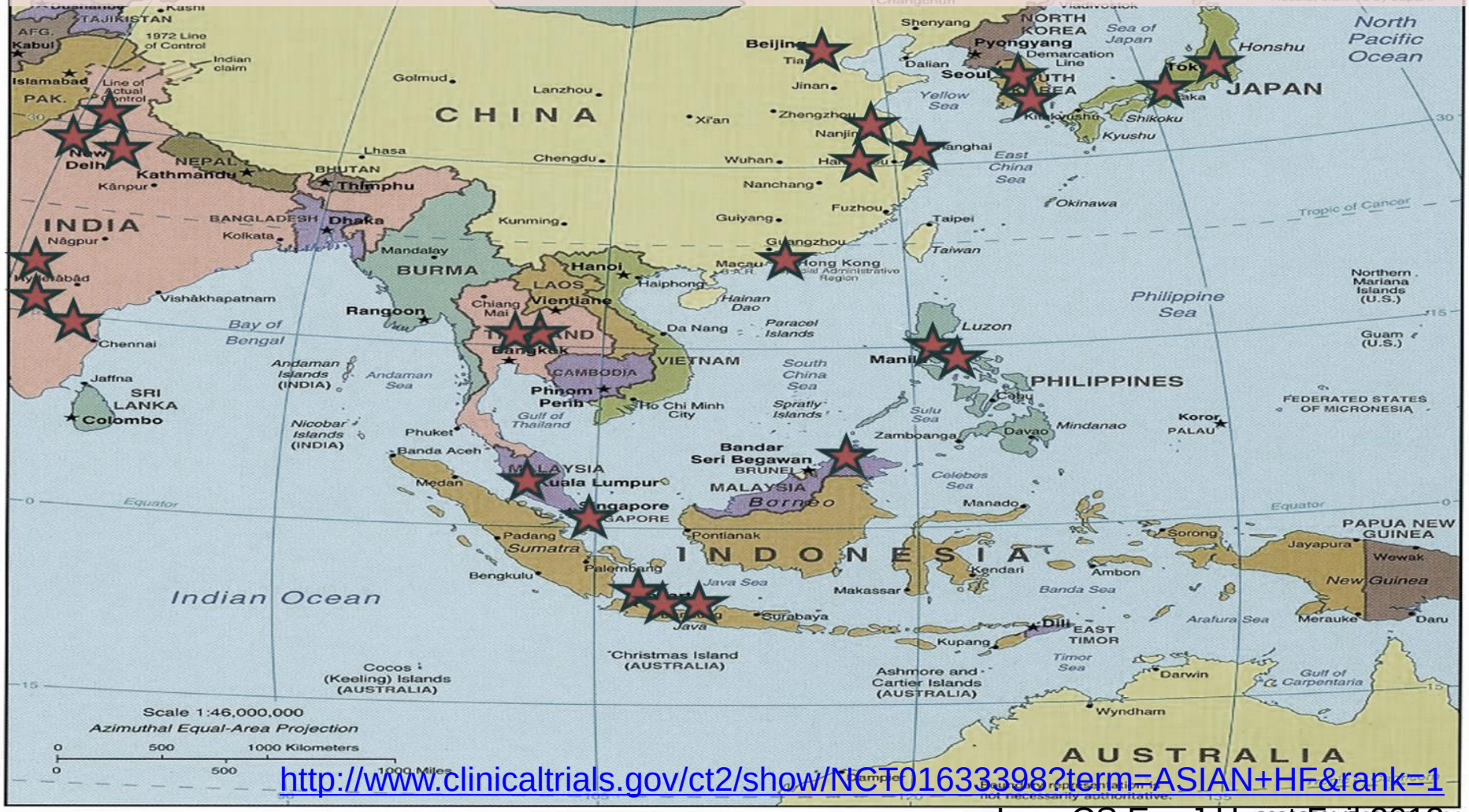




Bank, … Lam. JACC HF 2016

ASIAN-HF Registry

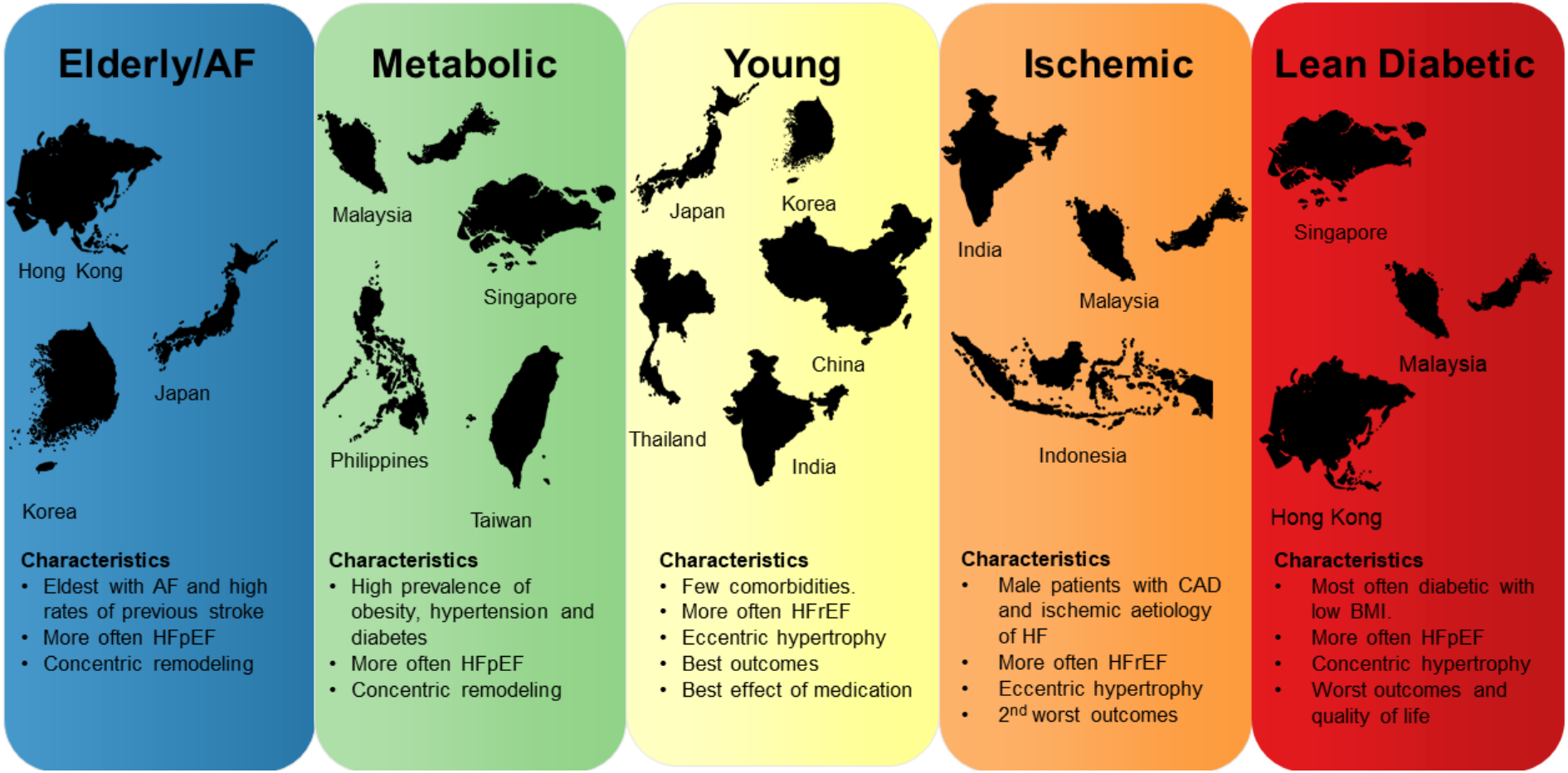
Prospective multinational (11 regions), multicenter (46 sites), observational study of Asian patients with Stage C HF; all with detailed characterization (echo, ECG) and adjudicated outcomes



http://www.clinicaltrials.gov/ct2/show/NCT01633398?term=ASIAN+HF&rank=1

Lam CS Eur J Heart Fail 2013

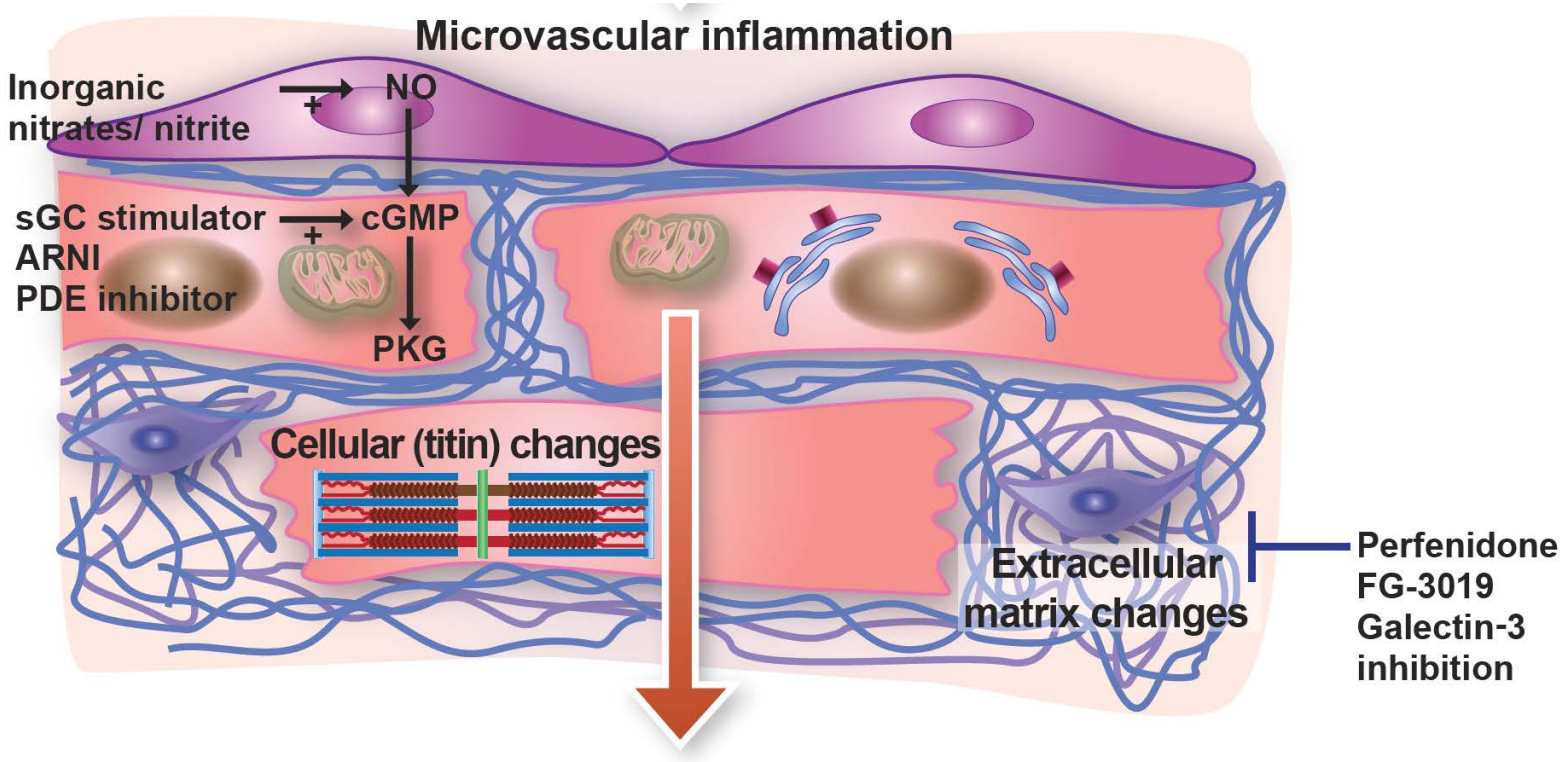
Comorbidity clusters in ASIAN-HF



Tromp PLOS Medicine 2018

Potential targets in HFpEF

1. Hemodynamic targets
2. Molecular targets



Lam, Voors, de Boer, Solomon, van Veldhuisen Eur Heart J 2018

Microvascular dysfunction in heart failure with preserved ejection fraction (HFpEF): Evidence from PROMIS-HFpEF

Carolyn S. P. Lam, Sanjiv J. Shah, Sara Svedlund, Antti Saraste, Camilla Hage, Ru San Tan, Maria Lagerström Fermer, Malin A. Broberg, Li-Ming Gan, Lars H. Lund

National Heart Centre Singapore & Duke-National University of Singapore (CSPL, RST); University Medical Centre Groningen, the Netherlands (CSPL); Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (SJS and LBN); Department of Clinical Physiology, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden (SS); Heart Center, Turku University Hospital and University of Turku, Turku, Finland (AS); Cardiology Unit and Heart and Vascular Theme, Karolinska Institutet, Department of Medicine, Stockholm, Sweden (CH and LL); Cardiovascular, Renal and Metabolism Translational Medicines Unit, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden (MLF, MAB, and LMG); Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden and Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden (LMG)

Aims

Prospective multicenter PRevalence Of Microvascular dySfunction in HFpEF (PROMIS-HFpEF) study

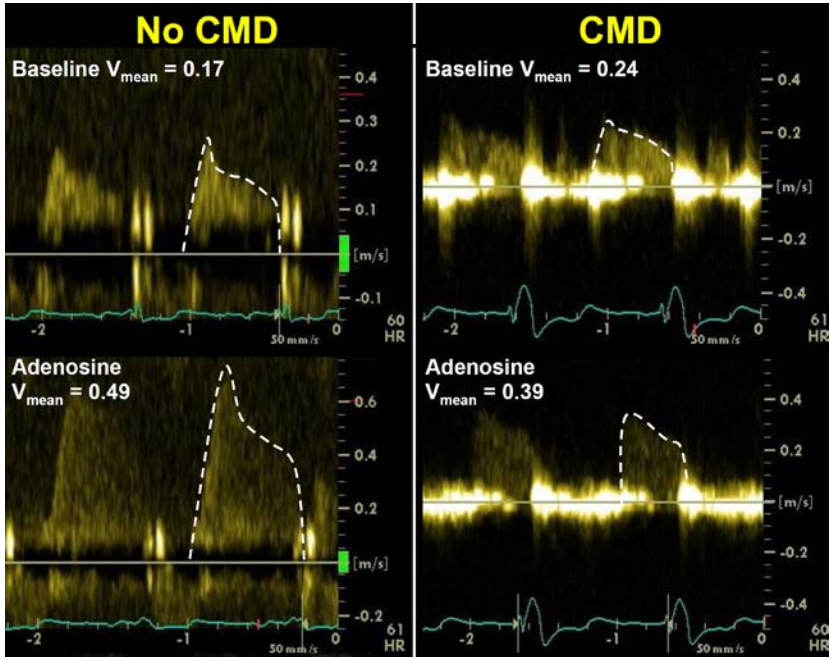
- To investigate the prevalence of CMD and its association with systemic endothelial dysfunction, HF severity, and myocardial dysfunction in a well-defined, prospective HFpEF population using a comprehensive functional imaging approach

Methods

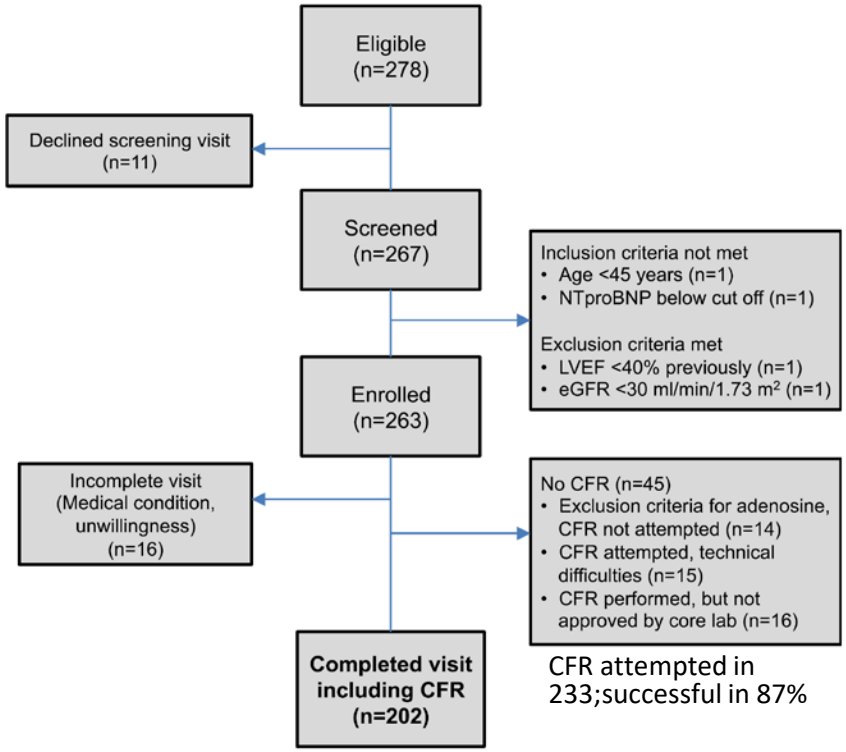
- Prospective patients with confirmed chronic HFpEF from Sweden, US, Finland and Singapore
- Major inclusion criteria:
  - Signs & symptoms of HF; stable NYHA II-IV
  - EF ≥ 40%
  - At least one of (1) ↑natriuretic peptides;[1] (2) HF hospitalization in last 12 months with LVH/LAE; (3) PCWP >15 mmHg (rest) or >25 mmHg (exercise); or (4) E/e' > 15
- Major exclusion criteria:
  - Significant unrevascularized epicardial CAD
  - Primary cardiomyopathy
  - Hemodynamically significant valve disease
  - Any history of EF<40%

Methods

- Coronary flow reserve (CFR) by transthoracic Doppler echo coronary flow velocity at rest and with adenosine
  - Read by core lab
  - CMD defined as CFR<2.5
- Systemic microvascular function by peripheral arterial tonometry (EndoPAT) reactive hyperemia index (RHI)
- Myocardial function by echo tissue Doppler and speckle-tracking



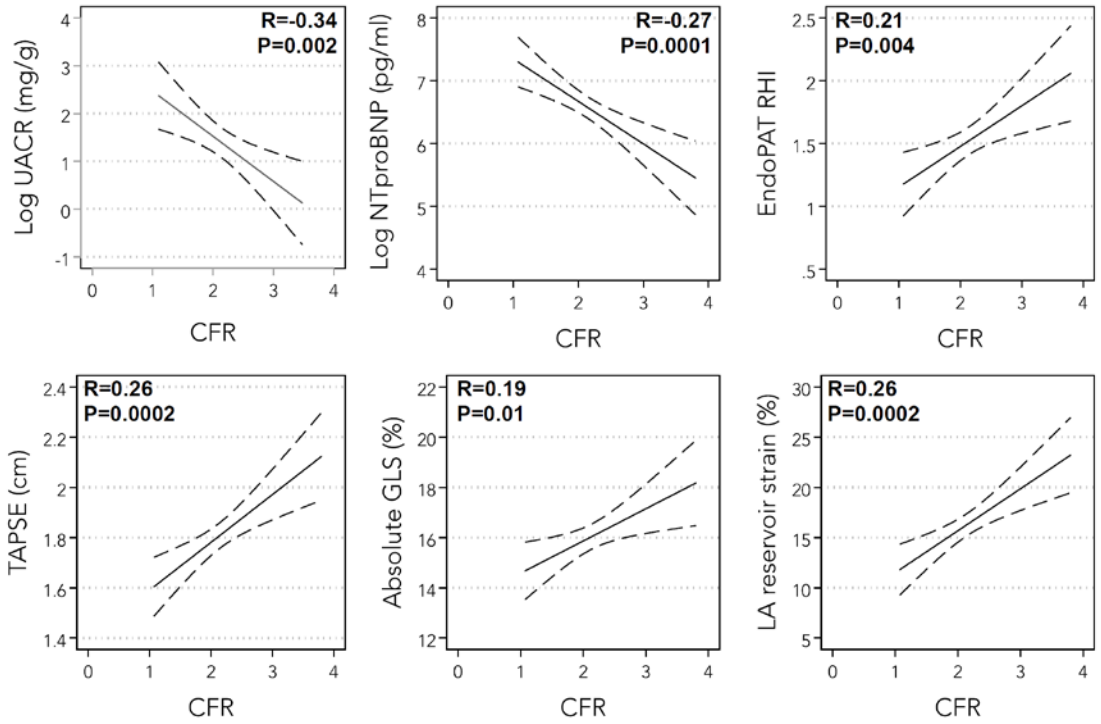
Results



Prevalence of CMD among 202 HFpEF with CFR = 75% (95% CI 69-81%)

- Mean (SD) CFR = 2.13 (0.51)
- Median (IQR) CFR = 2.08 (1.78-2.50)

Results



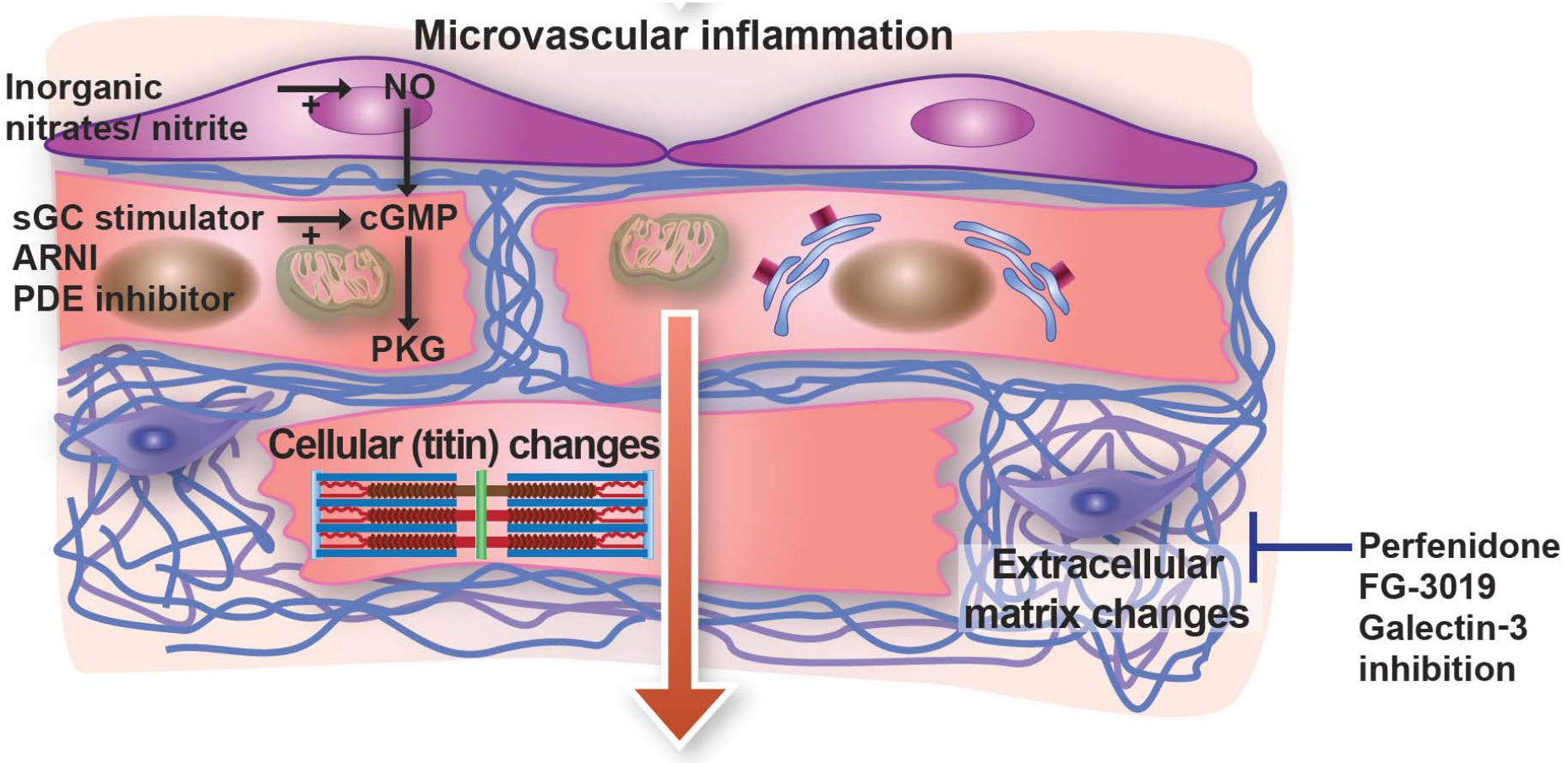
After multivariable adjustment[1] worse CFR was related to:

- higher UACR & NT-proBNP
- lower RHI, TAPSE, RV strain

PROMIS-HFpEF: Conclusions

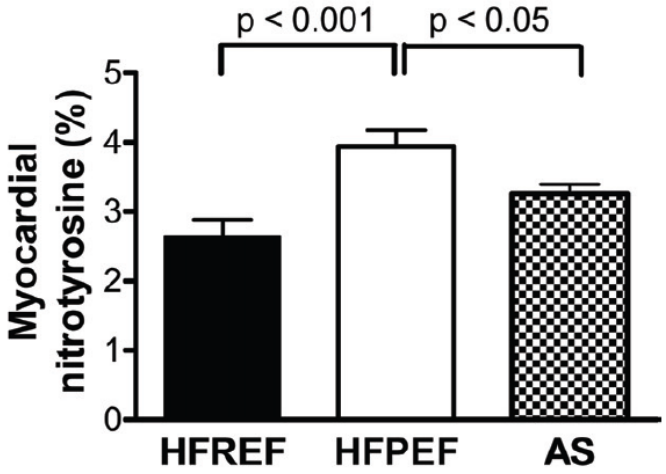
- Largest prospective multicenter study of CMD in HFpEF
- High (75%) prevalence of CMD in HFpEF in the absence of unrevascularized macrovascular CAD
- CMD is associated with HF severity (↑NT-proBNP), systemic endothelial dysfunction (↓ EndoPAT RHI, ↑UACR), and cardiac dysfunction (↓LV, LA, RV strain)
- Microvascular dysfunction may be a promising composite risk marker and therapeutic target in HFpEF

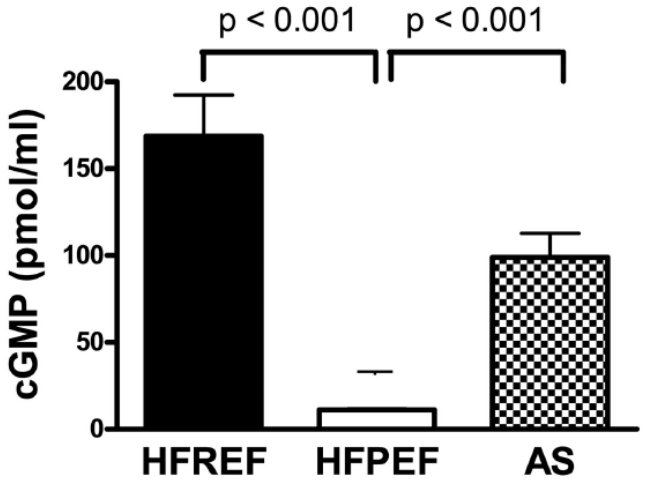
Molecular targets

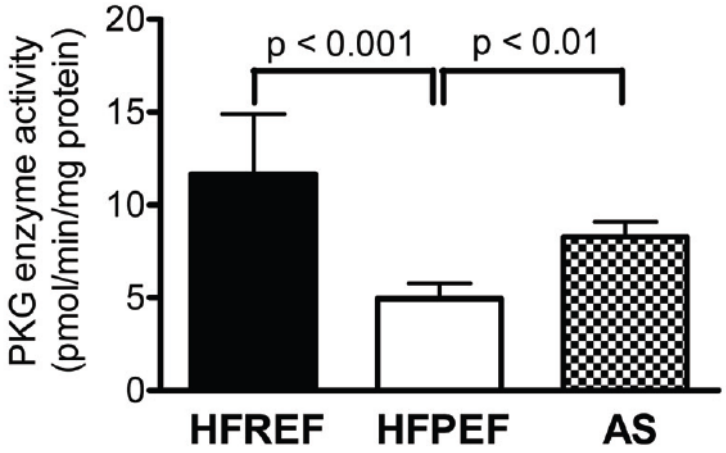


Lam, Voors, de Boer, Solomon, van Veldhuisen Eur Heart J 2018

Cardiomyocyte stiffness & low myocardial cGMP-PKG activity





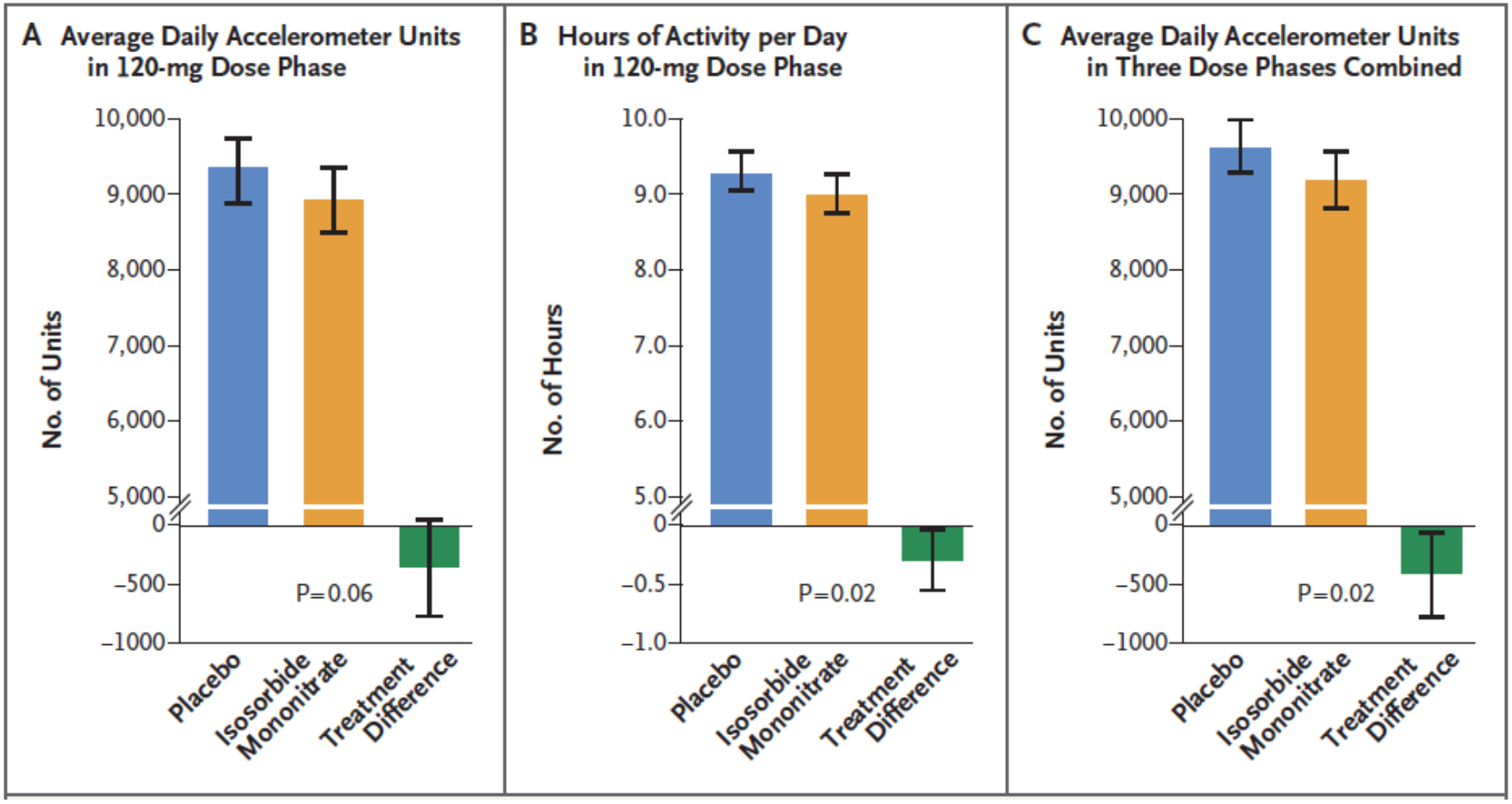


Franssen JACC HF 2015
Van Heerebeek Circulation 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction



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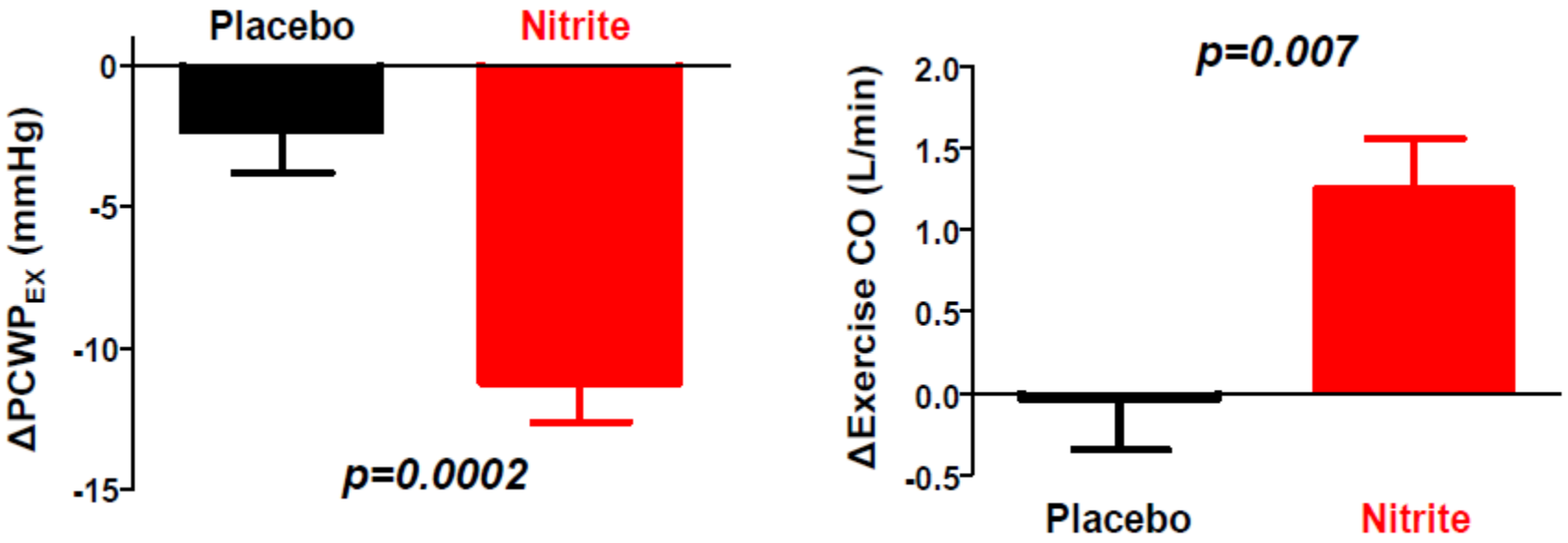
http://dx.doi.org/10.1016/j.jacc.2015.07.067

Sodium Nitrite Improves Exercise Hemodynamics and Ventricular Performance in Heart Failure With Preserved Ejection Fraction

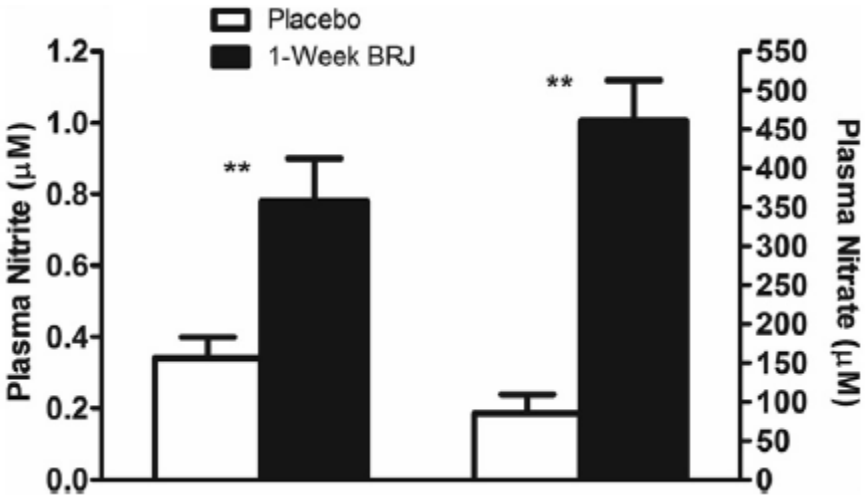
Barry A. Borlaug, MD, Katlyn E. Koepp, BS, Vojtech Melenovsky, MD, PhD

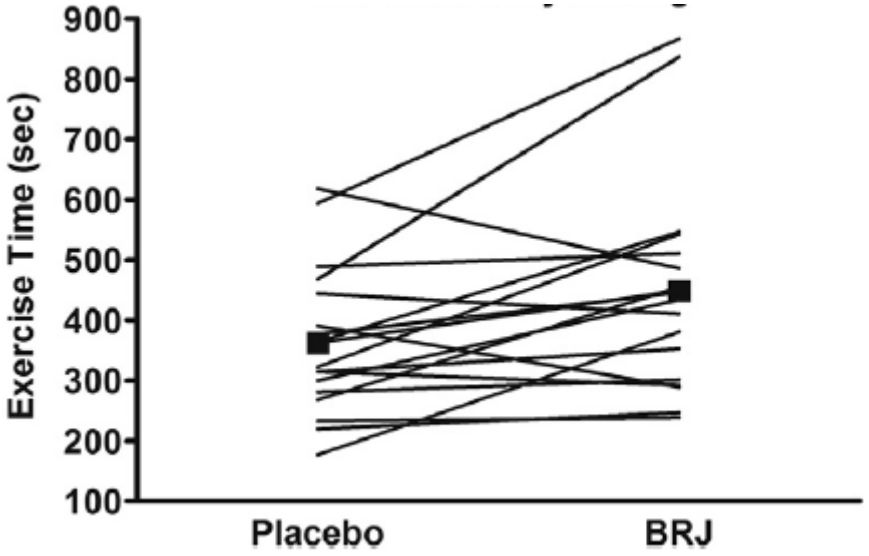


One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction

Joel Eggebeen, MS,[a] Daniel B. Kim-Shapiro, PhD,[b,c] Mark Haykowsky, PhD,[d] Timothy M. Morgan, PhD,[e] Swati Basu, PhD,[b,c] Peter Brubaker, PhD,[c,f] Jack Rejeski, PhD,[c,f] Dalane W. Kitzman, MD[a,c]

JACC: HEART FAILURE CME





HF AND TRANSPLANTATION

INDIE-HFpEF

Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF

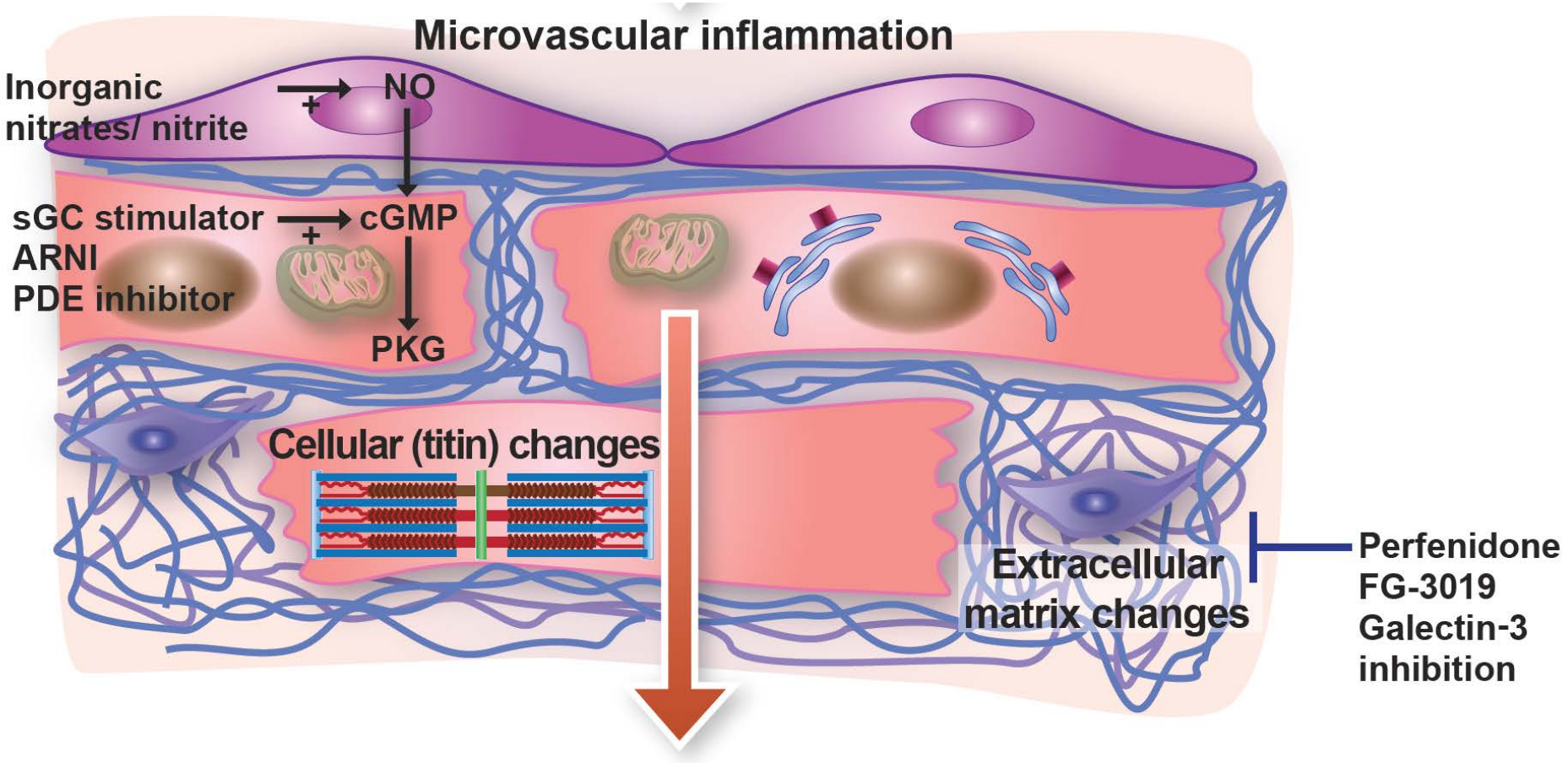
Assessment of aerobic capacity in patients with HF with preserved ejection fraction treated with inorganic nitrite.

Design:	randomized, crossover-assignment, placebo-controlled
Patients:	105
Centers:	20
Country:	United States

RESULTS: Compared with placebo, nitrite did not affect maximum exercise ($P = .27$) nor improve daily activity levels either by arbitrary units (5,503 vs. 5,497, respectively; $P = .91$) or relative to the baseline phase (97% vs. 100%, respectively; $P = .6$). Nitrite did not improve quality of life ($P = .32$), natriuretic peptide levels ($P = .74$) or NYHA functional class ($P = .43$). There was a trend toward a nonsignificant reduction in systolic BP with nitrite vs. placebo (121 mm Hg vs. 124 mm Hg; $P = .1$). There was no reduction in estimated filling pressures.

Borlaug BA, et al. Late-Breaking Clinical Trials III. *Presented at: American College of Cardiology Scientific Session; March 10-12, 2018; Orlando, Fla.*

Molecular targets

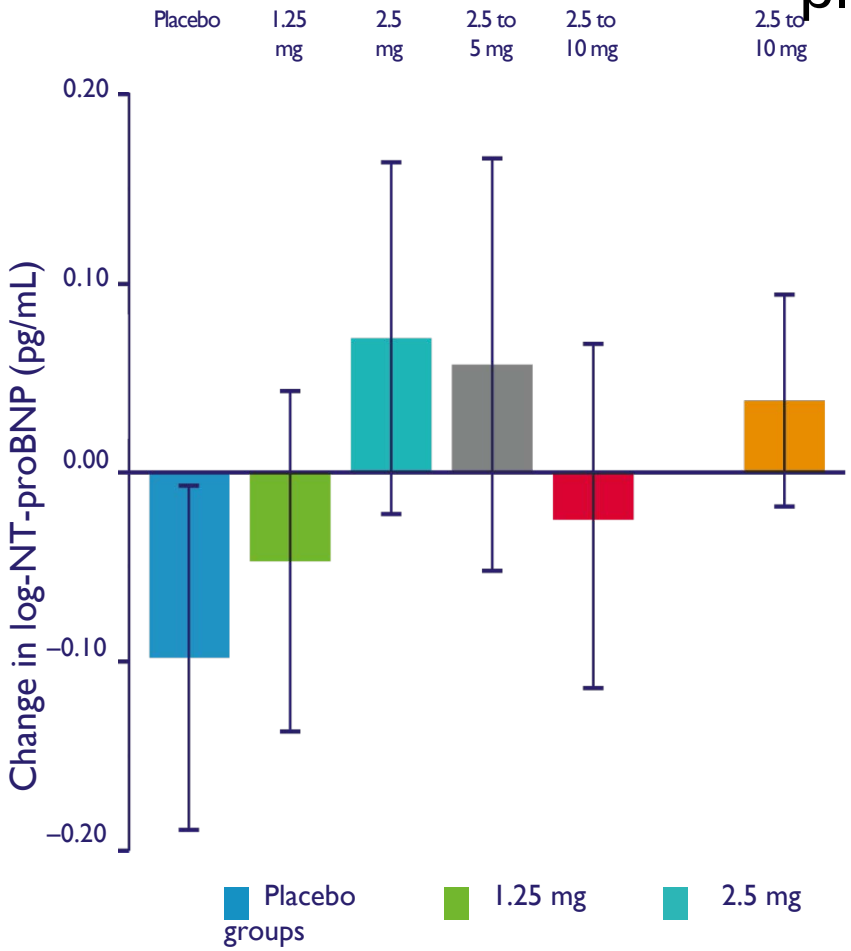


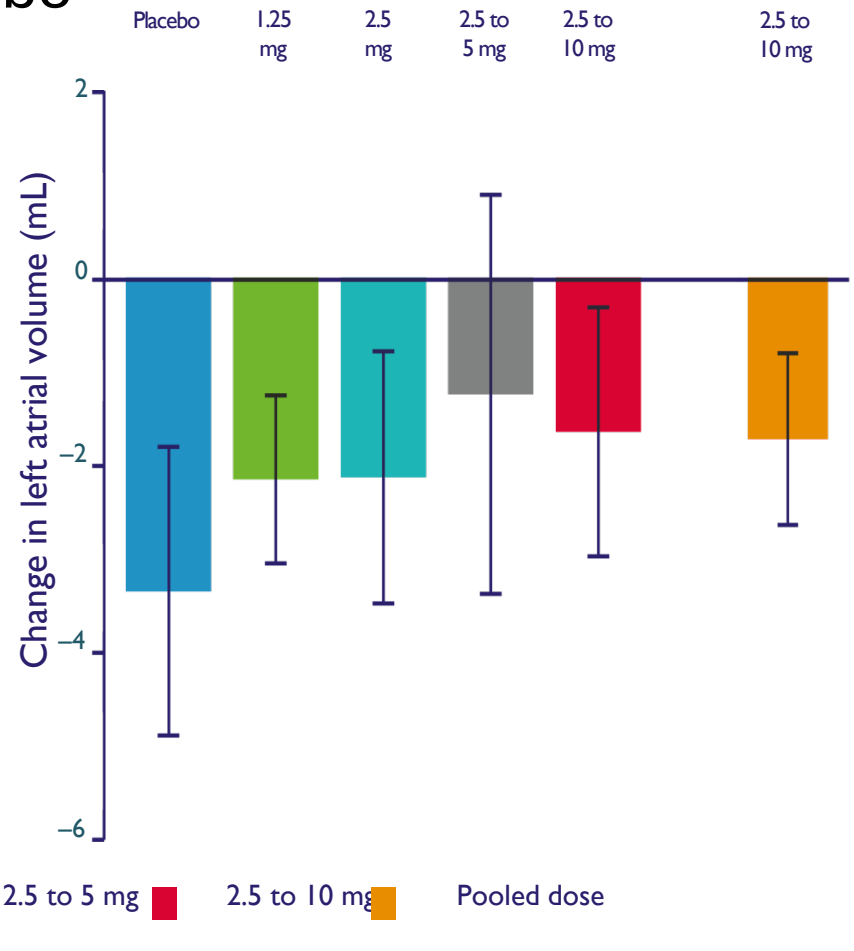
Lam, Voors, de Boer, Solomon, van Veldhuisen Eur Heart J 2018

SOCRATES-Preserved

Primary endpoints

No effect on log NT-proBNP or LAV at 12 weeks vs placebo





Placebo groups | 1.25 mg | 2.5 mg | 2.5 to 5 mg | 2.5 to 10 mg | Pooled dose

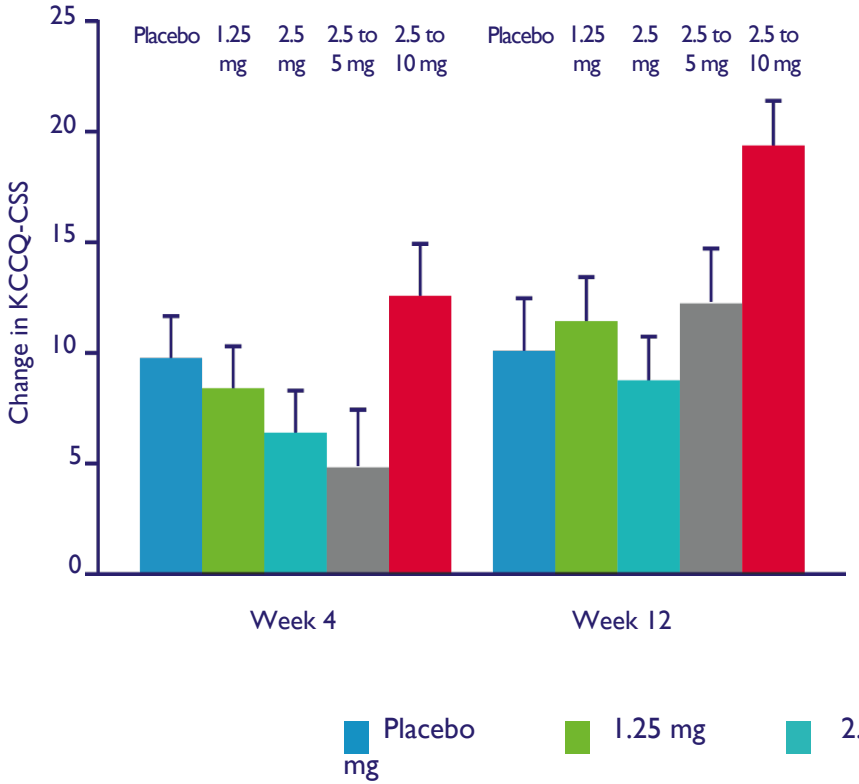
Data are mean ± standard error for the per-protocol analysis set

Presented by B. Pieske at HF Congress 2016

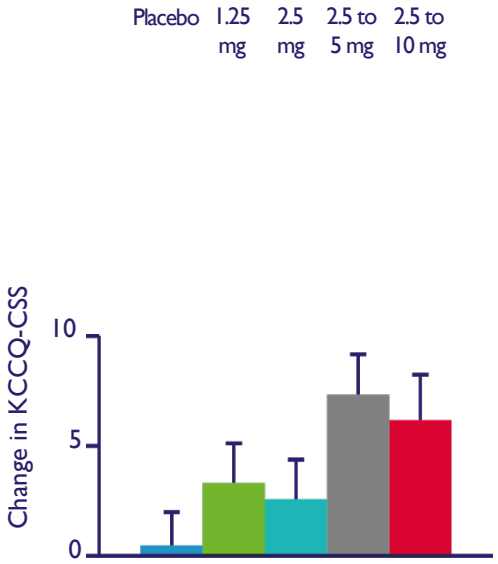
SOCRATES-Preserved
Pre-specified exploratory endpoint: Patient-reported health status

SOCRATES PRESERVED

Change from baseline in KCCQ clinical summary score



Change from week 4 in KCCQ clinical summary score at week 12



Minimum Clinically Important Difference = 5 points

Placebo mg | 1.25 mg | 2.5 mg | 2.5 to 5 mg | 2.5 to 10

Data are mean ± standard error for the full analysis set excluding those subjects with incorrectly assigned doses

Presented by B. Pieske at HF Congress 2016

Vericiguat in HFpEF

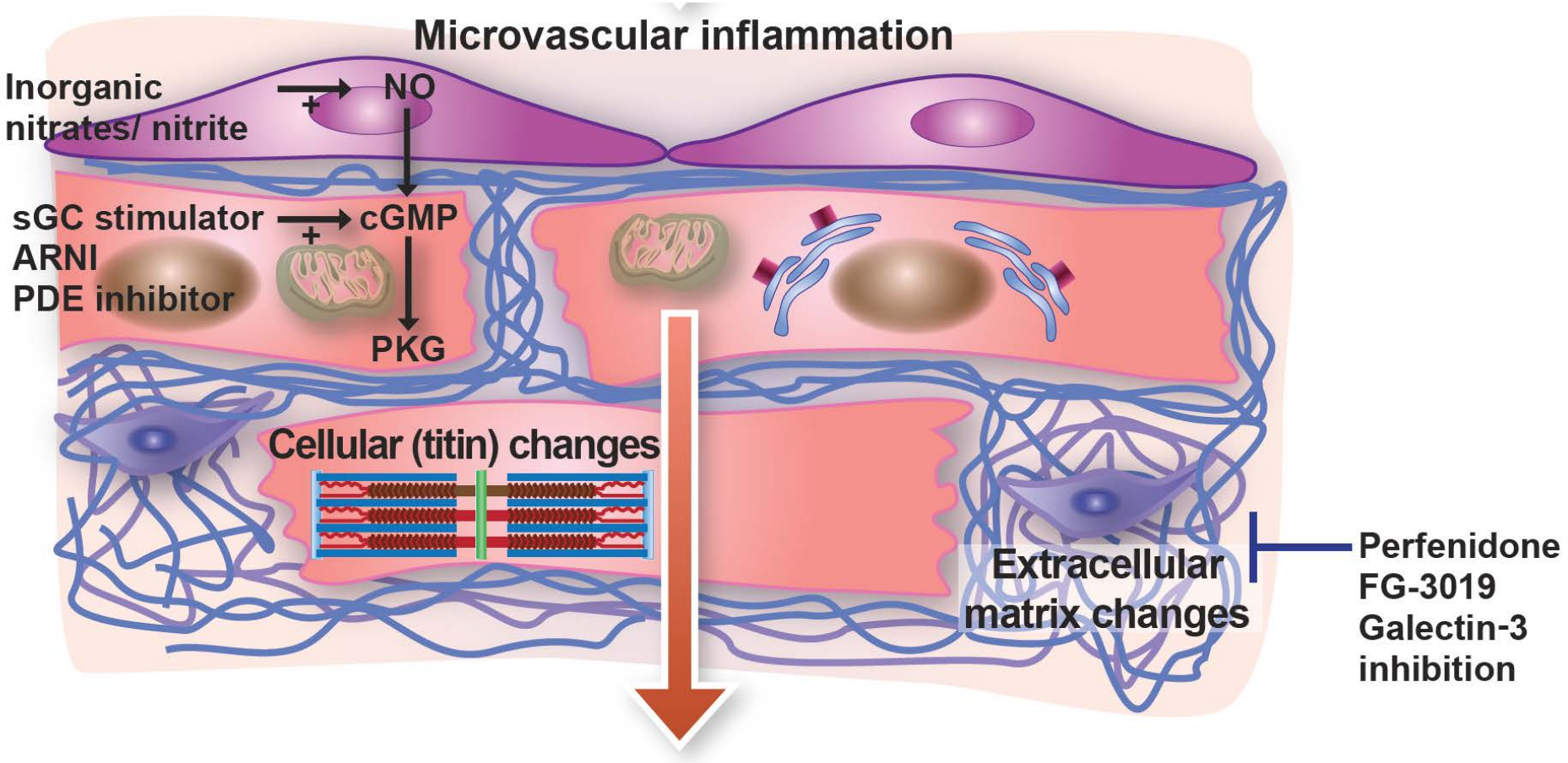
VITALITY-HFpEF
Study Overview and Background

A randomized parallel-group, placebo-controlled, double-blind, multi-center trial to e***V***aluate the eff***I***cacy and safe***T***y of the or***AL*** sGC st***I***mulator vericigua***T*** to improve ph***Y***sical functioning in activities of daily living in patients with HFpEF (***VITALITY-HFpEF***)

NCT03547583

https://clinicaltrials.gov/ct2/show/NCT03547583

Molecular targets



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PARAMOUNT: LCZ696 vs valsartan in chronic HFpEF

- Reduction in NT-proBNP from baseline to Week 12 was significantly greater with LCZ696 (200 mg BID) compared with valsartan (160 mg BID) (p=0.005)

NT-proBNP (geometric mean)	LCZ696 (n=134)	Valsartan (n=132)	LCZ696 vs valsartan
Baseline, pg/mL (95% CI)	783 (670, 914)	862 (733, 1,012)	0.77* (0.64, 0.92) p=0.005
Week 12, pg/mL (95% CI)	605 (512, 714)	835 (710, 981)	

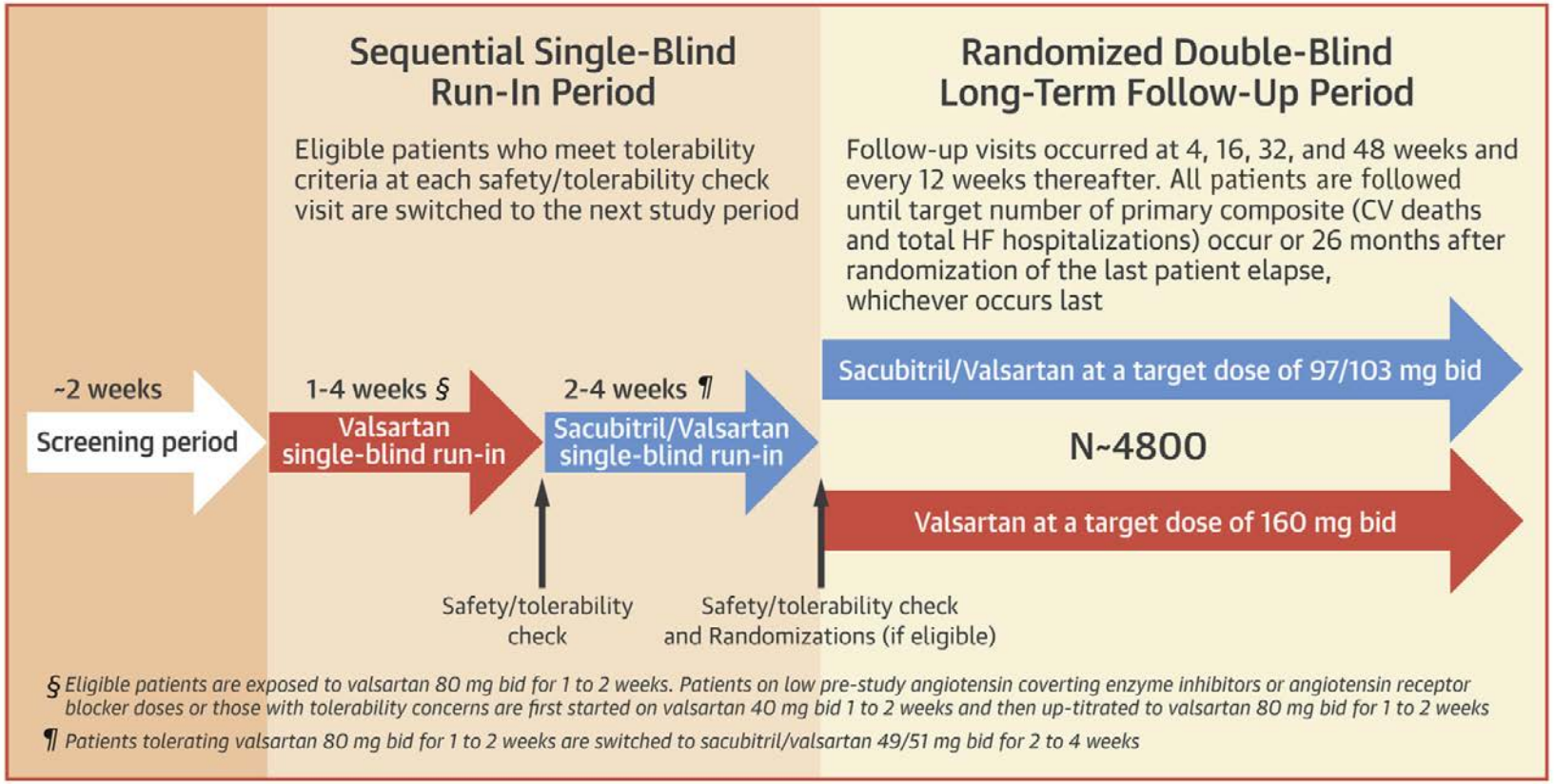
*0.77=ratio of the change from baseline treatment effect between LCZ696 and valsartan. LCZ696 reduced NT-proBNP 23% more than valsartan with a p value of 0.005.

Solomon et al. Lancet 2012;380:1387–95

Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction

Rationale and Design of the PARAGON-HF Trial

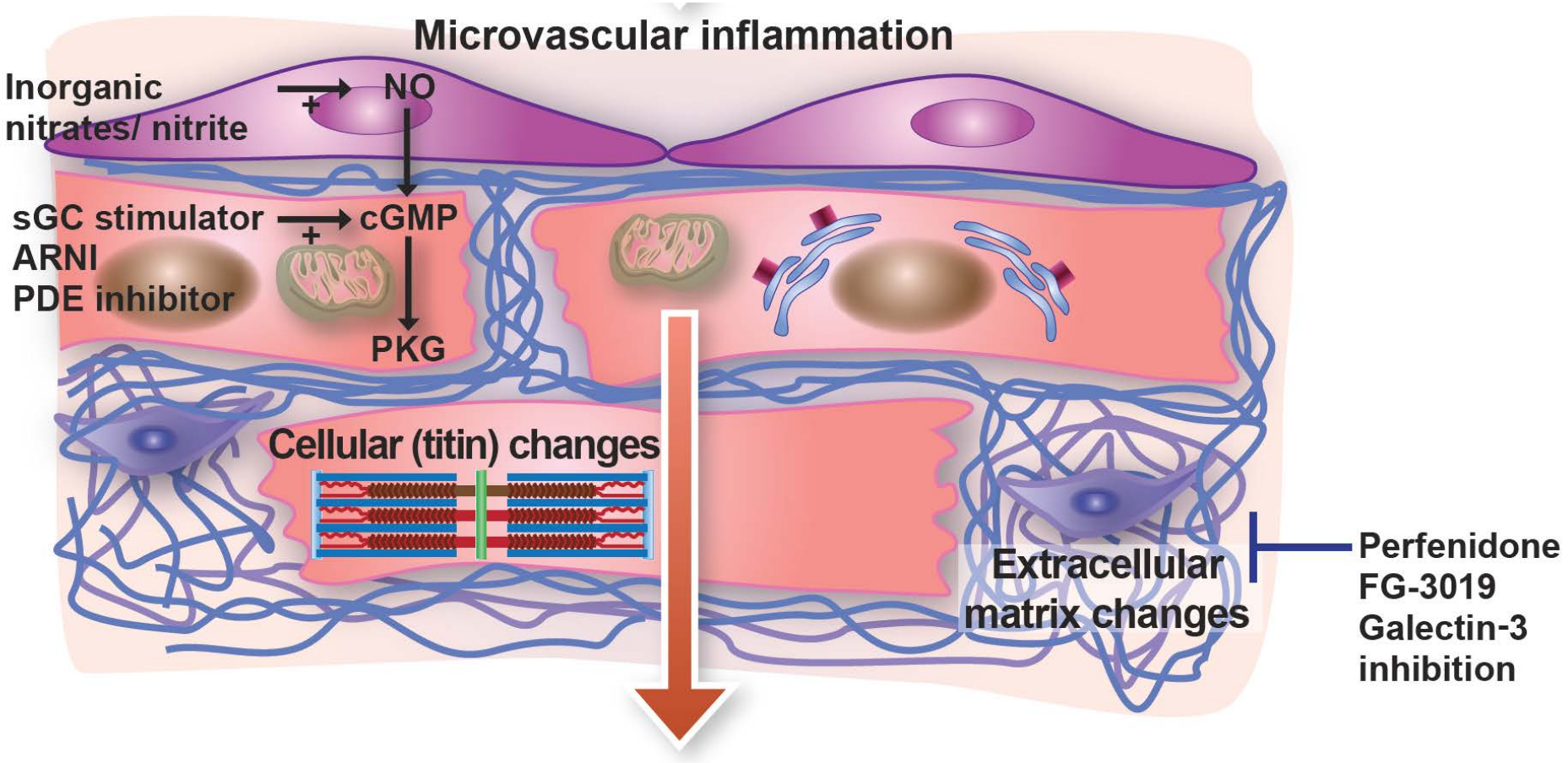
STUDY DESIGN



§ *Eligible patients are exposed to valsartan 80 mg bid for 1 to 2 weeks. Patients on low pre-study angiotensin coverting enzyme inhibitors or angiotensin receptor blocker doses or those with tolerability concerns are first started on valsartan 40 mg bid 1 to 2 weeks and then up-titrated to valsartan 80 mg bid for 1 to 2 weeks*

¶ *Patients tolerating valsartan 80 mg bid for 1 to 2 weeks are switched to sacubitril/valsartan 49/51 mg bid for 2 to 4 weeks*

Molecular targets



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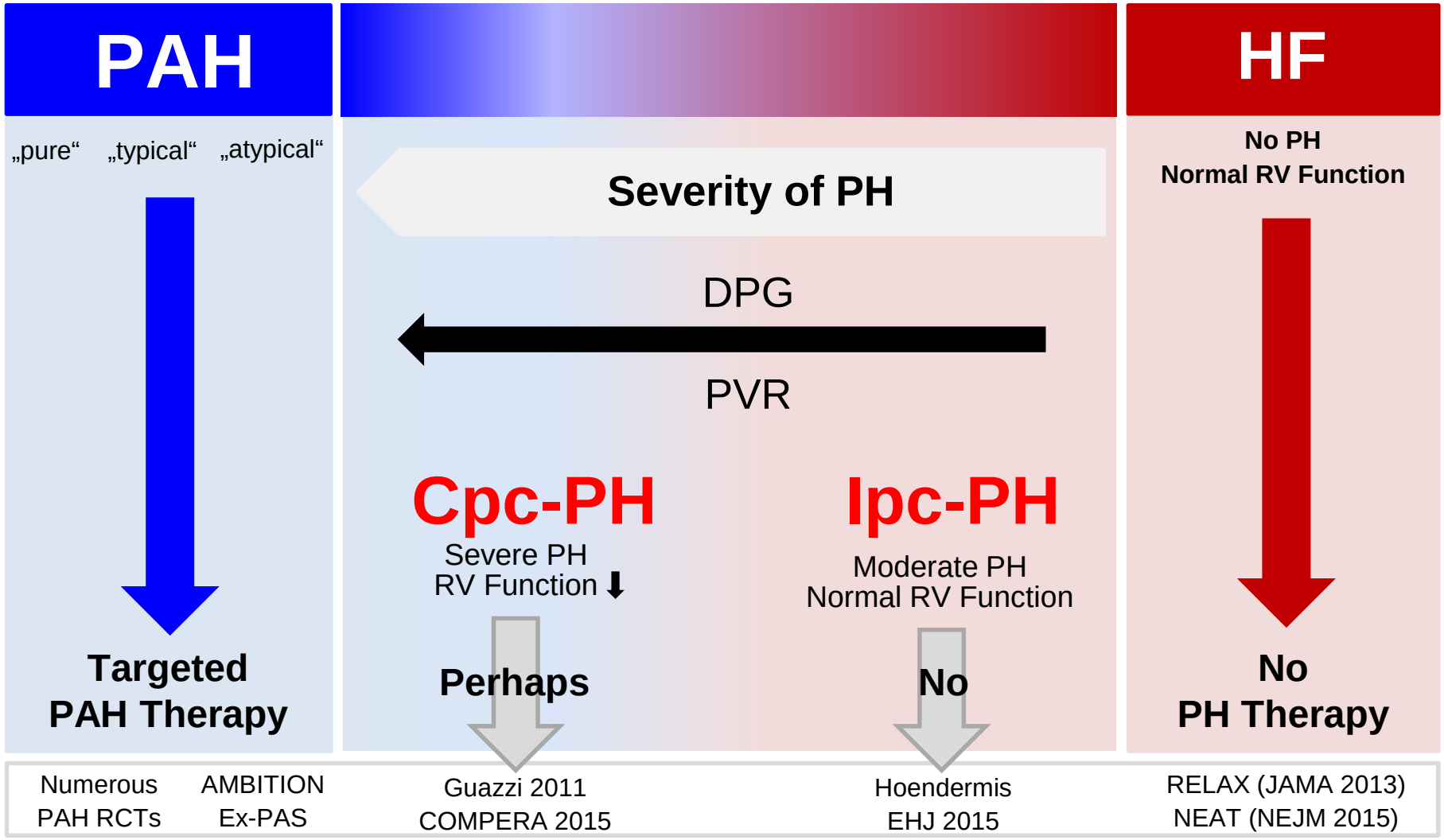
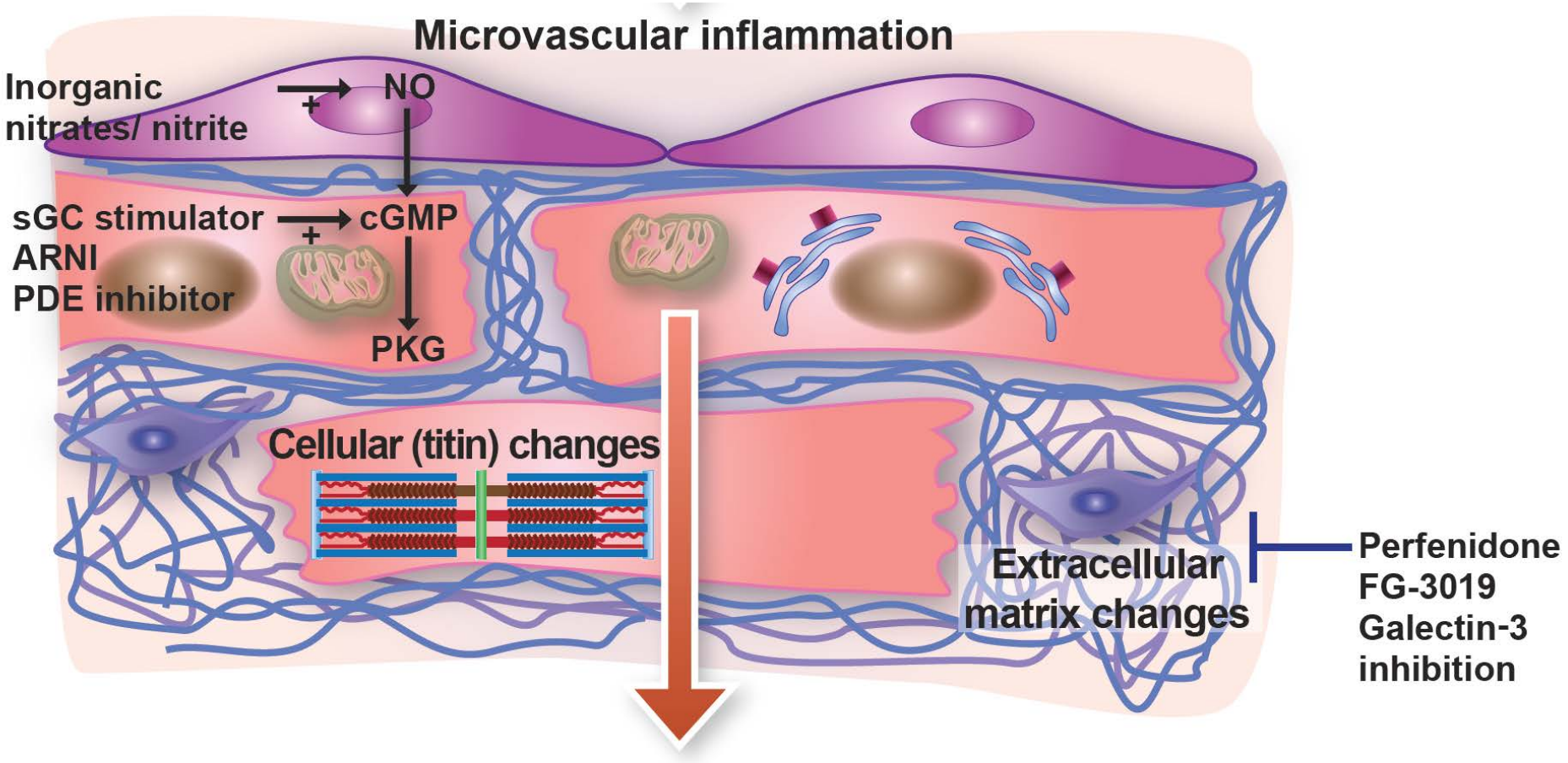
PAH vs. PH in Heart Failure: Spectrum of Phenotypes and Therapeutic Consequences



Cpc-PH: Combined post- and pre-capillary PH
Ipc-PH: Isolated post-capillary PH

Molecular targets



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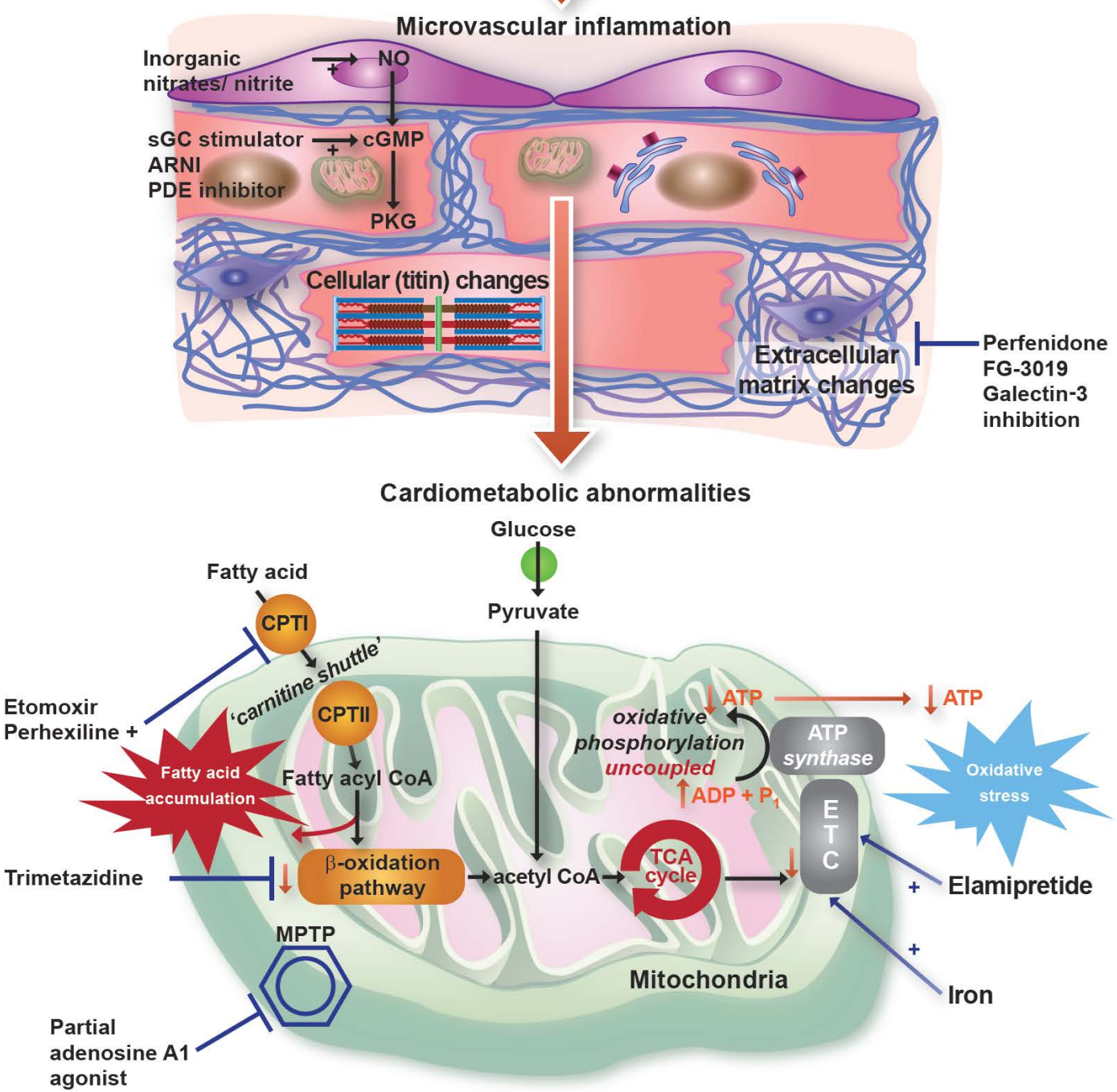

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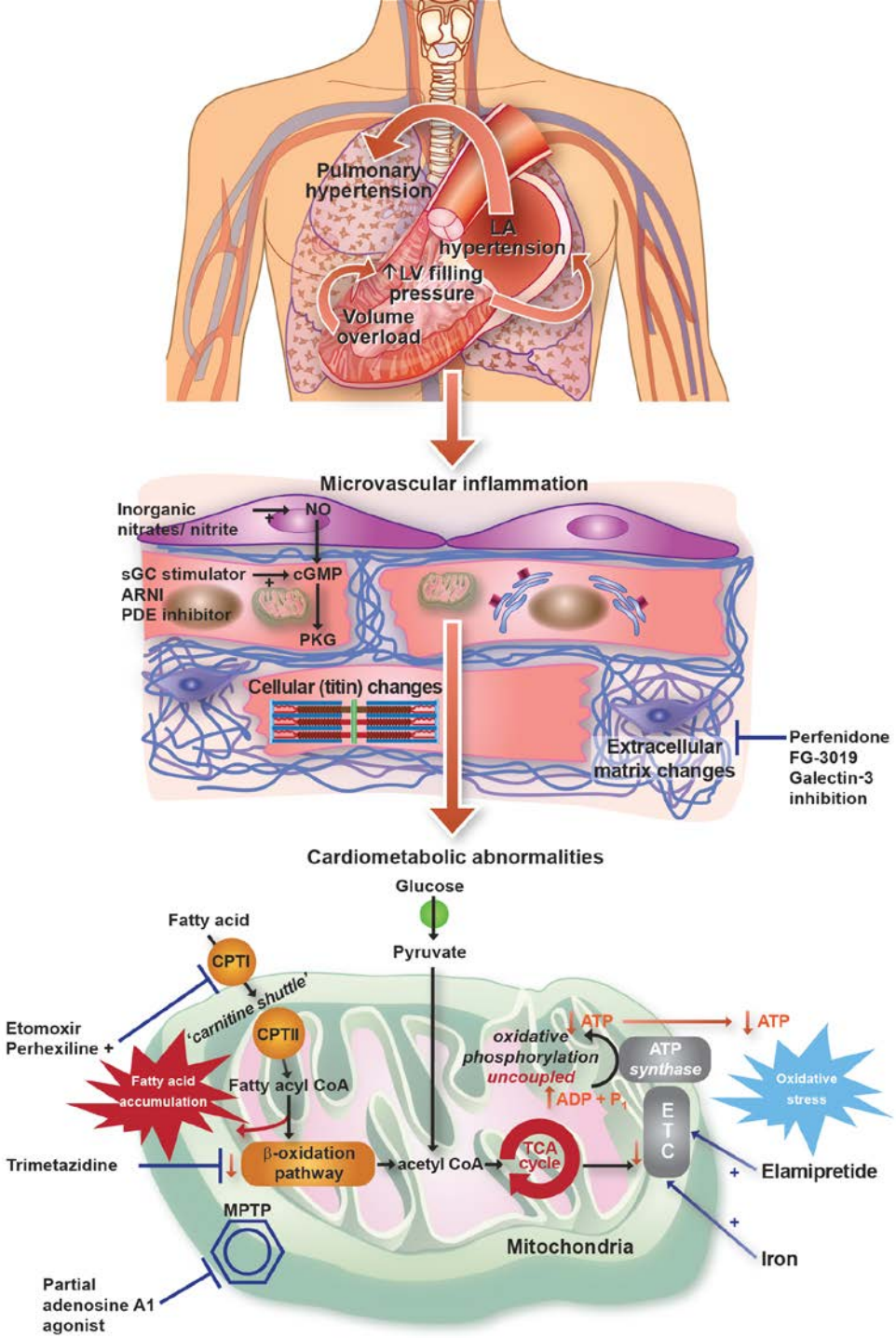

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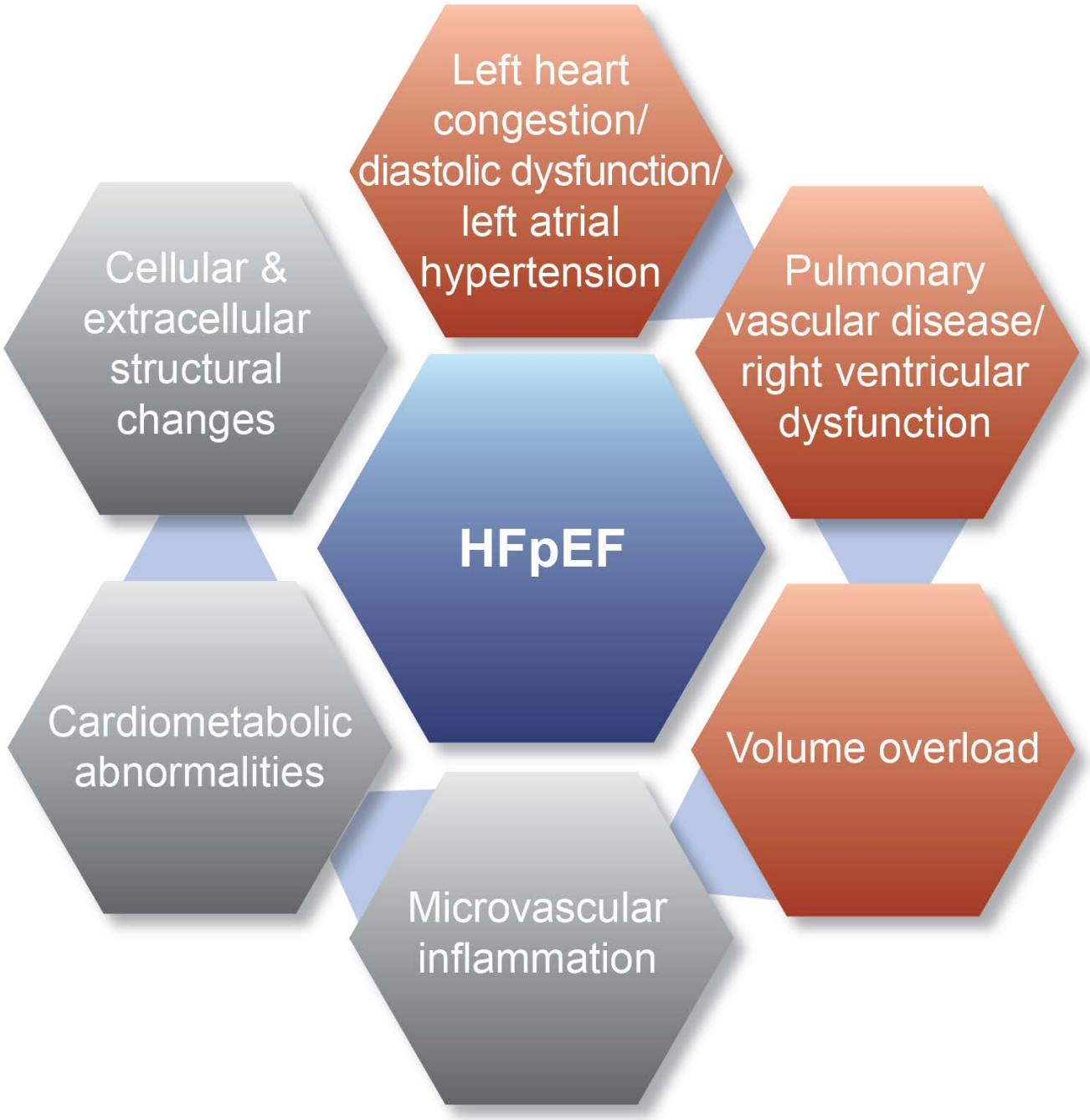

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Thank you