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

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Disclosures

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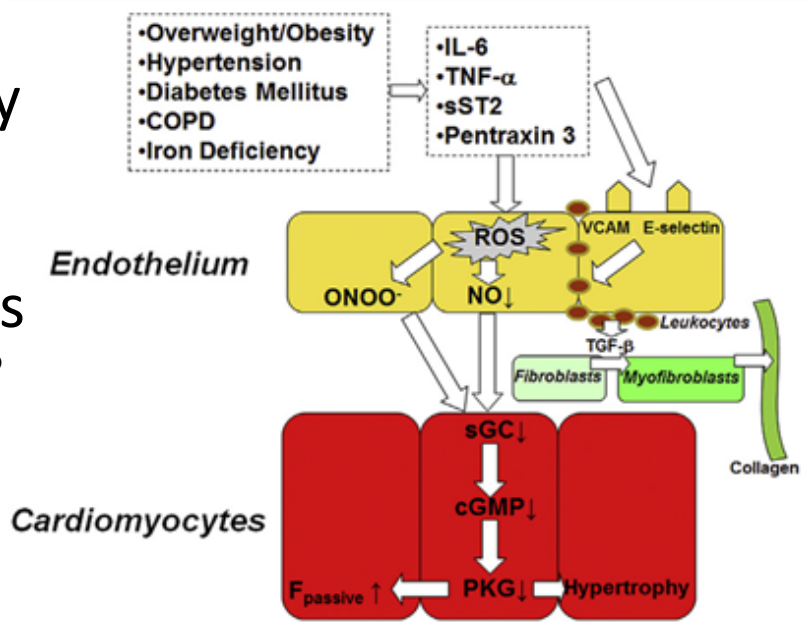
- Consulted for Astra Zeneca, Bayer, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, and Takeda

- PROMIS-HFpEF is an AstraZeneca initiated and sponsored study

Background

- No treatment yet shown to reduce morbidity and mortality in HFpEF[1]
- Coronary microvascular dysfunction (CMD) proposed as a novel mechanism in HFpEF[2-5]
- Clinical evidence of CMD in HFpEF limited to selected referral samples[6-10]



[1]Eur Heart J 2016;37:2129, [2]J Am Coll Cardiol 2013;62:263, [3]JACC Heart Fail 2016;4:312, [4]Heart 2016;102:257, [5]Eur Heart J 2018 doi: 10.1093/eurheartj/ehy301, [6]Microcirculation 2015;22:528, [7]Eur Heart J 2018;39:840, [8]Am J Physiol Heart Circ Physiol 2018;314:H1033, [9]JAHA 2016;5.pii: e002649, [10]Circ HF 2016;9.pii: e002562

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

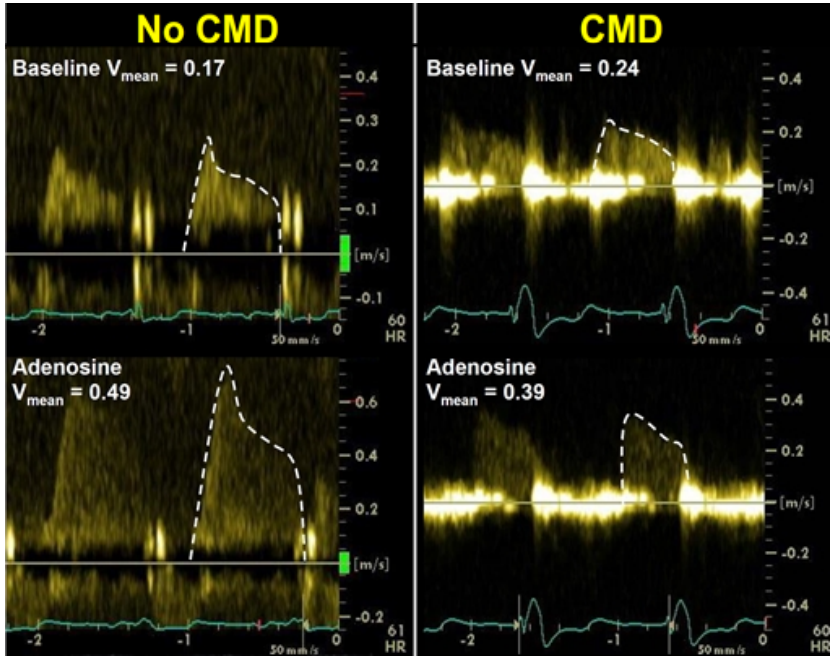
Methods

- 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%

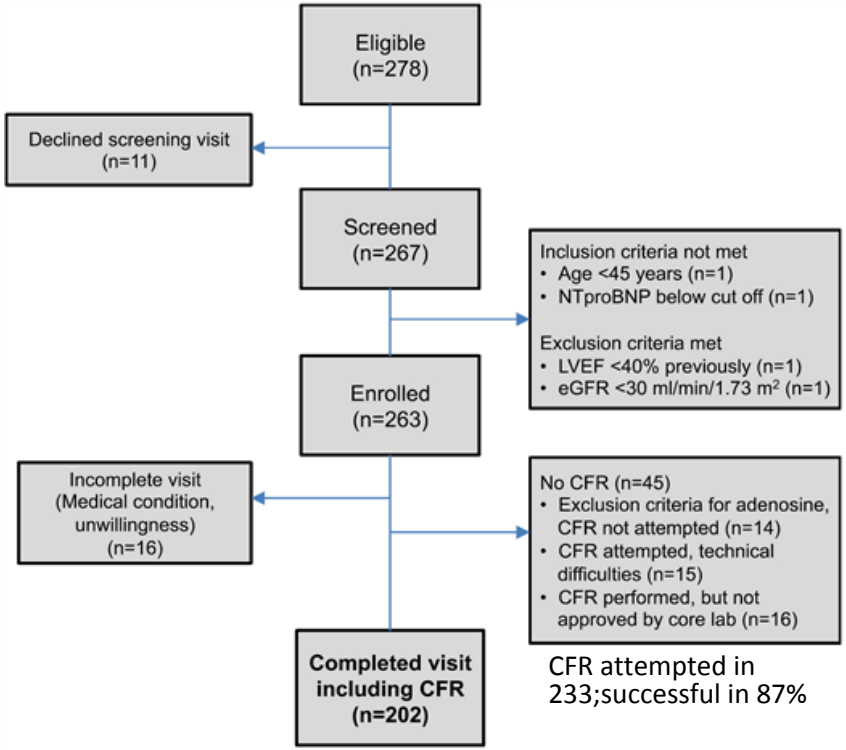
[1]In the last 1 year: Outpatient NTproBNP ≥ 300 ng/L or BNP ≥ 75 ng/L with sinus rhythm; NTproBNP ≥ 750 ng/L or BNP ≥ 200 ng/L with AF; Acute Inpatient NTproBNP ≥ 500 ng/L or BNP ≥ 125 ng/L with sinus rhythm, NT-proBNP ≥1250 ng/L or BNP ≥ 350 ng/L with AF

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

Characteristic	CMD absent (N=51)	CMD present (N=151)	P-value
Age, years	72.4±9.0	74.7±8.7	0.11
Female, n(%)	32(63)	79(52)	0.20
Comorbidities, n(%)			
• Hypertension	47(92)	123(81)	0.07
• Previously revascularized CAD	8(16)	31(21)	0.45
• Atrial fibrillation	18(35)	88(58)	0.004
• Diabetes	13(25)	45(30)	0.56
• Obesity	22(43)	49(32)	0.17
• Chronic kidney disease	25(49)	80(53)	0.63
• Current or prior cigarette smoker	22(43)	106(70)	<0.001

Characteristic	CMD absent	CMD present	P-value
• eGFR, mL/min/1.73 m^2	63±20	59±19	0.16
• UACR, mg/g	2.4 (1.1-3.7)	4.3 (1.4-18.8)	0.036
• NT-proBNP, pg/mL	597 (190-1410)	1050 (396-1930)	0.004
Doppler echo			
• LV mass index, g/m^2	102.1±26.1	110.3±36.6	0.14
• LV E/e' ratio	12.4±4.7	13.5±6.2	0.24
• RV wall thickness, cm	4.7±0.6	4.9±0.7	0.016
• TAPSE, mm	19.7±3.6	17.5±3.7	<0.001
• PASP, mmHg	40.5±10.8	45.6±15.3	0.05

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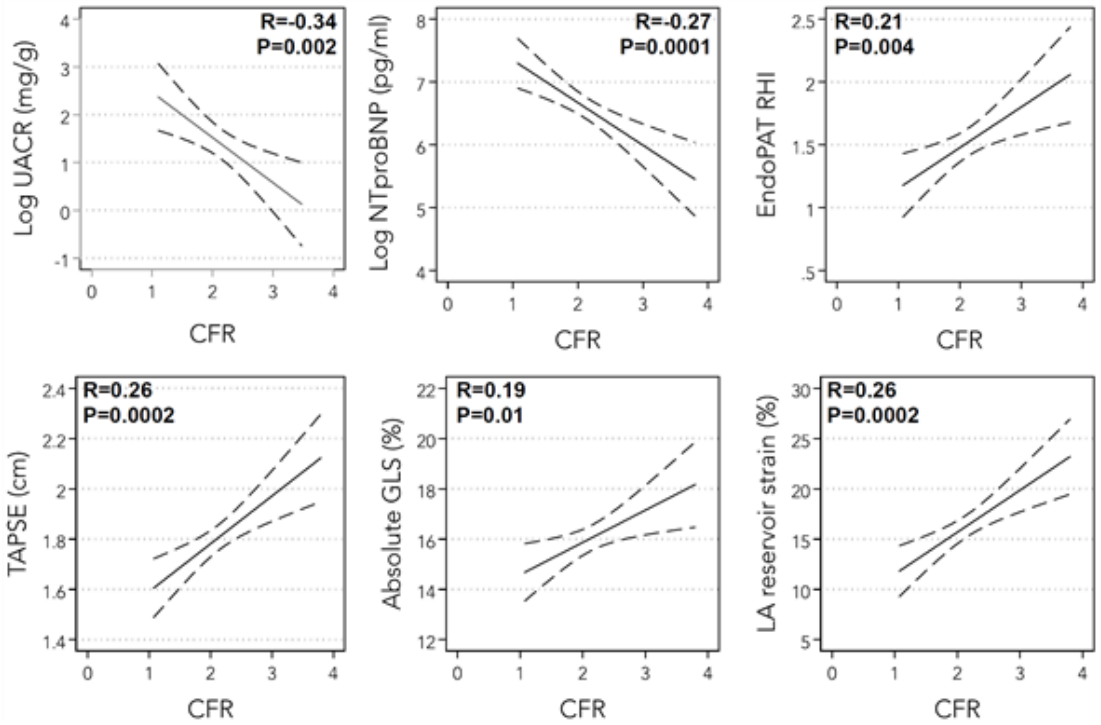
Speckle-tracking echocardiography			
• LV global longitudinal strain, %	17.0±3.5	15.7±3.5	0.023
• RV free wall strain, %	23.3±5.1	21.6±5.2	0.05
• LA reservoir strain, %	19.8±8.3	15.0±7.7	<0.001

Results



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

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

[1]for age, sex, body mass index, atrial fibrillation, diabetes, revascularized coronary disease, smoking, left ventricular mass, study site

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

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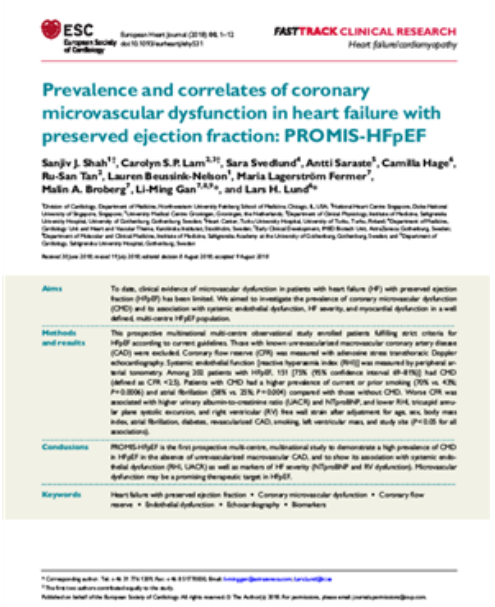
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Aims
Methods and results
Conclusions
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