University of Groningen

Association of Coronary Microvascular Dysfunction With Heart Failure Hospitalizations and Mortality in Heart Failure With Preserved Ejection Fraction

Hage, Camilla; Svedlund, Sara; Saraste, Antti; Faxen, Ulrika Ljung; Benson, Lina; Fermer, Maria Lagerstrom; Gan, Li-Ming; Shah, Sanjiv J.; Lam, Carolyn S. P.; Lund, Lars H.

Published in:
JOURNAL OF CARDIAC FAILURE

DOI:
[10.1016/j.cardfail.2020.08.010](https://doi.org/10.1016/j.cardfail.2020.08.010)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hage, C., Svedlund, S., Saraste, A., Faxen, U. L., Benson, L., Fermer, M. L., Gan, L-M., Shah, S. J., Lam, C. S. P., & Lund, L. H. (2020). Association of Coronary Microvascular Dysfunction With Heart Failure Hospitalizations and Mortality in Heart Failure With Preserved Ejection Fraction: A Follow-up in the PROMIS-HFpEF Study. *JOURNAL OF CARDIAC FAILURE*, 26(11), 1016-1021.
<https://doi.org/10.1016/j.cardfail.2020.08.010>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Brief Report

Association of Coronary Microvascular Dysfunction With Heart Failure Hospitalizations and Mortality in Heart Failure With Preserved Ejection Fraction: A Follow-up in the PROMIS-HFpEF Study

CAMILLA HAGE, RN, PhD,^{1,2} SARA SVEDLUND, MD, PhD,³ ANTTI SARASTE, MD, PhD,⁴ ULRIKA LJUNG FAXÉN, MD, PhD,¹ LINNA BENSON,¹ MARIA LAGERSTROM FERMER, PhD,⁵ LI-MING GAN, MD, PhD,^{5,6} SANJIV J. SHAH, MD,⁷ CAROLYN S.P. LAM, MD, PhD,^{8,9} AND LARS H. LUND, MD, PhD^{1,2}

Stockholm, Stockholm, and Gothenburg, Sweden; Turku, Finland; Chicago, Illinois; Singapore; and Groningen, the Netherlands

ABSTRACT

Background: Coronary microvascular dysfunction (CMD) is common in heart failure with preserved ejection fraction (HFpEF). We assessed the association of CMD with hospitalization and mortality in HFpEF.

Methods and Results: We assessed the 1-year outcomes in patients from the PROMIS-HFpEF study, a prospective observational study of patients with chronic stable HFpEF undergoing coronary flow reserve measurements. Outcomes were (1) time to cardiovascular (CV) death/first HF hospitalization, (2) CV death/recurrent HF hospitalizations, (3) all-cause death/first HF hospitalization, and (4) first and (5) recurrent all-cause hospitalizations. CMD was defined as coronary flow reserve of <2.5. Time to CV death/first hospitalization was compared by log-rank test and recurrent HF and all-cause hospitalizations by Poisson test. Of 263 patients enrolled, 257 were evaluable at 1 year. Where the coronary flow reserve was interpretable ($n = 201$), CMD was present in 150 (75%). The median follow-up was 388 days (Q1, Q3 365, 418). The outcome of CV death/first HF hospitalization occurred in 15 patients (4 CV deaths). The incidence rate was in CMD 96 per 1000 person-years, 95% confidence interval 54–159, vs non-CMD 0 per 1000 person-years, 95% confidence interval 0–68, $P = .023$, and remained significant after accounting for selected clinical variables. In patients with CMD, the incidence rates were significantly higher also for CV death/recurrent HF hospitalizations, all-cause death/first HF, and recurrent but not first all-cause hospitalization.

Conclusions: In this exploratory assessment of the prognostic role of CMD in HFpEF, CMD was independently associated with primarily CV- and HF-specific events. The high prevalence of CMD and its CV and HF specific prognostic role suggest CMD may be a potential treatment target in HFpEF. (*J Cardiac Fail* 2020;26:1016–1021)

Key Words: HFpEF, coronary microvascular dysfunction, coronary flow reserve, inflammation, CV death, HF hospitalization, outcome.

From the ¹Department of Medicine, Cardiology Unit, Karolinska Institutet, Stockholm, Sweden; ²Karolinska University hospital, Heart, Vascular and Neuro Theme, Karolinska University hospital, Stockholm, Sweden; ³Department of Clinical Physiology, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden; ⁴Heart Center, Turku University Hospital, University of Turku, Turku, Finland; ⁵Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; ⁶Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden; ⁷Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois; ⁸National Heart Centre Singapore, Duke-National University of Singapore, Singapore and ⁹University Medical Centre Groningen, Groningen, the Netherlands.

Manuscript received June 26, 2020; revised manuscript received August 4, 2020; revised manuscript accepted August 19, 2020.

Reprint requests: Camilla Hage, RN, PhD, Theme of Heart, Vascular and Neuro, Research Unit, Karolinska University Hospital, SE-171 76 Stockholm, Sweden. Telephone: +46 8 517 792 82; Fax number: +46 8 34 49 64. E-mail: camilla.hage@sl.se

See page 1020 for disclosure information.

1071-9164/\$ - see front matter

© 2020 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.cardfail.2020.08.010>

Heart failure with preserved ejection fraction ($\geq 50\%$; HFpEF) is associated with multiple noncardiac conditions suggested to drive high hospitalization and mortality rates. Still, cardiovascular (CV) mortality and especially HF hospitalization events are higher in HFpEF patients than in patients without HF but with similar age and sex distribution, and comparable noncardiac disease pattern.¹ One model suggests that comorbidity-driven systemic inflammation and endothelial inflammation lead to coronary microvascular dysfunction (CMD) resulting in myocardial structural and functional impairments and HFpEF.^{2,3} CMD is a strong independent predictor of CV events in patients with clinical indication for cardiac catheterization regardless of macrovascular coronary artery disease (CAD)^{4–7} and in HFpEF.^{8,9}

Aims

In the multi-national PRevalence Of Microvascular dysfunction in Heart Failure with Preserved Ejection Fraction (PROMIS-HFpEF) study we demonstrated that 75% of HFpEF patients have CMD defined as a coronary flow reserve of <2.5 .¹⁰ In this exploratory study, we report the association between CMD and outcomes and quality of life.

Methods

PROMIS-HFpEF included patients with stable HFpEF, with signs and symptoms of HF, a left ventricular ejection fraction of $\geq 40\%$, New York Heart Association functional class II–IV and (1) increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) or (2) recent HF hospitalization and structural heart disease according to the European Society of Cardiology Guidelines or (3) increased filling pressures. Pertinent exclusion criteria were unrevascularized macrovascular CAD and a previous left ventricular ejection fraction of $<40\%$. The primary end point was CMD (coronary flow reserve of <2.5 ; measured by echocardiography as adenosine-induced divided by resting left anterior descending artery flow velocity).¹⁰

The 1-year follow-up was assessed by phone call, chart review, and/or local registries regarding the outcomes of (1) time to CV death/first HF hospitalization, (2) CV death/recurrent HF hospitalizations, (3) all-cause death/first HF hospitalization and, (4) first and (5) recurrent all-cause hospitalizations.

Descriptive data are expressed as median and quartiles (Q1, Q3) or number (%), and compared by the Mann–Whitney *U* test and Fisher's exact test. The incidences for outcomes 1–5 are presented as rate per 1000 person-years (see Fig. 2) with Poisson confidence intervals (CIs) provided in text (number of person-years in the recurrent hospitalization calculation excluding time spent in hospital). In addition, the nonrecurrent outcomes were also compared by log-rank test and the recurrent hospitalization was tested between groups by Poisson test. Because there were no events in the non-CMD group, adjustments for covariates using Cox regression were not possible. Therefore, the

primary outcome was compared for CMD and adjusted, one at a time, for selected variables (age ≥ 75 years, female sex, median NT-proBNP ≥ 988 pg/mL], diabetes, atrial fibrillation, body mass index of ≥ 30 kg/m², and estimated glomerular filtration rate of ≥ 60 mL $\cdot$ min⁻¹ $\cdot$ [1.73 m²]⁻¹) using a stratified log-rank test. Outcomes were censored at death, loss to follow-up, or last contact. The significance level was set to 5%, 2-sided. Statistical analyses were performed using R version 3.6.1 (2019-07-05) (R Core Team, 2019) and SAS software version 9.3 (SAS Institute, Cary, NC).

The PROMIS-HFpEF study was approved by the institutional review boards at all centers and complies with the Declaration of Helsinki. All participants provided written informed consent.

Results

In all, 263 patients were enrolled, and 257 were evaluable at follow-up after 1 year. Among patients with evaluable baseline coronary flow reserve assessment, nearly all patients—201 of 202 (99%)—had follow-up data at 1 year (Fig. 1).

Table 1 displays baseline characteristics according to the presence of CMD, $n = 150$, 75%, or absence of CMD, $n = 51$, 25%. Patients with CMD compared with those without CMD were similar in age, had a slightly lower body mass index, and were more often smokers with atrial fibrillation. Patients with CMD had worse global left ventricular strain and worse left atrial reservoir strain, and a higher NT-proBNP and albumin/creatinine ratio (Table 1).¹⁰

In the 201 patients with baseline assessed CMD, the median follow-up time was 388 days, Q1; Q3 365; 418. The outcome of CV death or first HF hospitalization occurred in 15 patients; 4 were CV deaths (Fig. 2). The incidence rate in patients with CMD was 96 per 1000 patient-years, 95% CI 54–159, compared with non-CMD 0 per 1000 patient-years, 95% CI 0–68, $P = .023$. The incidence rate remained significant when stratified for age ≥ 75 , $P = .026$; sex, $P = .025$; history of macrovascular CAD, $P = .025$; diabetes mellitus, $P = .025$; atrial fibrillation, $P = .036$; obesity, body mass index of ≥ 30 kg/m², $P = .033$; median NT-proBNP of ≥ 963 ng/L, $P = .039$; and estimated glomerular filtration rate of ≥ 60 mL $\cdot$ min⁻¹ $\cdot$ [1.73 m²]⁻¹, $P = .022$, respectively. As shown in Fig. 2, the incidence of the composite of CV death/recurrent HF hospitalizations, $n = 21$ events, and all-cause death/first HF hospitalization, $n = 17$ events, were all in patients with CMD compared with no events in patients without CMD. The incidence rates of all-cause first and recurrent hospitalizations were also higher in patients with CMD, but the difference was not statistically significant for first all-cause hospitalization.

Quality of life was assessed by the Kansas City Cardiomyopathy Questionnaire at baseline and after 1 year. The baseline overall summary score did not change significantly from baseline to follow-up in patients with CMD, from 69 to 66, $P = .825$, or in patients without CMD, from 68 to 74, $P = .280$; between groups at follow-up, $P = .298$; $P\Delta = .492$.

Fig. 1. Flow chart of enrolled patients with completed 1-year follow-up. CFR, coronary flow reserve.

Fig. 2. Incidence rates of assessed outcomes in patients with and without coronary microvascular dysfunction. CMD, coronary microvascular dysfunction; CV, cardiovascular; HF, heart failure.

Table 1. Characteristics in the 257 patients in PROMIS-HFpEF and divided according to presence of coronary microvascular dysfunction

Demographic Variables	All Patients With Follow-up (n = 257)		Patients With Coronary Microvascular Dysfunction at Baseline (n = 150)		Patients Without Coronary Microvascular Dysfunction at Baseline (n = 51)		P Value
	n	Median	n	Median	n	Median	
Age (years)	257	75 (70, 81)	150	75 (71, 81)	51	73 (67, 79)	.119
Sex (female)		146 (57)	150	79 (53)	51	32 (63)	.255
Medical history at baseline							
NYHA functional class	255						.218
I		4 (1.6)		1 (0.7)		2 (4.0)	
II		188 (74)		115 (76)		34 (67)	
III		62 (24)		33 (22)		15 (29)	
IV		1 (0.4)		1 (0.7)		0 (0)	
Smoking	257	171 (67)	150	105 (70)	51	22 (43)	<.001
Non-HF CV disease	256	106 (41)	149	61 (41)	51	17 (33)	.406
Stroke/TIA	106	30 (28)	149	15 (10)	51	6 (12)	.374
Diabetes	257	74 (29)	150	45 (30)	51	13 (25)	.595
Atrial fibrillation	257	138 (54)	150	87 (58)	51	18 (35)	.006
Hypertension	257	213 (83)	150	122 (81)	51	47 (92)	.078
Pulmonary hypertension	257	46 (18)	150	27 (18)	51	10 (20)	.835
Malignancies	256	47 (18)	149	18 (12)	51	14 (27)	.014
Whereof current malignancies		4 (1.6)		2 (1.3)		1 (1.9)	1
Physical findings							
Heart rate (beats/min)	256	68 (60, 78)	150	69 (61, 79)	51	67 (59, 72)	.094
Systolic blood pressure (mm Hg)	256	139 (125, 152)	150	139 (128, 154)	51	135 (126, 156)	.882
Diastolic blood pressure (mm Hg)	256	76.5 (68, 85)	150	78 (68, 85)	51	76 (66, 83)	.405
BMI (kg/m ²)	256	28 (24, 33)	150	27 (24, 32)	51	29 (25, 36)	.050
Laboratory findings							
NT-proBNP (pg/mL)	250	988 (369, 1770)	148	1050 (389, 1910)	51	597 (190, 1410)	.006
Potassium (mmol/L)	245	4.2 (3.9, 4.5)	144	4.2 (3.9, 4.5)	50	4.2 (3.8, 4.4)	.159
Sodium (mmol/L)	250	140 (138, 142)	148	140 (138, 142)	51	141 (139, 142)	.131
eGFR (mL · min ⁻¹ · [1.73 m ²] ⁻¹)	250	62 (48, 74)	148	62 (48, 72)	51	64 (54, 76)	.220
Uric acid (μmol/L)	249	404 (327, 494)	147	405 (338, 505)	51	380 (327, 464)	.230
Blood urea nitrogen (mmol/L)	187	8 (6, 11)	107	8 (6, 11)	38	7 (6, 9)	.185
Hemoglobin (g/dL)	248	129 (118, 140)	147	130 (119, 140)	51	128 (118, 140)	.606
hs-TnT (ng/mL)	244	14	142	14 (10, 26)	51	10 (10, 16)	.002
Glucose, fasting (mmol/L)	249	5.8 (5.3, 6.9)	148	5.8 (5.4, 7.1)	51	5.5 (5.1, 6.6)	.179
HbA1c (mmol/mol)	219	41 (38, 49)	123	42 (37, 51)	48	40 (38, 47)	.540
Cholesterol (mmol/L)	250	4.2 (3.4, 4.9)	148	4.0 (3.3, 4.9)	51	4.5 (3.5, 4.9)	.069
LDL (mmol/L)	250	2.2 (1.7, 2.9)	148	2.1 (1.6, 2.9)	51	2.6 (1.8, 3.1)	.054
Triglycerides (mmol/L)	250	1.1 (0.8, 1.6)	148	1.1 (0.8, 1.6)	51	1.0 (0.8, 1.4)	.248
Urine albumin/creatinine	100	3.1 (1.3, 8.7)	55	3.6 (1.3, 17.6)	20	2.4 (1.1, 3.7)	.049
Echocardiographic findings							
LVEF (%)	248	60 (55, 64)	148	59 (54, 65)	51	62 (57, 64)	.101
E/e'	246	12.3 (9.3, 16.2)	146	12.5 (9.4, 15.9)	51	11.7 (8.3, 15.5)	.323
LAVI (mL/m ²)	249	38 (31, 45)	149	38 (31, 46)	51	35 (29, 42)	.149
LVMI (g/m ²)	250	103 (84, 125)	150	103 (83, 128)	51	101 (84, 115)	.303
LV global longitudinal strain	236	17 (13, 19)	142	16 (14, 18)	49	18 (15, 19)	.018
PCWP (mm Hg)	246	18 (16, 20)	146	18 (17, 20)	51	18 (16, 20)	.846
Left atrial reservoir strain	245	13 (9, 22)	145	12 (9, 21)	51	20 (12, 26)	.001
Pharmacologic treatment							
RAS antagonist	257	112 (44)	150	80 (53)	51	26 (51)	.871
Beta blocker	257	194 (75)	150	115 (77)	51	33 (65)	.101
Mineralocorticoid receptor antagonist	257	73 (28)	150	35 (23)	51	17 (33)	.195
Loop diuretic	257	128 (50)	150	79 (53)	51	30 (59)	.516
Calcium channel blocker	257	86 (33)	150	50 (33)	51	20 (39)	.497
Anticoagulant	257	210 (82)	150	124 (83)	51	36 (71)	.073
Statin	257	144 (56)	150	88 (59)	51	27 (53)	.514
Glucose-lowering agent	257	67 (26)	150	43 (29)	51	10 (20)	.270

Continuous variables are presented as median and lower and upper quartiles (Q1, Q3) and categorical variables as numbers (%), when not otherwise stated.

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDF, heart failure; HFpEF, heart failure with preserved ejection fraction; hs-TnT, high sensitivity troponin T; LAVI, left atrial volume index; LDL, low-density lipoprotein cholesterol; LV, left ventricle; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PROMIS-HFpEF, national Prevalence Of Microvascular dysfunction in Heart Failure with Preserved Ejection Fraction; RAS, renin-angiotensin system; TIA, transient ischemic attack.

Conclusions

In this prespecified exploratory analysis of the association between CMD and outcomes in HFpEF, we observed an association between the presence of CMD and the risk of CV and HF events. The overall number of events was small; therefore, these findings should be viewed with caution, but the consistency of the results and across outcomes provides support for a potential association of CMD with adverse outcomes in HFpEF.

Previous reports in HFpEF suggest a relatively greater contribution of non-CV hospitalization and mortality events^{11,12} as compared with in HFpEF. In our patients with HFpEF, the majority of deaths were CV (4 of 6), all occurring in the CMD group. Although with few events, these preliminary findings lend support to previous reports in patients with suspected CAD⁷ and in HFpEF, correlating CMD with death and/or HF hospitalizations.^{8,9} In HFpEF, upregulated inflammation initiating CMD and subclinical atherosclerosis may act as disease drivers impairing outcome.^{13–15} Additive information on CMD status may also be more accessible evaluated noninvasively through circulating biomarkers.¹³

The PROMIS-HFpEF study was not primarily designed for assessing outcomes, and the low and uneven distribution of event rates only enabled individually adjustments. Therefore, these findings should be interpreted with caution. Still, CMD was consistently associated with all outcomes, even after accounting for variables of clinical importance. The results provide support for a potential association of CMD with specifically CV and HF events in HFpEF. This potentially offers CMD not only as a treatment target, but also as a general enrichment enrolment criterion in future HFpEF trials, with interventions hypothesized to decrease CV events.

Acknowledgments

The following study staff are acknowledged for their work in the PROMIS-HFpEF study: Ann Lindström, Ashwin Venkatesh, Ann Hultman-Cadring, Neal Pohlman, Juliet Ryan, Tuija Vasankari, Miriam Käveryd Holmström, and Sofie André.

Funding

Supported by AstraZeneca. C.H. is supported by Stockholm Country Council (grant 20180899). S.J.S. is supported by the U.S. National Institutes of Health grants [R01 HL105755 and R01 HL127028] and American Heart Association grants [#16SFRN28780016 and #15CVGPS27260148]. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore. L.H.L. is supported by grants from the Swedish Research Council [grants 2013-23897-104604-23 and 523-2014-2336], the Swedish Heart Lung Foundation [grants 20120321 and 20150557], and the Stockholm County Council [grant 20190525].

Disclosures

C.H. has received consulting fees from Novartis, MSD and Roche Diagnostics. S.J.S. has received research grants from Actelion, AstraZeneca, Corvia, and Novartis; and consulting fees from Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Ironwood, Merck, Novartis, Sanofi, Tenax, and United Therapeutics. C.S.L. has received research support from Boston Scientific, Bayer, Roche Diagnostics, Medtronic, and Vifor Pharma; and has consulted for AstraZeneca, Bayer, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, and Takeda. A. S. received research grants from Academy of Finland and Finnish Foundation for Cardiovascular Research during the conduct of the study; and consulting fees from GE healthcare, Novartis, Abbot, AstraZeneca. L.H.L. has received research grants from Novartis, Boehringer-Ingelheim, Vifor Pharma, and AstraZeneca, and consulting fees from Novartis, Merck, Boehringer-Ingelheim, Sanofi, Vifor Pharma, and AstraZeneca. M.L.F., M.A.B., and L.M.G. are all employees of AstraZeneca R&D. All other authors have no disclosures.

References

1. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? *J Am Coll Cardiol* 2012;60:2349–56. <https://doi.org/10.1016/j.jacc.2012.04.064>.
2. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263–71. <https://doi.org/10.1016/j.jacc.2013.02.092>.
3. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschope C, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016;4:312–24. <https://doi.org/10.1016/j.jchf.2015.10.007>.
4. Gan LM, Svedlund S, Wittfeldt A, Eklund C, Gao S, Matejka G, et al. Incremental value of transthoracic Doppler echocardiography—assessed coronary flow reserve in patients with suspected myocardial ischemia undergoing myocardial perfusion scintigraphy. *J Am Heart Assoc* 2017;6:e004875. <https://doi.org/10.1161/JAHA.116.004875>.
5. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014;129:2518–27. <https://doi.org/10.1161/CIRCULATIONAHA.113.008507>.
6. Brainin P, Frestad D, Prescott E. The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol* 2018;254:1–9. <https://doi.org/10.1016/j.ijcard.2017.10.052>.
7. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J* 2018;39:840–9. <https://doi.org/10.1093/eurheartj/ehx721>.
8. Allan T, Dryer K, Fearon WF, Shah SJ, Blair JEA. Coronary microvascular dysfunction and clinical outcomes in patients with heart failure with preserved ejection fraction. *J Card Fail* 2019;25:843–5. <https://doi.org/10.1016/j.cardfail.2019.08.010>.

9. Yang JH, Obokata M, Reddy YNV, Redfield MM, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;22:432–41. <https://doi.org/10.1002/ejhf.1671>.
10. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J* 2018;39:3439–50. <https://doi.org/10.1093/eurheartj/ehy531>.
11. Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2018;5:685–94. <https://doi.org/10.1002/ehf2.12283>.
12. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;19:1574–85. <https://doi.org/10.1002/ejhf.813>.
13. Tromp J, Hage C, Ouwerkerk W, Sanders-van Wijk S, Svedlund S, Saraste A, et al. Biomarker correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction. *Circulation* 2019;140:1359–61. <https://doi.org/10.1161/CIRCULATIONAHA.119.042569>.
14. Camici PG, Tschope C, Carli MFD, Rimoldi O, Van Linthout S. Coronary microvascular dysfunction in hypertrophy and heart failure. *Cardiovasc Res* 2020;116:806–16. <https://doi.org/10.1093/cvr/cvaa023>.
15. Hage C, Michaelsson E, Linde C, Donal E, Daubert JC, Gan LM, et al. Inflammatory biomarkers predict heart failure severity and prognosis in patients with heart failure with preserved ejection fraction: a holistic proteomic approach. *Circulation Cardiovasc Genet* 2017;10:e001633. <https://doi.org/10.1161/CIRCGENETICS.116.001633>.