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Prevalence of Coronary Artery Disease and Coronary Microvascular Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction

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IMPORTANCE Coronary artery disease (CAD) and coronary microvascular dysfunction (CMD) may contribute to the pathophysiologic characteristics of heart failure with preserved ejection fraction (HFpEF). However, the prevalence of CAD and CMD have not been systematically studied.

OBJECTIVE To examine the prevalence of CAD and CMD in hospitalized patients with HFpEF.

DESIGN, SETTING, AND PARTICIPANTS A total of 106 consecutive patients hospitalized with HFpEF were evaluated in this prospective, multicenter, cohort study conducted between January 2, 2017, and August 1, 2018; data analysis was performed from March 4 to September 6, 2019. Participants underwent coronary angiography with guidewire-based assessment of coronary flow reserve, index of microvascular resistance, and fractional flow reserve, followed by coronary vasoreactivity testing. Cardiac magnetic resonance imaging was performed with late gadolinium enhancement and assessment of extracellular volume. Myocardial perfusion was assessed qualitatively and semiquantitatively using the myocardial-perfusion reserve index.

MAIN OUTCOMES AND MEASURES The prevalence of obstructive epicardial CAD, CMD, and myocardial ischemia, infarction, and fibrosis.

RESULTS Of 106 participants enrolled (53 [50%] women; mean [SD] age, 72 [9] years), 75 had coronary angiography, 62 had assessment of coronary microvascular function, 41 underwent coronary vasoreactivity testing, and 52 received cardiac magnetic resonance imaging. Obstructive epicardial CAD was present in 38 of 75 participants (51%, 95% CI, 39%-62%); 19 of 38 (50%; 95% CI, 34%-66%) had no history of CAD. Endothelium-independent CMD (ie, coronary flow reserve <2.0 and/or index of microvascular resistance ≥25) was identified in 41 of 62 participants (66%; 95% CI, 53%-77%). Endothelium-dependent CMD (ie, abnormal coronary vasoreactivity) was identified in 10 of 41 participants (24%; 95% CI, 13%-40%). Overall, 45 of 53 participants (85%; 95% CI, 72%-92%) had evidence of CMD and 29 of 36 (81%; 95% CI, 64%-91%) of those without obstructive epicardial CAD had CMD. Cardiac magnetic resonance imaging findings included myocardial-perfusion reserve index less than or equal to 1.84 (ie, impaired global myocardial perfusion) in 29 of 41 patients (71%; 95% CI, 54%-83%), visual perfusion defect in 14 of 46 patients (30%; 95% CI, 19%-46%), ischemic late gadolinium enhancement (ie, myocardial infarction) in 14 of 52 patients (27%; 95% CI, 16%-41%), and extracellular volume greater than 30% (ie, diffuse myocardial fibrosis) in 20 of 48 patients (42%; 95% CI, 28%-56%). Patients with obstructive CAD had more adverse events during follow-up (28 [74%]) than those without obstructive CAD (17 [46%]).

CONCLUSIONS AND RELEVANCE In this cohort study, 91% of patients with HFpEF had evidence of epicardial CAD, CMD, or both. Of those without obstructive CAD, 81% had CMD. Obstructive epicardial CAD and CMD appear to be common and often unrecognized in hospitalized patients with HFpEF and may be therapeutic targets.

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Myocardial ischemia due to epicardial coronary artery disease (CAD), coronary microvascular dysfunction (CMD), or both, may represent a disease mechanism and therapeutic target in some patients with heart failure with preserved ejection fraction (HFpEF).[1-3]

Myocardial ischemia can cause left-ventricular (LV) diastolic and systolic dysfunction, both of which are common in HFpEF.[4,5] Inflammation-associated CMD may also play a role in the pathophysiologic characteristics of HFpEF,[6] which is a possibility supported by noninvasive studies, an autopsy series, and small invasive studies.[3,7-9]

However, to our knowledge, the prevalence of epicardial CAD, CMD, and coronary endothelial dysfunction have not been systematically studied in patients with HFpEF. We performed comprehensive invasive and noninvasive assessments of epicardial and microvascular function to evaluate the prevalence of CAD, CMD, and coronary endothelial dysfunction in prospectively recruited hospitalized patients with HFpEF.

Key Points

Question What is the prevalence of obstructive epicardial coronary artery disease and coronary microvascular dysfunction in hospitalized patients with heart failure with preserved ejection fraction?

Findings In a cohort study, 106 consecutive participants with preserved ejection fraction were evaluated with coronary angiography, invasive coronary physiologic and vasoreactivity testing, and cardiac magnetic resonance imaging. A total of 51% of the study participants had obstructive epicardial coronary artery disease, 66% had endothelium-independent coronary microvascular dysfunction, and 24% had endothelium-dependent coronary microvascular dysfunction.

Meaning The findings of this study suggest that obstructive epicardial coronary artery disease and coronary microvascular dysfunction are common and often unrecognized in hospitalized patients with heart failure with preserved ejection fraction and may be therapeutic targets.

Methods

Consecutive patients hospitalized with HFpEF were evaluated in this prospective, multicenter, cohort study conducted between January 2, 2017, and August 1, 2018; data analysis was performed from March 4 to September 6, 2019. Patients with HFpEF were prospectively recruited from 3 centers. The inclusion and exclusion criteria are described in the eMethods in the Supplement. The major exclusion criteria included an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 (to allow safe administration of contrast agents during investigations) and severe frailty (ie, Clinical Frailty Scale score >6),[10] because invasive coronary angiography was considered high-risk and clinically inappropriate in patients with these limitations.

Study procedures included invasive coronary angiography with guidewire-based physiologic assessment and vasoreactivity testing. In the absence of contraindications, patients also underwent multiparametric cardiac magnetic resonance imaging (CMRI). All participants provided written informed consent and the study was approved by the West of Scotland Research Ethics Committee; participants did not receive financial compensation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

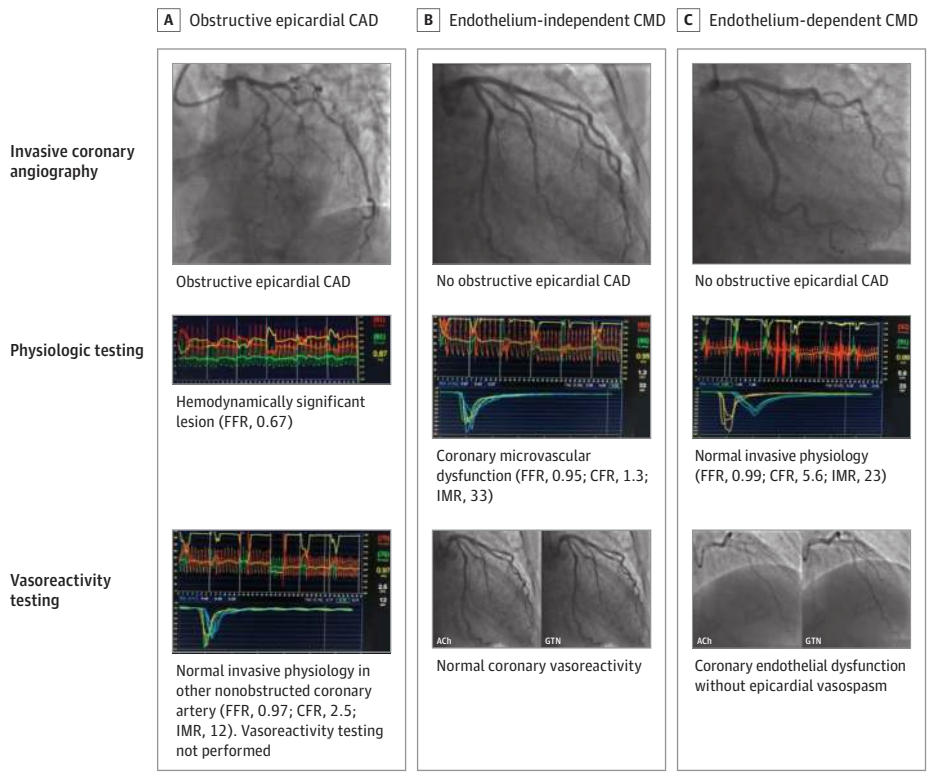
Testing

Invasive coronary assessment was performed by experienced operators, and computer-assisted quantitative coronary angiography analysis was performed using QAngio XA 7.3 (Medis). Coronary guidewire assessment was performed on a single major epicardial coronary artery. The left anterior descending artery was the preferred vessel, although if use of this artery was technically impossible, the left circumflex or right coronary artery was used instead; details of measurement of fractional flow reserve, coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) are given in the eMethods in the Supplement and shown in **Figure 1**. Obstructive epicardial CAD was defined as greater than 70% stenosis of a major epicardial coronary artery (≥50% stenosis if the left main coronary artery was affected) or a 50% to 70% stenosis with a fractional flow reserve value less than or equal to 0.80.[11] In patients with obstructive epicardial stenosis, CFR and IMR were measured in another (nonobstructed) coronary artery to ensure accurate assessment of microvascular function. Coronary flow reserve represents the coronary vasodilator capacity (epicardial and microvascular) and was calculated using thermodilution as the resting mean transit time divided by the hyperemic mean transit time.[12] The IMR reflects the minimal resistance offered by the coronary microvasculature and was calculated as the product of the mean distal coronary artery pressure and the mean transit time measured simultaneously during hyperemia.[13] Endothelium-independent CMD was defined as a CFR less than 2.0 and/or an IMR greater than or equal to 25.[12,13]

Coronary vasomotor function was assessed using intracoronary infusions of acetylcholine (eMethods in the Supplement; Figure 1). Coronary vasoreactivity testing was not performed in most patients with obstructive epicardial disease owing to the risk of acute myocardial ischemia from the combination of obstructive CAD and coronary spasm.[14] Microvascular coronary vasospasm, reflecting endothelium-dependent CMD and vascular smooth muscle dysfunction, was defined as 20% to 90% luminal constriction and/or ischemic electrocardiographic changes in response to intracoronary acetylcholine infusions.[15,16] Epicardial coronary vasospasm was defined as greater than 90% luminal constriction and ischemic electrocardiographic changes in response to intracoronary acetylcholine infusions.[17] An overview of the clinical diagnoses based on the invasive coronary assessment findings is presented in Figure 1.

If no contraindications were noted, CMRI was performed with gadolinium contrast, T1 mapping, and adenosine stress perfusion imaging (MAGNETOM Prisma 3.0 T; Siemens Healthcare). The details of the CMRI protocols are given in the eMethods in the Supplement. Perfusion imaging was analyzed

Figure 1. Overview of Clinical Diagnoses Based on Invasive Coronary Assessment Findings



Three cases investigated with invasive coronary angiography, physiologic testing, and/or vasoreactivity testing. A, A case of obstructive epicardial coronary artery disease (CAD) with a flow-limiting lesion identified on fractional flow reserve (FFR) testing. B, A case of endothelium-independent coronary microvascular dysfunction (CMD) without obstructive epicardial CAD, with an abnormal coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) but normal coronary vasoreactivity. C, A case of endothelium-dependent CMD with no obstructive epicardial CAD and normal CFR and IMR, but abnormal coronary vasoreactivity (without epicardial vasospasm). ACh indicates acetylcholine; GTN, glyceryl trinitrate.

using QMass 8.1 (Medis), and the myocardial-perfusion reserve index (MPRI) was calculated.[18,19] Impaired global myocardial perfusion was defined as an MPRI less than or equal to 1.84.[20] Cardiac magnetic resonance imaging–proven myocardial infarction was defined as subendocardial or transmural late gadolinium enhancement (LGE) in the distribution of a coronary artery territory, and an extracellular volume greater than 30% was considered to represent diffuse myocardial fibrosis.[21]

Patients were followed up for a minimum of 12 months, using electronic medical record linkage, to document readmissions, death, and the causes of readmissions and deaths. We assessed the following composite end points: all-cause death or hospitalization for any reason, all-cause death or hospitalization for a cardiovascular cause, all-cause death or hospitalization for HF, and all-cause death or hospitalization for a non-CV cause.

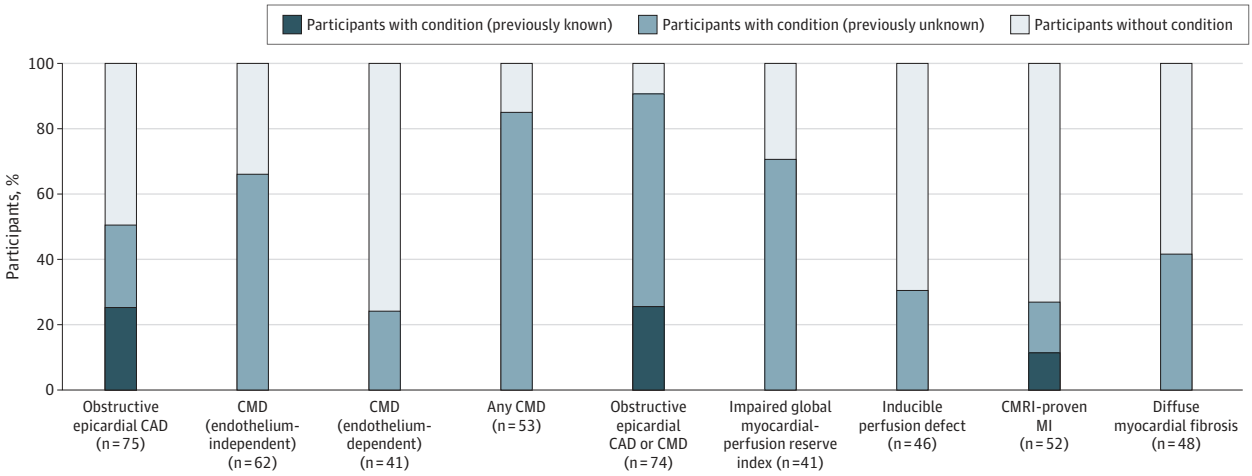
Statistical Analysis

We calculated the prevalence (95% CI) of obstructive epicardial CAD, endothelium-independent and -dependent CMD, and CMRI evidence of impaired myocardial perfusion, myocardial infarction, and diffuse myocardial fibrosis in the study participants. The participants were then divided into those with and those without each condition and the clinical characteristics and investigation results were compared. We used the *t* test or nonparametric equivalent, when indicated, to compare continuous variables and the χ^2 test or nonparametric equivalent, when indicated, to compare categorical variables. Time-to-event analysis was analyzed using the Kaplan-Meier method. With 2-sided, unpaired testing the significance threshold was $P < .05$. All statistical analyses were performed using Stata, version 14.2 (StataCorp LLC).

Results

Between January 2, 2017, and August 1, 2018, 2285 consecutive patients hospitalized with suspected HF were screened, of whom 628 had a diagnosis of HFpEF (eFigure 1 in the Supplement). Of these, 106 patients (17%) met the inclusion criteria and agreed to participate in the study. The most common reasons for exclusion were severe frailty (196 [38%]), severe kidney impairment (104 [20%]), and lack of capacity to consent (88 [17%]). Twenty-three enrolled patients (22%) did not undergo invasive angiography or CMRI, predominantly owing to a deterioration in clinical status. Seventy-five participants (71%) underwent invasive angiography and 52 individuals (49%) underwent CMRI. Sixty-two participants who underwent angiography (58% of all participants; 83% of those undergoing angiography) had coronary physiologic function testing and 41 (39% of all participants; 55% of those undergoing angiography) had vasoreactivity testing. Of the 52 participants undergoing CMRI, 44 (42% of all participants; 85% of those having CMRI) had both invasive coronary angiography and CMRI. The median time from presentation to CMRI was 17 (interquartile range, 10-31) days and to invasive coronary assessment was 87 (interquartile range, 56-98) days. The mean (SD) age of the participants was 72 (9) years, 53 (50%) were women, and 53 (50%)

Figure 2. Prevalence of Coronary Artery Disease (CAD), Coronary Microvascular Dysfunction (CMD), and Imaging Evidence of Impaired Myocardial Perfusion, Myocardial Infarction (MI), and Diffuse Myocardial Fibrosis



CMRI indicates cardiac magnetic resonance imaging.

were men. On admission, 56% patients were in New York Heart Association functional class III and 42% were in class IV. Most participants had mild frailty (mean [SD] CFR, 3.4 [1.2]).[10]

Obstructive CAD

Obstructive epicardial CAD was present in 38 of 75 participants (51%; 95% CI, 39%-62%) who underwent angiography (**Figure 2**; eFigure 2 in the Supplement); 20 participants (53%) had 1-vessel, 13 (34%) had 2-vessel, and 5 (13%) had 3-vessel disease. Nineteen of 38 participants (50%; 95% CI, 34%-66%) had no history of CAD. Those with obstructive CAD were more frequently male and more likely to have a history of CAD, myocardial infarction, coronary revascularization, and chronic kidney disease than those without obstructive disease (**Table 1**). Patients with obstructive CAD had higher estimated LV filling pressures on echocardiography and were less likely to have mild to moderate valve disease than those without obstructive epicardial disease.

Coronary Microvascular Dysfunction

Endothelium-independent CMD was present in 41 of the 62 participants (66%; 95% CI, 53%-77%) who underwent coronary physiologic function testing (Figure 2; eFigure 2 in the Supplement). The prevalence of CMD was similar in participants with (62%) and without (69%) obstructive CAD. The clinical characteristics of participants with and without CMD were generally similar, although patients with CMD had higher B-type natriuretic peptide levels (**Table 2**).

Coronary flow reserve and IMR were both normal in 21 patients (34%); 13 patients (21%) had normal CFR but high IMR (ie, preserved flow reserve and high microvascular resistance), 9 patients (15%) had low CFR and normal IMR (ie, impaired flow reserve and normal microvascular resistance), and 19 patients (31%) had low CFR and high IMR (ie, impaired flow reserve and high microvascular resistance) (eFigure 3 in the Supplement). There were no significant differences between the characteristics of these groups (eTable 1 in the Supplement).

None of the 41 participants who underwent vasoreactivity testing demonstrated epicardial coronary artery vasoconstriction in response to acetylcholine infusion, but 10 patients (24%; 95% CI, 13%-40%) had microvascular vasospasm (Figure 2; eFigure 2 in the Supplement). These patients were more often women and had more atrial fibrillation than those without coronary microvascular endothelial or smooth muscle dysfunction, but fewer had a smoking history and they had less LGE (**Table 3**).

Any CMD (ie, either endothelium independent or dependent) was present in 45 of 53 participants (85%; 95% CI, 72%-92%) (Figure 2; eFigure 2 in the Supplement); vasoreactivity testing was contraindicated in 9 participants with obstructive epicardial CAD but no endothelium-independent CMD. Twenty-nine of 36 participants (81%; 95% CI, 64%-91%) without obstructive epicardial CAD had CMD. The prevalence of CMD was not significantly different in patients with and without obstructive CAD. Participants with CMD more frequently had preexisting HF, more atrial fibrillation, lower troponin levels, and lower LV ejection fraction than those without CMD (eTable 2 in the Supplement). The overlap of the invasive coronary assessment findings is displayed in eFigure 4 in the Supplement.

Impaired Myocardial Perfusion

Forty-six participants underwent adenosine stress perfusion CMRI, of whom 41 had adequate semiquantitative assessment of MPRI. Twenty-nine of the 41 participants had an MPRI less than or equal to 1.84 (71%; 95% CI, 54%-83%), consistent with impaired global myocardial perfusion, and 14 of 46 participants had a qualitative inducible perfusion defect (30%; 95% CI, 19%-46%) (Figure 2).

Those with low MPRI had fewer myocardial infarctions, larger left atrial volumes, and a higher extracellular volume on

Table 1. Clinical Characteristics by Presence or Absence of Obstructive Epicardial CAD

Characteristic	No. (%)			*P* value
	All coronary angiography (n = 75)	No obstructive epicardial CAD (n = 37)	Obstructive epicardial CAD (n = 38)	
Age, mean (SD), y	72 (9)	72 (9)	73 (9)	.40
Sex				
Women	37 (49)	23 (62)	14 (37)	.03
Men	38 (51)	14 (62)	24 (63)	
BMI, mean (SD)	33 (8)	34 (38)	31 (7)	.08
Clinical frailty scale				
1: Very fit	1 (1)	1 (3)	0	.26
2: Well	15 (20)	8 (22)	7 (18)	
3: Managing well	28 (37)	15 (41)	13 (34)	
4: Vulnerable	15 (20)	5 (14)	10 (26)	
5: Mildly frail	13 (17)	5 (14)	8 (21)	
6: Moderately frail	3 (4)	3 (8)	0	
NYHA functional class				
II	2 (3)	1 (3)	1 (3)	.94
III	40 (53)	19 (51)	21 (55)	
IV	33 (44)	17 (46)	16 (42)	
Vital signs, mean (SD)				
Heart rate, bpm	83 (25)	90 (28)	73 (21)	.01
Systolic blood pressure, mm Hg	150 (29)	152 (31)	148 (29)	.58
Medical history				
Previous heart failure diagnosis	28 (37)	13 (35)	15 (39)	.70
Any CAD	26 (35)	7 (19)	19 (50)	<.01
MI	17 (23)	4 (11)	13 (34)	.02
Angina	11 (15)	3 (8)	8 (21)	.11
Revascularization	12 (16)	2 (5)	10 (26)	.01
Percutaneous coronary intervention	11 (15)	2 (5)	9 (24)	.03
Coronary artery bypass grafting	3 (4)	0	3 (8)	.08
Hypertension	55 (73)	28 (76)	27 (71)	.65
Atrial fibrillation	49 (65)	26 (70)	23 (61)	.38
Cerebrovascular disease	15 (20)	5 (14)	10 (26)	.17
Peripheral arterial disease	8 (11)	2 (5)	6 (16)	.15
Diabetes	39 (52)	15 (41)	24 (63)	.05
Chronic kidney disease	22 (29)	6 (16)	16 (42)	.01
Smoking history	42 (56)	20 (54)	22 (58)	.74
Admission medication				
Loop diuretic	36 (48)	18 (49)	18 (47)	.91
ACEI/ARB	50 (67)	22 (59)	28 (74)	.19
β-Blocker	48 (64)	22 (59)	26 (68)	.42
Mineralocorticoid receptor antagonist	3 (4)	1 (3)	2 (5)	.57
Antiplatelet	27 (36)	8 (22)	19 (50)	.01
Statin	52 (69)	23 (62)	29 (76)	.18
Laboratory test				
eGFR, mean (SD), mL/min/1.73 m^2	64 (20)	68 (21)	61 (19)	.17
CRP, median (IQR), mg/dL	1.4 (0.5-2.3)	1.2 (0.4-2.4)	1.5 (0.5-1.8)	.80
Hb, mean (SD), g/dL	12.3 (1.9)	12.5 (1.8)	12.1 (2.0)	.43
hsTnI, median (IQR), ng/L	16 (9-29)	16 (10-27)	18 (7-34)	.89
No.	46	21	25	
BNP, median (IQR), pg/mL	319 (173-856)	323 (185-717)	315 (167-904)	.90
No.	38	17	21	
NT-proBNP, median (IQR), pg/mL	1376 (894-2819)	1532 (1287-2819)	1132 (818-2494)	.37
Echocardiography, mean (SD)				
LVEF, %	59 (6)	60 (6)	58 (6)	.37
E/e'	14.9 (6.3)	12.9 (4.3)	16.4 (7.3)	.03
LA volume index, mL/m^2	45 (16)	47 (16)	44 (16)	.37
Estimated PASP, mm Hg	40 (16)	38 (13)	41 (19)	.57
Valve disease (mild or moderate)	57 (76)	33 (89)	24 (63)	<.01

(continued)

Table 1. Clinical Characteristics by Presence or Absence of Obstructive Epicardial CAD (continued)

Characteristic	No. (%)			*P* value
	All coronary angiography (n = 75)	No obstructive epicardial CAD (n = 37)	Obstructive epicardial CAD (n = 38)	
CMRI, mean (SD)				
No.	44	20	24	
LVEF, %	60 (7)	61 (6)	59 (7)	.23
LVEDV index, mL/m^2	76 (22)	69 (21)	82 (22)	.05
LV mass index, g/m^2	67 (16)	65 (19)	69 (13)	.47
LA volume index, mL/m^2	68 (22)	70 (15)	66 (26)	.51
RVEF, %	53 (9)	52 (9)	54 (8)	.36
RVEDV index, mL/m^2	80 (28)	75 (25)	84 (30)	.29
Any LGE	27 (61)	9 (45)	18 (75)	.04
Ischemic LGE	13 (30)	2 (10)	11 (46)	<.01
Nonischemic LGE	16 (36)	7 (35)	9 (38)	.86
Native T1, ms	1283 (64)	1268 (74)	1296 (53)	.17
ECV, %	28.4 (4.2)	26.5 (3.3)	29.9 (4.3)	.01
MPRI, median (IQR)	1.49 (1.33-1.85)	1.65 (1.39-1.87)	1.41 (1.26-1.75)	.23
Inducible perfusion defect	13 (34)	5 (29)	8 (38)	.57
Ischemic LV segments	2 (4)	3 (5)	2 (4)	.76
Invasive assessment				
No.	75	37	38	
Angiographically normal	11 (15)	11 (30)	NA	NA
Coronary artery assessed with invasive physiologic testing				
No.	62	36	26	
LAD	43 (69)	28 (78)	15 (58)	
LCx	8 (13)	2 (6)	6 (23)	.10
RCA	11 (18)	6 (17)	5 (19)	
Resting T_{mn}, median (IQR), s	0.71 (0.42-1.22)	0.94 (0.56-1.35)	0.51 (0.34-0.80)	<.01
Hyperemic T_{mn}, median (IQR), s	0.35 (0.21-0.51)	0.38 (0.22-0.55)	0.31 (0.18-0.39)	.07
FFR, median (IQR)[a]	0.91 (0.86-0.94)	0.91 (0.85-0.94)	0.91 (0.88-0.94)	.95
CFR, median (IQR)	2.1 (1.4-2.7)	2.4 (1.5-3.1)	2.0 (1.2-2.4)	.06
CFR <2.0	28 (45)	15 (42)	15 (50)	.52
IMR, median (IQR)	23 (15-39)	27 (19-43)	18 (12-26)	.02
IMR ≥25	32 (52)	21 (58)	11 (42)	.21
Endothelium-independent CMD	41 (66)	25 (69)	16 (62)	.52
No.	41	36	5	
Endothelium-dependent CMD	10 (24)	10 (28)	0	.18
No.	69	35	34	
LVEDP, mean (SD), mm Hg	12 (5)	12 (4)	12 (7)	.90

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; CRP, C-reactive protein; E/e', estimated LV filling pressures on echocardiography; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; Hb, hemoglobin; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; IQR, interquartile range; LA, left atrial; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NA, not applicable; NT-proBNP, N-terminal prohormone BNP; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RCA, right coronary artery; RVEDV, right-ventricular end-diastolic volume; RVEF, right-ventricular ejection fraction; T_{mn}, mean transit time.

SI conversion factors: To convert BNP to nanograms per liter, multiply by 1; CRP to milligrams per liter, multiply by 10; Hb to grams per liter, multiply by 10.

[a] In patients with obstructive epicardial stenosis, FFR value measured in another nonobstructed coronary artery.

CMRI than those with preserved global myocardial perfusion (eTable 3 in the Supplement). Participants with and without a low MPRI value had similar rates of obstructive epicardial CAD, endothelium-independent CMD, and endothelium-dependent CMD.

Patients with an inducible perfusion defect were younger and had more history of CAD, myocardial infarction, revascularization, and smoking, but had less atrial fibrillation than those with no perfusion defect (eTable 4 in the Supplement). Participants with an inducible perfusion defect had larger LV volumes and higher LV mass shown on CMRI than those without a perfusion defect. Those with a perfusion defect had a higher burden of ischemic LGE than those without an inducible defect, but a similar global MPRI. Participants with and without a perfusion defect had similar rates of epicardial CAD, endothelium-independent CMD, and endothelium-dependent CMD.

Table 2. Clinical Characteristics by Presence or Absence of Endothelium-Independent Coronary Microvascular Dysfunction

Characteristic	No. (%)			*P* value
	All coronary physiologic testing (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	
Age, mean (SD), y	72 (9)	74 (8)	72 (9)	.41
Sex				
Women	33 (53)	11 (52)	22 (54)	.92
Men	29 (47)	10 (48)	19 (46)	
BMI, mean (SD)	33 (8)	33 (9)	33 (7)	.80
Clinical frailty scale				
1: Very fit	1 (2)	1 (5)	0	.54
2: Well	12 (19)	5 (24)	7 (17)	
3: Managing well	24 (39)	8 (38)	16 (39)	
4: Vulnerable	11 (18)	4 (19)	7 (17)	
5: Mildly frail	11 (18)	3 (14)	8 (20)	
6: Moderately frail	3 (5)	0	3 (7)	
NYHA functional class				
II	2 (3)	1 (5)	1 (2)	.68
III	31 (50)	9 (43)	22 (54)	
IV	29 (47)	11 (52)	18 (44)	
Vital signs, mean (SD)				
Heart rate, bpm	85 (26)	89 (32)	82 (22)	.36
Systolic blood pressure, mm Hg	151 (31)	155 (33)	149 (30)	.44
Medical history				
Previous HF diagnosis	23 (37)	5 (24)	18 (44)	.12
Any CAD	19 (31)	7 (33)	12 (29)	.74
MI	13 (21)	4 (19)	9 (22)	.79
Angina	6 (10)	3 (14)	3 (7)	.38
Revascularization	8 (13)	2 (10)	6 (15)	.57
PCI	8 (13)	2 (10)	6 (15)	.57
CABG	1 (2)	0	1 (2)	.47
Hypertension	47 (76)	15 (71)	32 (78)	.56
AF	40 (65)	11 (52)	29 (71)	.15
CVD	13 (21)	6 (29)	7 (17)	.29
PAD	7 (11)	4 (19)	3 (7)	.17
Diabetes	33 (53)	11 (52)	22 (54)	.92
CKD	19 (31)	9 (43)	10 (24)	.14
Smoking history	34 (55)	11 (52)	23 (56)	.78
Admission medication				
Loop diuretic	28 (45)	8 (38)	20 (49)	.42
ACEI/ARB	42 (68)	13 (62)	29 (71)	.48
β-Blocker	42 (68)	14 (67)	28 (68)	.90
MRA	1 (2)	0	1 (2)	.47
Antiplatelet	21 (34)	9 (43)	12 (29)	.28
Statin	42 (68)	12 (57)	30 (73)	.20
Laboratory tests				
eGFR, mean (SD), mL/min/1.73 m^2	65 (21)	63 (15)	66 (24)	.58
CRP, median (IQR), mg/L	13 (5-21)	9 (4-22)	13 (7-21)	.61
Hb, mean (SD), g/L	123 (19)	119 (20)	125 (19)	.32
hsTnI, median (IQR), ng/L	16 (7-29)	20 (14-36)	16 (5-25)	.22
No.	37	11	26	
BNP, median (IQR), pg/mL	355 (177-904)	197 (123-623)	569 (189-1253)	.04
No.	33	13	20	
NT-proBNP, median (IQR), pg/mL	1385 (1040-2819)	1366 (414-2494)	1459 (1152-2948)	.37
Echocardiography, mean (SD)				
LVEF, %	58 (6)	60 (6)	57 (5)	.06
E/e'	14.1 (4.9)	13.5 (4.2)	14.4 (5.3)	.54
LA volume index, mL/m^2	46 (15)	43 (11)	47 (17)	.26
Estimated PASP, mm Hg	39 (14)	42 (16)	36 (12)	.25
Valve disease (mild or moderate)	50 (81)	17 (81)	33 (80)	.97

(continued)

Table 2. Clinical Characteristics by Presence or Absence of Endothelium-Independent Coronary Microvascular Dysfunction (continued)

Characteristic	No. (%)			P value
	All coronary physiologic testing (n = 62)	No endothelium-independent CMD (n = 21)	Endothelium-independent CMD (n = 41)	
CMRI, mean (SD)				
No.	35	11	24	
LVEF, %	59 (7)	58 (7)	59 (7)	.81
LVEDV index, mL/m^2	74 (22)	75 (19)	74 (23)	.94
LV mass index, g/m^2	67 (15)	70 (18)	65 (13)	.32
LA volume index, mL/m^2	68 (22)	65 (14)	69 (25)	.63
RVEF, %	52 (9)	49 (8)	54 (9)	.18
RVEDV index, mL/m^2	77 (22)	84 (27)	73 (18)	.19
Any LGE	22 (63)	7 (64)	15 (62)	.95
Ischemic LGE	10 (29)	3 (27)	7 (29)	.91
Nonischemic LGE	13 (37)	4 (36)	9 (38)	.95
Native T1, ms	1279 (67)	1308 (70)	1266 (63)	.10
ECV, %	28.0 (4.2)	29.5 (3.4)	27.4 (4.5)	.23
MPRI, median (IQR)	1.66 (1.39-1.87)	1.55 (1.33-1.85)	1.70 (1.39-1.97)	.37
Inducible perfusion defect	11 (38)	4 (40)	7 (37)	.87
Ischemic LV segments	3 (4)	3 (5)	3 (4)	.98
Invasive assessment				
Obstructive epicardial CAD	26 (42)	10 (48)	16 (39)	.52
Angiographically normal	11 (18)	3 (14)	8 (20)	.61
Coronary artery assessed with invasive physiologic tests				
LAD	43 (69)	17 (81)	26 (63)	.29
LCx	8 (13)	1 (5)	7 (17)	
RCA	11 (18)	3 (14)	8 (20)	
Resting T_{mn}, median (IQR), s	0.71 (0.42-1.22)	0.66 (0.45-0.81)	0.83 (0.42-1.27)	.27
Hyperemic T_{mn}, median (IQR), s	0.35 (0.21-0.51)	0.23 (0.18-0.30)	0.41 (0.33-0.65)	<.001
FFR, median (IQR)[a]	0.91 (0.86-0.94)	0.90 (0.85-0.91)	0.93 (0.89-0.95)	.03
CFR, median (IQR)	2.1 (1.4-2.7)	2.6 (2.4-3.1)	1.7 (1.3-2.4)	<.001
IMR, median (IQR)	23 (15-39)	15 (12-20)	29 (23-45)	<.001
No.	41	12	29	
Endothelium-dependent CMD	10 (24)	4 (33)	6 (21)	.39
No.	59	21	38	
LVEDP, mean (SD), mm Hg	12 (5)	12 (4)	13 (6)	.42

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; CRP, C-reactive protein; CVD, cerebrovascular disease; E/e', estimated LV filling pressures on echocardiography; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; Hb, hemoglobin; HF, heart failure; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; IQR, interquartile range; LA, left atrial; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone BNP; NYHA, New York Heart Association; PAD, peripheral arterial disease; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVEDV, right-ventricular end-diastolic volume; RVEF, right-ventricular ejection fraction; T_{mn}, mean transit time.

SI conversion factors: To convert BNP to nanograms per liter, multiply by 1; CRP to milligrams per liter, multiply by 10; Hb to grams per liter, multiply by 10.

[a] In patients with obstructive epicardial stenosis, FFR value measured in another non-obstructed coronary artery.

Imaging Evidence of Myocardial Infarction

Fifty-two participants underwent LGE CMRI. Fourteen individuals (27%; 95% CI, 16%-41%) had subendocardial or transmural LGE in the distribution of a coronary artery territory consistent with previous myocardial infarction (Figure 2), of whom 8 patients had no clinical history of myocardial infarction. Participants with CMRI evidence of myocardial infarction were more likely to have a clinical history of CAD, myocardial infarction, and coronary revascularization, and were less likely to have atrial fibrillation than those without CMRI evidence of myocardial infarction (eTable 5 in the Supplement). Those with CMRI-proven myocardial infarction had more obstructive CAD than those without evidence of myocardial infarction, but there were similar rates of endothelium-independent and endothelium-dependent CMD.

Diffuse Myocardial Fibrosis

Of the 48 patients who had pre- and post-contrast T1 mapping, 20 (42%; 95% CI, 28%-56%) had an extracellular volume greater than 30%, consistent with diffuse myocardial fibrosis (Figure 2). There were no major differences in the clinical characteristics of individuals with and without a high extracellular volume (eTable 6 in the Supplement). On CMRI, participants with diffuse myocardial fibrosis had larger right

Table 3. Clinical Characteristics by Presence or Absence of Endothelium-Dependent Coronary Microvascular Dysfunction

Characteristic	No. (%)			*P* value
	All coronary vasoreactivity testing (n = 41)	No endothelium-dependent CMD (n = 31)	Endothelium-dependent CMD (n = 10)	
Age, mean (SD), y	71 (9)	71 (10)	71 (9)	.84
Sex				
Women	25 (61)	16 (52)	9 (90)	.03
Men	16 (39)	15 (48)	1 (10)	
BMI, mean (SD)	34 (8)	34 (8)	34 (10)	.82
Clinical frailty scale				
1: Very fit	1 (2)	1 (3)	0	.87
2: Well	8 (20)	6 (19)	2 (20)	
3: Managing well	17 (41)	13 (42)	4 (40)	
4: Vulnerable	6 (15)	4 (13)	2 (20)	
5: Mildly frail	6 (15)	4 (13)	2 (20)	
6: Moderately frail	3 (7)	3 (10)	0	
NYHA functional class				
II	2 (5)	2 (6)	0	.64
III	21 (51)	15 (48)	6 (60)	
IV	18 (44)	14 (45)	4 (40)	
Vital signs, mean (SD)				
Heart rate, bpm	90 (27)	89 (27)	92 (27)	.74
Systolic blood pressure, mm Hg	152 (30)	155 (32)	142 (18)	.22
Medical history				
Previous HF diagnosis	15 (37)	11 (35)	4 (40)	.80
Any CAD	9 (22)	7 (23)	2 (20)	.86
MI	6 (15)	5 (16)	1 (10)	.63
Angina	3 (7)	2 (5)	1 (10)	.71
Revascularization	4 (10)	2 (5)	2 (20)	.21
PCI	4 (10)	2 (5)	2 (20)	.21
CABG	0	0	0	NA
Hypertension	31 (76)	24 (77)	7 (70)	.63
AF	28 (68)	18 (58)	10 (100)	.01
CVD	7 (17)	6 (19)	1 (10)	.49
PAD	3 (7)	3 (10)	0	.31
Diabetes	18 (44)	15 (48)	3 (30)	.31
CKD	8 (20)	8 (26)	0	.07
Smoking history	23 (56)	21 (68)	2 (20)	<.01
Admission medication				
Loop diuretic	20 (49)	14 (45)	6 (60)	.41
ACEI/ARB	26 (63)	21 (68)	5 (50)	.31
β-Blocker	25 (61)	17 (55)	8 (80)	.16
MRA	1 (2)	1 (3)	0	.57
Antiplatelet	11 (27)	10 (32)	1 (10)	.17
Statin	28 (68)	22 (71)	6 (60)	.52
Laboratory tests				
eGFR, mean (SD), mL/min/1.73 m^2	69 (22)	67 (23)	75 (17)	.37
CRP, median (IQR), mg/L	12 (5-24)	14 (7-35)	5 (4-18)	.14
Hb, mean (SD), g/L	126 (19)	126 (21)	124 (10)	.68
hsTnI, median (IQR), ng/L	16 (10-25)	16 (10-29)	16 (9-25)	.68
No.	23	19	4	
BNP, median (IQR), pg/mL	323 (177-794)	355 (177-1017)	254 (154-559)	.57
No.	21	15	6	
NT-proBNP, median (IQR), pg/mL	1385 (1132-2819)	1366 (1132-3076)	1562 (540-2108)	.97
Echocardiography, mean (SD)				
LVEF, %	59 (6)	58 (6)	62 (7)	.11
E/e'	12.8 (4.0)	13.0 (4.1)	11.9 (3.6)	.56
LA volume index, mL/m^2	47 (17)	45 (17)	55 (17)	.15
Estimated PASP, mm Hg	37 (13)	36 (14)	40 (12)	.45
Valve disease (mild or moderate)	35 (85)	26 (84)	9 (90)	.63

(continued)

Table 3. Clinical Characteristics by Presence or Absence of Endothelium-Dependent Coronary Microvascular Dysfunction (continued)

Characteristic	No. (%)			P value
	All coronary vasoreactivity testing (n = 41)	No endothelium-dependent CMD (n = 31)	Endothelium-dependent CMD (n = 10)	
CMRI, mean (SD)				
No.	22	18	4	
LVEF, %	60 (7)	59 (7)	64 (5)	.21
LVEDV index, mL/m^2	71 (22)	74 (22)	58 (17)	.17
LV mass index, g/m^2	64 (17)	67 (17)	52 (9)	.12
LA volume index, mL/m^2	72 (24)	72 (27)	71 (9)	.91
RVEF, %	52 (9)	52 (10)	53 (6)	.96
RVEDV index, mL/m^2	75 (23)	79 (22)	61 (20)	.18
Any LGE	11 (50)	11 (61)	0	.03
Ischemic LGE	4 (22)	4 (22)	0	.30
Nonischemic LGE	8 (73)	8 (44)	0	.10
Native T1, ms	1276 (75)	1272 (74)	1295 (90)	.59
ECV, %	27.4 (4.1)	27.3 (4.1)	27.7 (4.4)	.88
MPRI, median (IQR)	1.60 (1.39-1.87)	1.60 (1.39-1.87)	1.60 (1.49-1.71)	.87
Inducible perfusion defect	5 (26)	4 (27)	1 (25)	.95
Ischemic LV segments	2 (4)	2 (5)	1 (1)	.42
Invasive assessment				
Obstructive epicardial CAD	5 (12)	5 (16)	0	.18
Angiographically normal	11 (27)	7 (23)	4 (40)	.28
Coronary artery assessed with invasive physiologic tests				
LAD	30 (73)	21 (68)	9 (90)	
LCx	4 (10)	3 (10)	1 (10)	.25
RCA	7 (17)	7 (23)	0	
Resting T_{mn}, median (IQR), s	0.84 (0.49-1.28)	0.99 (0.54-1.42)	0.56 (0.34-1.22)	.15
Hyperemic T_{mn}, median (IQR), s	0.36 (0.21-0.54)	0.42 (0.23-0.66)	0.27 (0.20-0.38)	.10
FFR, median (IQR)[a]	0.92 (0.87-0.94)	0.91 (0.85-0.94)	0.94 (0.91-0.95)	.22
CFR, median (IQR)	2.3 (1.4-3.0)	2.4 (1.3-3.0)	2.0 (1.5-3.8)	.99
CFR <2.0	19 (46)	14 (45)	5 (50)	.79
IMR, median (IQR)	26 (18-42)	29 (20-50)	21 (14-28)	.07
IMR ≥25	23 (56)	19 (61)	4 (40)	.24
Endothelium-independent CMD	29 (71)	23 (74)	6 (60)	.39
No.	40	30	10	
LVEDP, mean (SD), mm Hg	12 (5)	12 (5)	12 (5)	.90

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; CMRI, cardiac magnetic resonance imaging; CRP, C-reactive protein; CVD, cerebrovascular disease; E/e', estimated LV filling pressures on echocardiography; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; Hb, hemoglobin; HF, heart failure; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; IQR, interquartile range; LA, left atrial; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal prohormone BNP; NYHA, New York Heart Association; PAD, peripheral arterial disease; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RCA, right coronary artery; RVEDV, right-ventricular end-diastolic volume; RVEF, right-ventricular ejection fraction; T_{mn}, mean transit time.

SI conversion factors: To convert BNP to nanograms per liter, multiply by 1; CRP to milligrams per liter, multiply by 10; Hb to grams per liter, multiply by 10.

[a] In patients with obstructive epicardial stenosis, FFR value was measured in another nonobstructed coronary artery.

ventricular end-diastolic volumes and lower MPRI than participants with a normal extracellular volume. Those with an elevated extracellular volume had more obstructive CAD than those with a normal extracellular volume, but a similar rate of endothelium-independent and -dependent CMD. The overlap of the CMRI findings is displayed in eFigure 5 in the Supplement.

Clinical Outcomes

During a median follow-up of 18 (interquartile range, 14-22) months, the composite outcomes examined were more common in patients with vs without obstructive epicardial CAD, although the number of events was small (eFigure 6 in the Supplement). Patients with obstructive CAD had more adverse events during follow-up (28 [74%]) than those without obstructive CAD (17 [46%]). Eight patients (21% of those with obstructive CAD) underwent percutaneous coronary revascularization.

There were no significant differences in outcomes between patients with and without endothelium-independent CMD (eFigure 7 and eFigure 8 in the Supplement), endothelium-dependent CMD (eFigure 9 in the Supplement), or any

CMD (eFigure 10 in the Supplement), but the number of events was small. The composite outcomes were more common in patients with vs without an impaired global MPRI (eFigure 11 in the Supplement). Those with an inducible perfusion defect (eFigure 12 in the Supplement), imaging evidence of myocardial infarction (eFigure 13 in the Supplement), and an elevated extracellular volume (eFigure 14 in the Supplement) had more adverse clinical outcomes than those without.

Discussion

We found that 91% of patients hospitalized with HFpEF had epicardial CAD, CMD, or both. Of those without epicardial CAD, more than 80% had CMD (endothelium-independent or -dependent). Reliable estimates of prevalence of epicardial CAD can be obtained only from invasive or noninvasive coronary imaging or autopsy studies. One autopsy study including 119 patients with HFpEF examined over a 33-year period reported that 65% of the patients had 50% or more stenosis of at least 1 epicardial coronary artery.[7] Several coronary angiography studies have been conducted, reporting a CAD prevalence of 35% to 76%, although these studies have largely been convenience samples of patients undergoing clinically indicated coronary angiography, have used different anatomic criteria to define CAD, and did not include coronary physiologic function assessments.[1,22-30] Consequently, it is unclear whether the high CAD prevalence reported represents referral bias or whether the real burden of CAD in patients with HFpEF is underrecognized. We conducted a systematic study to assess CAD prevalence in a relatively unselected HFpEF cohort using coronary angiography, although, inevitably, there was still selection bias due to the exclusion of patients with severe kidney dysfunction, frailty, or both. We also conducted invasive coronary physiologic function studies to determine whether stenoses were flow-limiting and to detect CMD, and CMRI to assess myocardial perfusion and fibrosis (ie, to ensure systematic assessment of CAD, myocardial ischemia/infarction, and myocardial fibrosis in HFpEF).

Half of the patients with invasively documented CAD in this study had no history of CAD, highlighting the high burden of unrecognized CAD in HFpEF, consistent with other studies.[7,22] In addition, we found that neither semiquantitative CMR perfusion imaging (using MPRI) nor the presence of a visual perfusion defect predicted obstructive epicardial CAD on invasive investigation, suggesting that angiography may be necessary to diagnose CAD in patients with HFpEF. This finding is consistent with the results of one retrospective study that reported poor diagnostic accuracy of noninvasive ischemia testing in detecting epicardial CAD.[1] The reasons why CMRI assessments of myocardial perfusion did not identify obstructive CAD are uncertain but may include the presence of impaired perfusion due to CMD, the absence of reversible ischemia in the context of nonviable myocardium, or collateral perfusion of a territory supplied by a diseased epicardial artery. Furthermore, MPRI represents global myocardial perfusion, which may not be influenced by areas of regional ischemia.

In this exploratory analysis, we found that patients with obstructive epicardial CAD had higher rates of adverse clinical outcomes than those without obstructive disease, predominantly related to hospitalizations, although there were few events overall. To our knowledge, the most appropriate medical therapy and the potential role of revascularization in HFpEF have never been investigated in randomized clinical trials.

Another novel finding was that two-thirds of patients had endothelium-independent CMD identified on invasive coronary physiologic function testing, with a similar prevalence in those with (62%) and without (69%) obstructive epicardial disease. A similar prevalence of CMD was found in a convenience sample of 30 patients with HFpEF undergoing clinically indicated angiography.[9] However, in another retrospective study of 162 patients with HFpEF undergoing clinically indicated coronary microvascular function testing over a 25-year period, only 43% of the participants had endothelium-independent CMD (defined as CFR ≤2.5).[8]

In the PROMIS-HFpEF study, echocardiographic measurement of CFR in the left anterior descending coronary artery identified CMD in 75% of the participants, using a CFR threshold less than 2.5 (compared with 65% in our study using the same cutoff point). Epicardial CAD was not systematically excluded in PROMIS-HFpEF and clinically unrecognized obstructive CAD, which was present in 39% of our cohort, could have confounded the results. In addition to the different techniques used to measure CFR, other variations in study design may have contributed to different prevalence estimates, including the clinical status of the HFpEF population studied (ambulatory vs hospitalized) and the lower LV ejection fraction inclusion criterion (≥40%) in PROMIS-HFpEF. Earlier studies, including PROMIS-HFpEF, have found that CMD is associated with adverse outcomes in patients with HFpEF.[31,32]

In assessing endothelium-dependent coronary vasomotor function by administering intracoronary acetylcholine, we found that only 24% of the patients had microvascular vasospasm, reflecting coronary microvascular endothelial dysfunction and smooth muscle dysfunction. Our findings suggest that CMD in patients with HFpEF is predominantly due to endothelium-independent abnormalities, such as abnormal vascular remodeling, extrinsic vascular compression, and microvascular rarefaction, rather than endothelial and vascular smooth muscle dysfunction. This finding may explain the neutral outcomes of trials of therapies targeting nitric oxide-cyclic guanosine monophosphate protein kinase G signaling.[33]

We also examined the potential myocardial consequences associated with CAD and CMD in HFpEF, finding that 27% of the patients had imaging evidence of myocardial infarction on LGE. Even among those with no clinical history, 18% had evidence of clinically unrecognized myocardial infarction on CMRI. Our prevalence estimate of previous myocardial infarction is lower than the estimate in an autopsy study in patients with HF and LV ejection fraction greater than or equal to 40% (42% on gross pathologic examination),[7] but higher than in a CMRI study using LGE in ambulatory patients with HFpEF (10%).[34]

Myocardial fibrosis may contribute to myocardial stiffness and diastolic dysfunction in HFpEF.[7,35] Extracellular volume assesses myocardial fibrosis, and 42% of our patients had high extracellular volume (>30%). Although the numbers were small, patients with high extracellular volume had more adverse events than those with normal extracellular volume, consistent with previous evidence that myocardial fibrosis is associated with poor outcomes in HFpEF.[36-38] Mineralocorticoid receptor antagonists might be most beneficial when targeted at patients with high extracellular volume.

In summary, we found 91% of participants with hospitalized HFpEF had evidence of epicardial CAD, CMD, or both (Figure 2). Of those without obstructive epicardial CAD, over 80% of patients had CMD.

Limitations

The study has limitations. Although we sought to conduct a systematic study of consecutive hospitalized patients with HFpEF at 3 centers, most of such patients did not meet inclusion criteria or did not agree to participate in the study. Furthermore, the enrolled patients did not undergo all study procedures, limiting our ability to fully compare coronary evaluation modalities across most patients. Some patients dropped out before invasive and noninvasive investigations, predominantly owing to a deterioration in their clinical status or kidney function. It was necessary to exclude patients with severe kidney dysfunction to allow safe administration of contrast agents during the imaging studies. In addition, patients with severe frailty were excluded because invasive assessment was believed to be clinically inappropriate. These factors limit the generalizability of the study results to these groups.

The delay between recruitment and performing the invasive coronary assessment may have affected the results of coronary microvascular testing. Elevated LV filling pressures can contribute to CMD as a result of extravascular compression of arterioles.[39] Invasively assessed LV end-diastolic pressure was normal in more than half of the study participants, but they may not have had the assessment performed during the index hospitalization.

Our results may not be representative of ambulatory patients with HFpEF and we did not have an age- and comorbidity-matched control group, which would have been ethically difficult. The clinical outcomes were not adjudicated and are exploratory; further studies are required to assess the prognostic impact of invasively assessed epicardial CAD and CMD in HFpEF.

Conclusions

In this cohort study, epicardial CAD and CMD were common in the patients analyzed. These conditions might be unrecognized in hospitalized patients with HFpEF and may be therapeutic targets.

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Supervision: Berry, Oldroyd, Rocchiccioli, Murphy, Ford, McEntegart, Lang, Jhund, Campbell, McMurray, Petrie.

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from Theracos, with Glasgow University paid by Theracos for time spent as principal investigator for the BEST trial and meetings related to this trial; Theracos has also paid travel and accommodations for some of these meetings, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support from DalCor Pharmaceuticals, with payment to Glasgow University for time spent as steering committee member for the Dal-GenE trial and meetings related to this trial, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support from Merck, with payment to Glasgow University for time spent on the data safety monitoring committee for the MK-3102 program and for the VICTORIA trial and meetings related to these trials, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support from GlaxoSmithKline, with payment to Glasgow University for time spent as coprincipal investigator and steering committee member for the Harmony-Outcomes trial (albiglutide) and 2 trials, ASCEND-D and ASCEND-ND, using daprodustat, and meetings related to these trials, and GlaxoSmithKline also paid travel and accommodations for some of these meetings, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to these trials/drugs; payment from Bristol Myers Squibb to Glasgow University for time spent as a steering committee member for the STAND-UP clinical trial (using an HNO donor) in heart failure and meetings related to this trial, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support, with payment from Vifor-Fresenius to Glasgow University paid by Kings College Hospital (who received a grant from KRUK and Vifor-Fresenius who manufacture intravenous iron) for time spent as steering committee member for the PIVOTAL trial (using intravenous iron) and for running the end point adjudication committee for this trial, as well as meetings related to PIVOTAL. Kings College Hospital also paid for travel and accommodations for some of these meetings with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support from Kidney Research UK (KRUK) with payment made to Glasgow University by Kings College Hospital (who received a grant from KRUK and Vifor-Fresenius who manufactures intravenous iron) for time spent as a steering committee member for the PIVOTAL trial (using intravenous iron) and for running the end point adjudication committee for this trial, as well as meetings related to the PIVOTAL trial, with Kings College Hospital also paying for travel and accommodations for some of these meetings through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; payment from Alnylam to Glasgow University for time spent on the advisory board committee for the ALN-AGT trial and meetings related to this trial, with payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; nonfinancial support from AbbVie, with Glasgow University paid by AbbVie (who manufactures atrasentan) for time spent as a steering committee member for the SONAR trial (using atrasentan) and meetings related to this trial, with AbbVie also paying for travel and accommodations for some of these meetings and payments made through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to this trial/this drug; payment for advice about development of praliciguat as a potential therapy for heart failure from Cyclerion to Glasgow University, has been paid by Cyclerion, other from Cardurion My employer, Glasgow University, has been paid by Cardurion for participation in a company advisory board about development of a PDE 9 inhibitor in heart failure; has received nonfinancial support from Novartis, who paid Glasgow University for time spent as an executive committee member and then coprincipal investigator of ATMOSPHERE, coprincipal investigator of the PARADIGM-HF trial, and executive/steering committee member for PARACHUTE-HF, PARADISE-MI, and PERSPECTIVE trials (with sacubitril/valsartan), and meetings/presentations related to these trials and aliskiren and sacubitril/valsartan, including payment for travel and accommodations for some of these meetings through a consultancy with Glasgow University, and Dr McMurray did not received personal payments in relation to these trials/drugs; Glasgow University has also been paid by Novartis for Dr McMurray's participation in a company advisory board that meets twice per year and covers the cardiometabolic field; nonfinancial support from Servier, with payment to Glasgow University for activities related to role as steering committee member for the GALACTIC-HF trial through a consultancy with Glasgow University, and Dr McMurray did not receive personal payments in relation to these trials/this drug; and lecture fees from Abbott, Hickma, Sun Pharmaceuticals, and Servier outside the submitted work. 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