Supplementary Online Content

Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol*. Published online June 23, 2021. doi:10.1001/jamacardio.2021.1825

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methods

Patient recruitment, inclusion and exclusion criteria

Between January 2017 and August 2018, consecutive patients hospitalized with suspected heart failure (HF) were screened for inclusion in the study. Patients with HF with preserved ejection fraction (HFpEF, defined according to the 2016 European Society for Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure[1]) were prospectively recruited from three centres in Scotland, UK. The inclusion criteria were: symptoms and signs of HF; elevated natriuretic peptide levels (B-type natriuretic peptide [BNP] ≥100 pg/mL or N-terminal prohormone BNP [NT-proBNP] ≥300 pg/mL); an LV ejection fraction (LVEF) ≥50%; and evidence of relevant structural heart disease on echocardiography (i.e. LV hypertrophy [maximal diastolic LV septal or posterior wall thickness ≥13 mm]; and/or left atrial [LA] dilatation [indexed LA volume >34 mL/m^2]; and/or evidence of elevated LV filling pressures [E/e' ≥13 with a mean e' <9 cm/s]). Major exclusion criteria were: acute coronary syndrome (troponin elevation in the context of a primary diagnosis of HF was not an exclusion); significant valvular heart disease (i.e. greater than moderate left-sided valve disease); known or suspected hypertrophic/infiltrative cardiomyopathy or constrictive pericarditis; a previously documented LVEF <40%; and those unable or unwilling to provide written informed consent. Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 were excluded to allow the safe administration of contrast agents during invasive and non-invasive investigations. Patients with severe frailty (i.e. Clinical Frailty Scale [CFS] >6)[2] were also excluded as invasive coronary angiography was considered clinically inappropriate and to carry excessive risk.

Study procedures

Invasive coronary assessment

Invasive coronary assessment was performed at a large regional cardiac center (Golden Jubilee National Hospital, Clydebank, UK) by operators with extensive experience in invasive coronary physiology (K.G.O., J.P.R, M.M.L.). LV end-diastolic pressure (LVEDP) was routinely measured. The attending interventional cardiologist described the coronary anatomy of study participants and quantitative coronary angiography (QCA) analysis was performed using computer-assisted analysis (QAngio XA 7.3, Medis, Leiden, Netherlands).

Guidewire-based coronary physiologic testing

Coronary guidewire assessment was performed on a single major epicardial coronary artery. The left anterior descending artery was the preferred vessel, although if technical factors precluded guidewire-based assessment of this vessel (e.g. severe coronary stenosis, tortuosity), the left circumflex or right coronary artery was used instead. A pressure- and temperature-sensitive coronary guidewire (Abbott Vascular *PressureWire Certus*) was advanced through a guide catheter to the distal portion of the vessel of interest. Adenosine was administered by intravenous infusion (140 μg/kg/min) to induce steady-state hyperemia and thermodilution was performed by intra-coronary injection of 3 mL of room temperature saline to assess the fractional flow reserve (FFR), coronary flow reserve (CFR), and index of microcirculatory resistance (IMR) (Figure 1). FFR was calculated as the distal coronary to aortic pressure ratio (Pd/Pa) during hyperemia.[3] Obstructive epicardial CAD was defined as: >70% stenosis of a major epicardial coronary artery (≥50% stenosis if left main coronary artery), or a 50-70% stenosis with an FFR ≤0.80.[4] In patients with a significant epicardial stenosis, CFR and IMR were measured in another (non-obstructed) coronary artery in order to assure accurate assessment of coronary microvascular function. CFR represents the coronary vasodilator capacity (epicardial and microvascular) and was calculated using thermodilution as the resting mean transit time (T_{mn}) divided by the hyperemic T_{mn}.[5] The IMR reflects the minimal resistance offered by the coronary microvasculature and was calculated as the product of the mean distal coronary artery pressure (Pd) and the T_{mn} measured simultaneously during hyperemia.[6] Endothelium-independent CMD was defined as a CFR <2.0 and/or an IMR ≥25.[5,6]

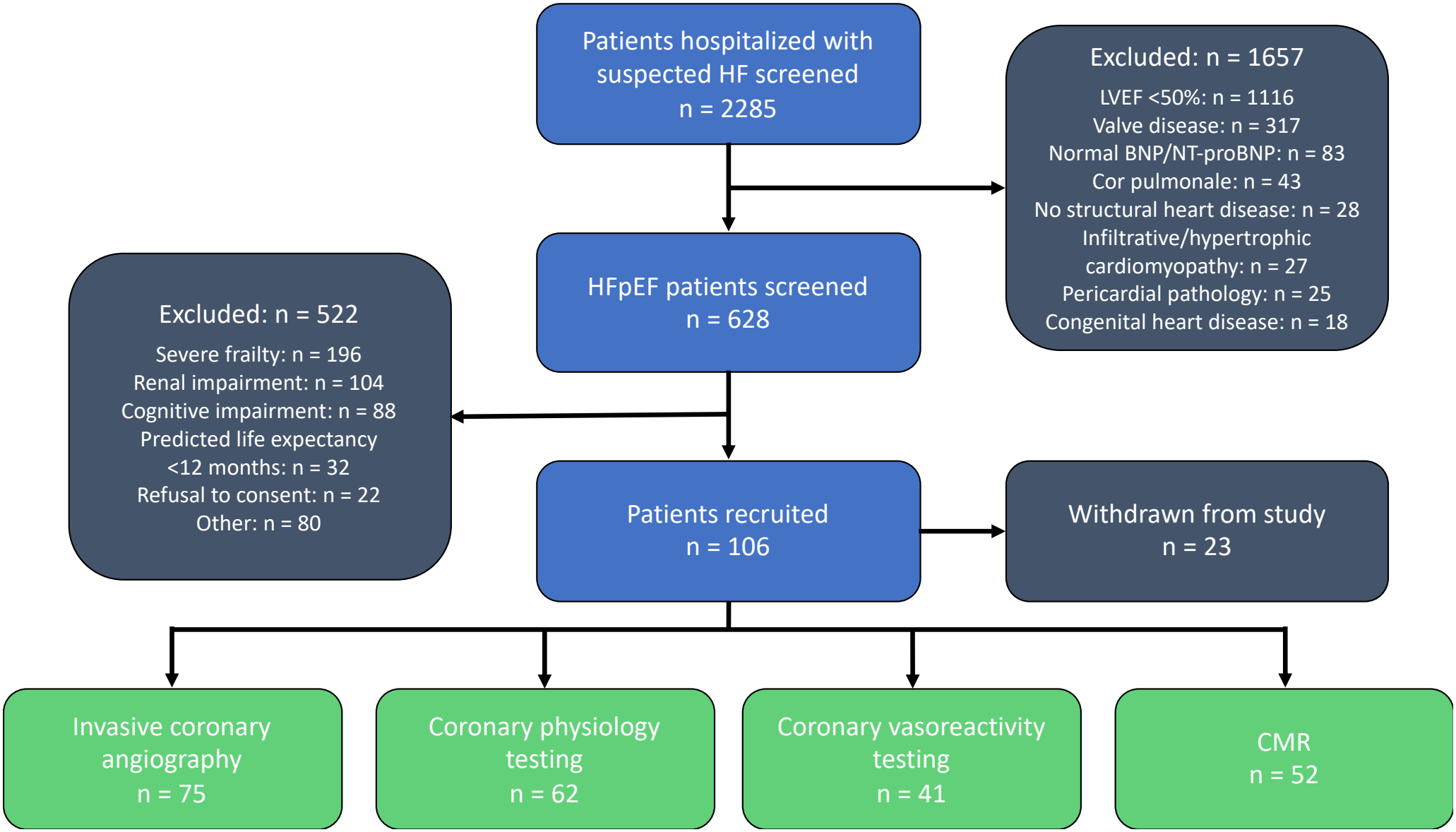
Coronary vasoreactivity testing

Coronary vasomotor function was assessed using sequential intra-coronary infusions of incremental doses of acetylcholine (ACh) through the guiding catheter (Figure 1). Coronary vasoreactivity testing was not carried out in most patients with obstructive epicardial CAD due to the risk of acute myocardial ischemia from the combination of obstructive epicardial stenosis and coronary artery spasm.[7] The infused doses of ACh were 0.364 μg, 3.64 μg, and 36.4 μg over two minutes followed by coronary vasospasm provocation testing (100 μg ACh bolus for left coronary artery or 50 μg for the right coronary artery over 20 seconds).[8,9] Finally, endothelium-independent vasodilator function was assessed by intra-coronary administration of 300 μg of glyceryl trinitrate (GTN). Following each ACh infusion, the ACh bolus and GTN administration, coronary angiography and a 12-lead electrocardiogram (ECG) were performed. QCA of the target coronary artery was performed by a trained cardiologist (C.J.R). The coronary artery measurements were performed in the region where the greatest change had occurred during coronary reactivity testing. End-diastolic cine frames that best demonstrated the segment were selected and calibration of the cine images was performed. Coronary artery diameter change (% from baseline) was measured in response to both ACh and GTN.[10] A second trained and blinded observer (T.J.F.) performed QCA on a consecutive sample of 20% of cases, with high concordance for measurements of percentage lumen diameter vasoconstriction during ACh vasospasm assessment (intraclass correlation coefficient for average measures 0.95 (95% confidence interval [CI] 0.82-0.99; $p<0.001$). Microvascular coronary vasospasm, reflecting endothelium-dependent CMD and vascular smooth muscle dysfunction, was defined as 20-90% luminal constriction and/or ischemic ECG changes in response to intra-coronary ACh infusions.[11,12] Epicardial coronary vasospasm was defined as >90% luminal constriction and ischemic ECG changes in response to intra-coronary ACh infusions or bolus.[13] Ischemic ECG changes were defined as: ≥1 mm horizontal or down-sloping ST-segment depression or ST-segment elevation; or pathological T-wave inversion in response to ACh administration.

Cardiac magnetic resonance imaging

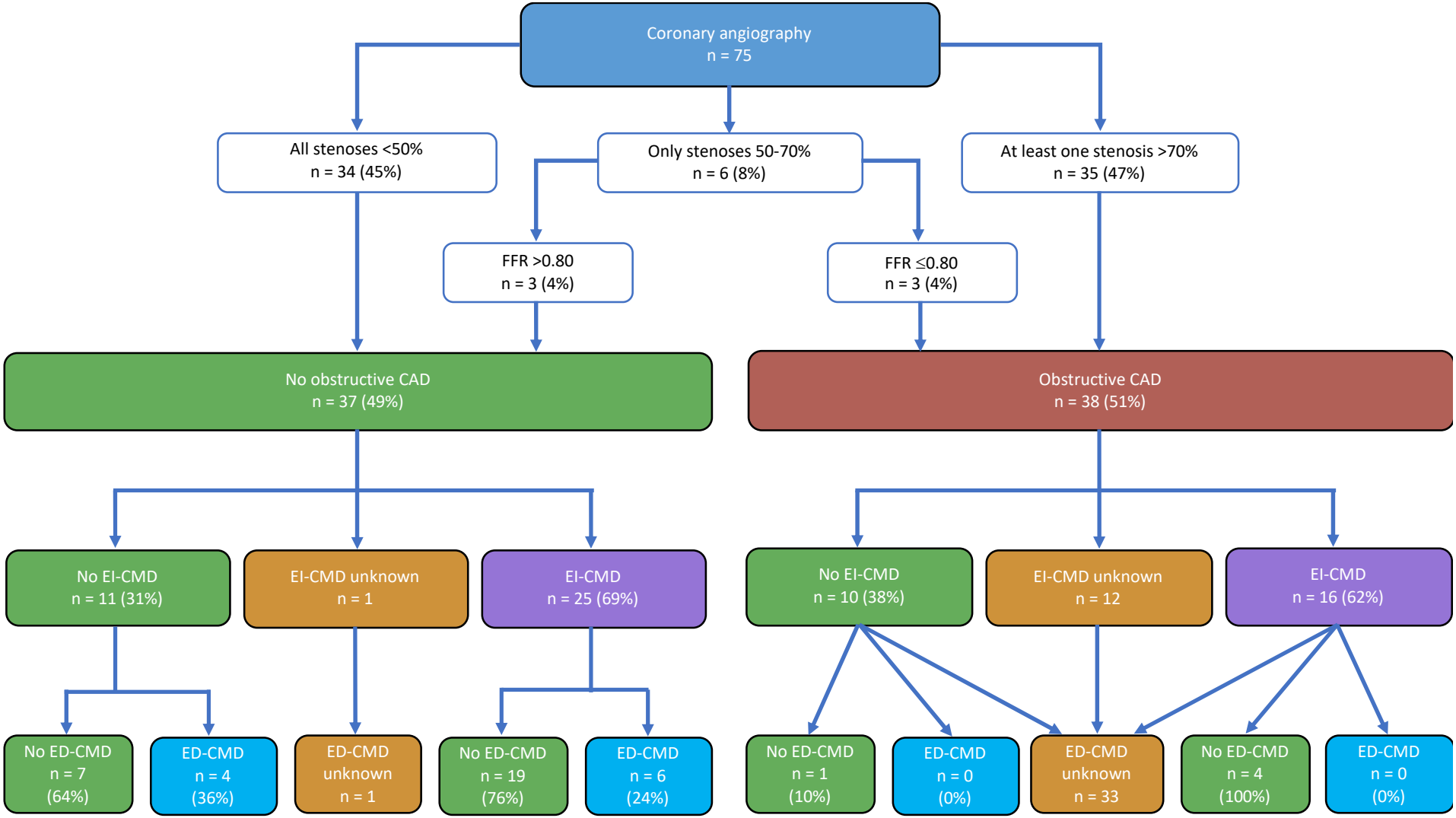
In those with no contraindication, CMR was performed with gadolinium contrast, T1 mapping, and adenosine stress perfusion imaging. All scans were performed on a 3.0 Tesla scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) based at the Glasgow Clinical Research Imaging Facility, Queen Elizabeth University Hospital, Glasgow, UK. Patients were instructed to abstain from caffeine for 24 hours prior to the examination. The CMR protocol included cine imaging (balanced steady-state free precession), adenosine stress perfusion imaging, late gadolinium enhancement (LGE) phase-sensitive inversion-recovery acquisitions, and T1 mapping (pre- and post-contrast) sequences. Perfusion imaging was performed (intravenous infusion of adenosine at 140 to 210 μg/kg/min to achieve an adequate hemodynamic stress response) with the acquisition of three matched short-axis stress and rest perfusion images. A total dose of 0.15 mmol/kg gadolinium-based contrast (*Gadovist*) was administered (0.05 mmol/kg bolus for first-pass stress perfusion, 0.05 mmol/kg bolus for first-pass rest perfusion, and 0.05 mmol/kg top-up bolus for LGE imaging). A modified Look-Locker inversion recovery sequence (MOLLI) was used for T1 mapping and performed in three matched short-axis slices in mid-diastole prior to (native T1) and 20 minutes after contrast (for quantification of extracellular volume [ECV]). Cine, LGE and first-pass perfusion imaging were independently evaluated by two experienced observers (C.J.R., C.B.). T1 and ECV maps were generated based on inline-generated, motion-corrected raw images using QMap 2.2.24 (Medis, Leiden, Netherlands) and global native T1 and ECV were calculated. Myocardial segments (based on the American Heart Association [AHA] coronary arterial 17-segment model[14]) with focal ischemic LGE were excluded from native T1 and ECV analysis. Perfusion imaging was analysed using QMass 8.1 (Medis, Leiden, Netherlands) to obtain the intensity over time curves at rest and stress for each myocardial segment and the blood-pool. The slope of the first-pass contrast enhancement for each of the myocardial segment was divided by the LV blood-pool slope and the ratio of the myocardial-perfusion index during stress to rest was defined as the myocardial-perfusion reserve index (MPRI).[15,16] Impaired global myocardial perfusion was defined as an MPRI of ≤1.84.[17] Regional myocardial perfusion was also assessed using qualitative assessment of first-pass perfusion imaging. CMR-proven myocardial infarction (MI) was defined as subendocardial or transmural LGE in the distribution of a coronary artery territory, and an ECV of >30% was considered to represent diffuse myocardial fibrosis[18].

eFigure 1: Study screening and recruitment flow diagram.



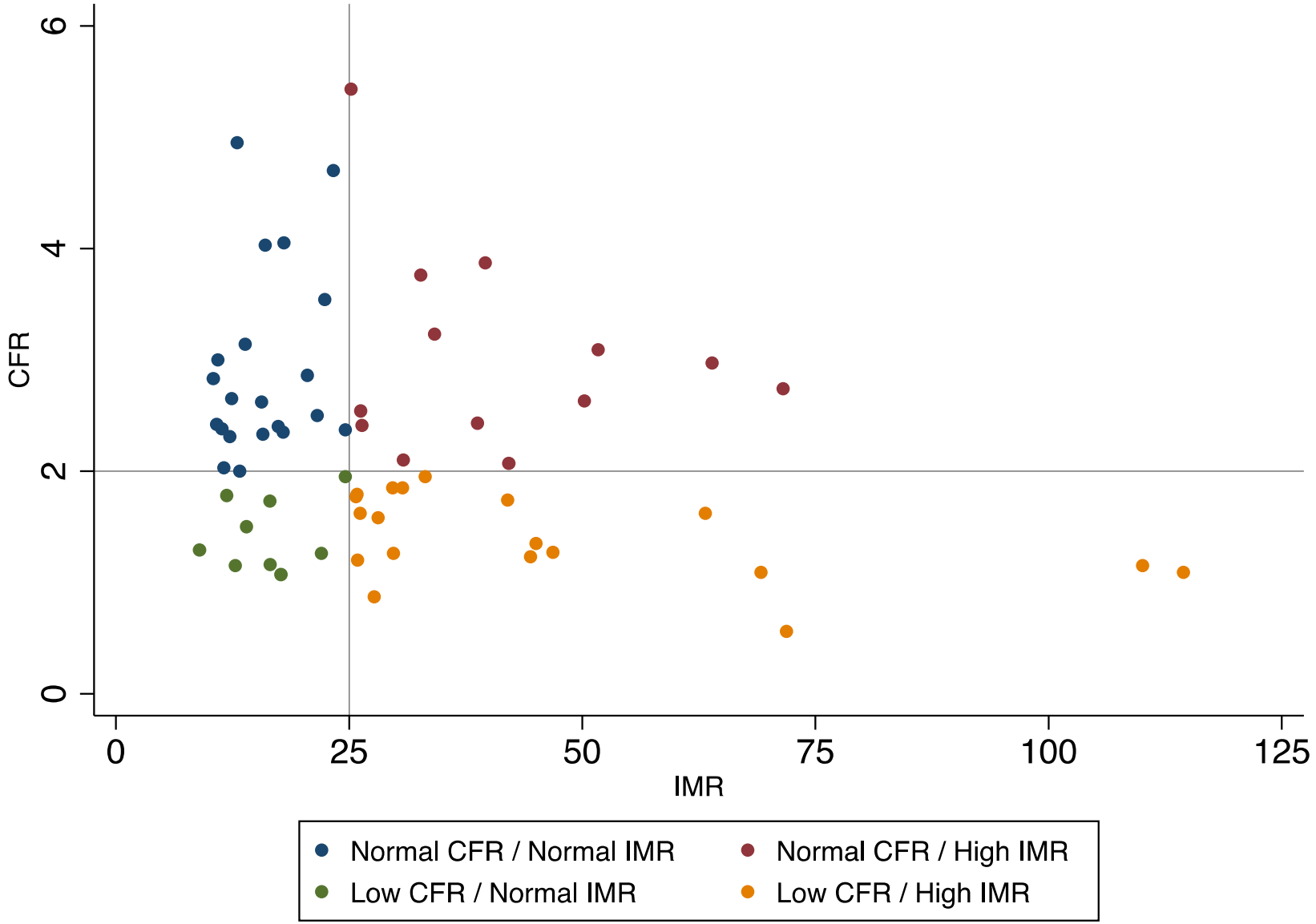
BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; HF, heart failure; HFpEF, HF with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone BNP.

eFigure 2: Overview of invasive coronary assessment.



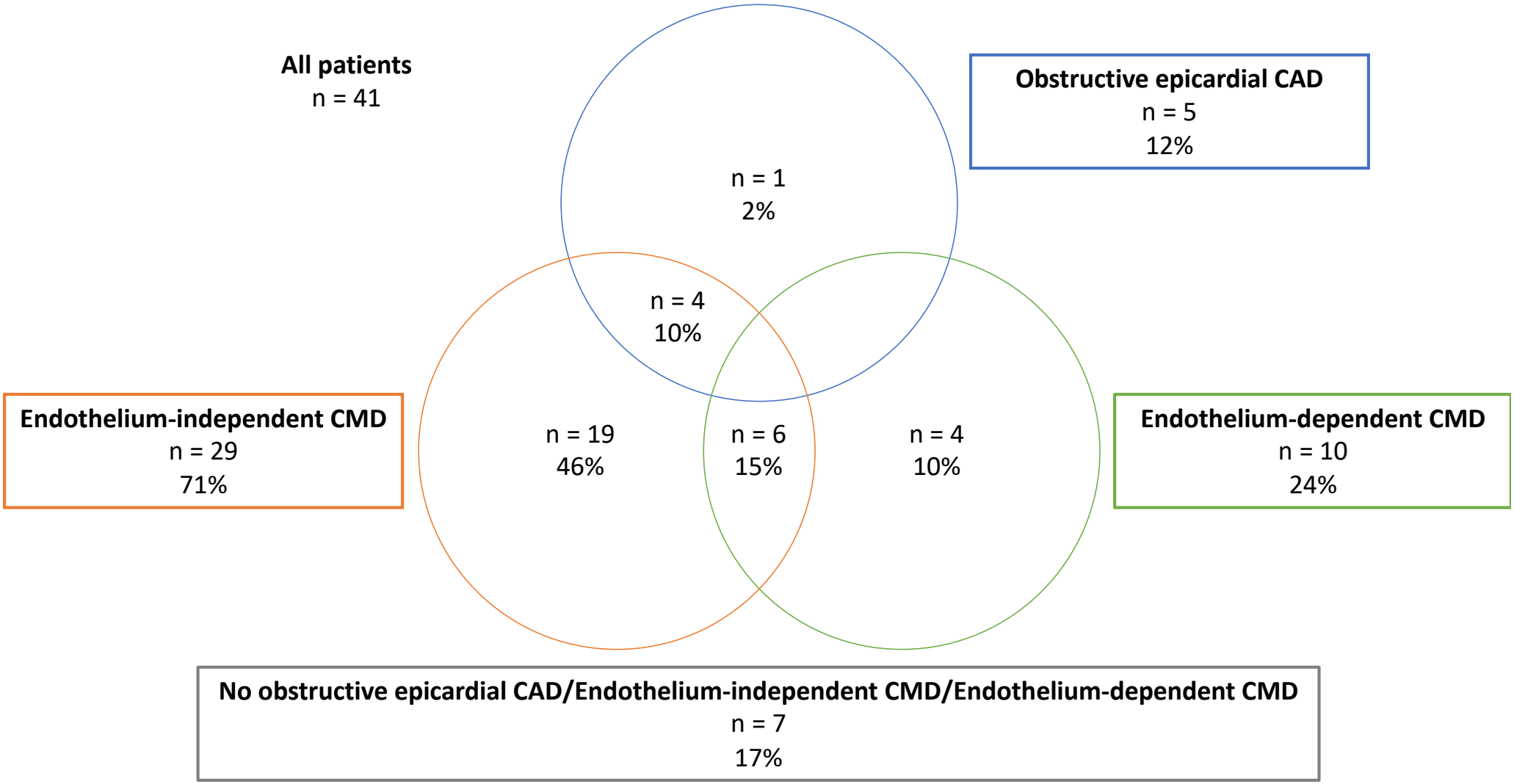
CAD, coronary artery disease; ED-CMD, endothelium-dependent coronary microvascular dysfunction; EI-CMD, endothelium-independent coronary microvascular dysfunction; FFR, fractional flow reserve.

eFigure 3: Microvascular status based on coronary flow reserve and the index of microcirculatory resistance.



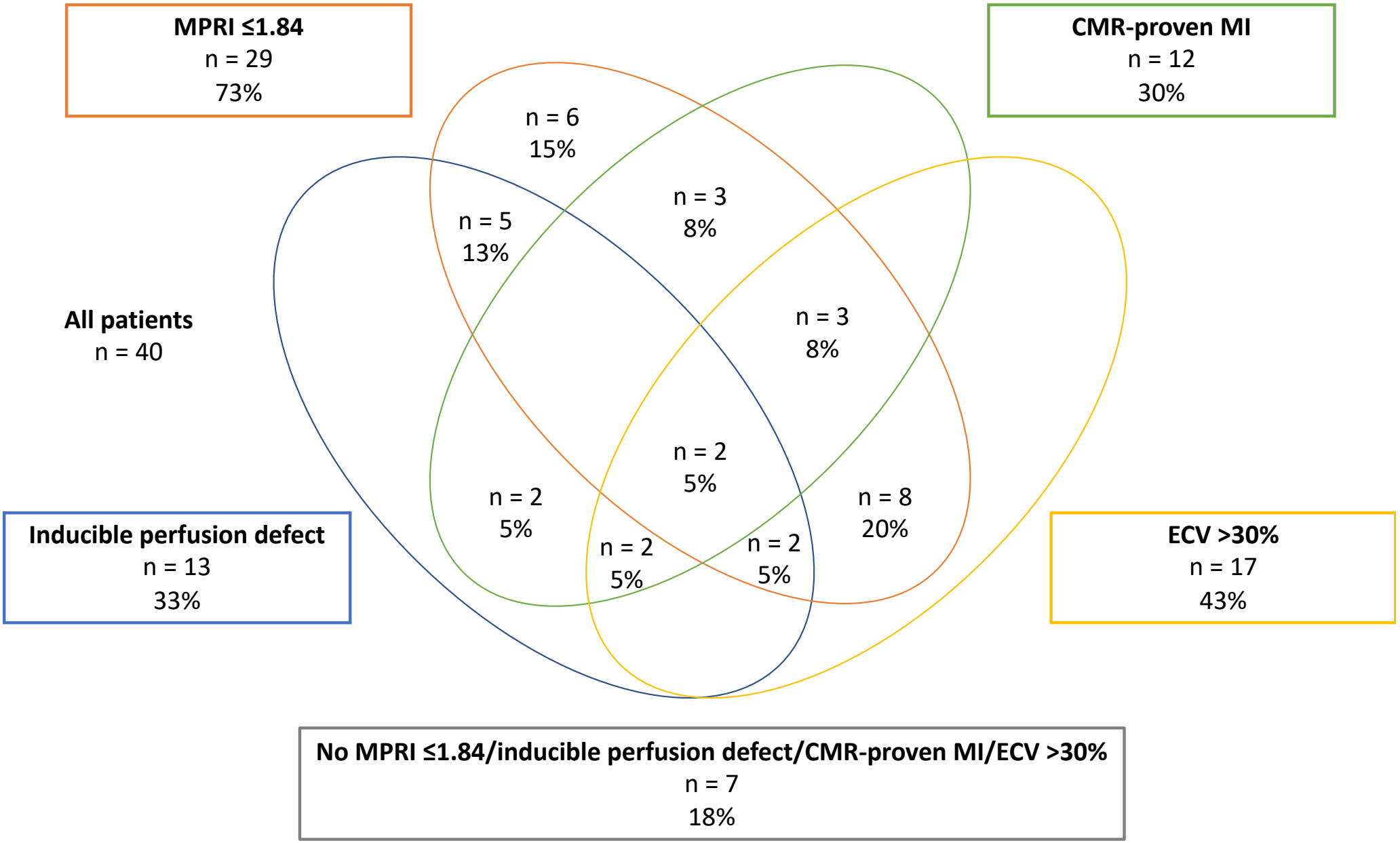
CFR, coronary flow reserve; IMR, index of microcirculatory resistance.

eFigure 4: Venn diagram of invasive coronary assessment findings.



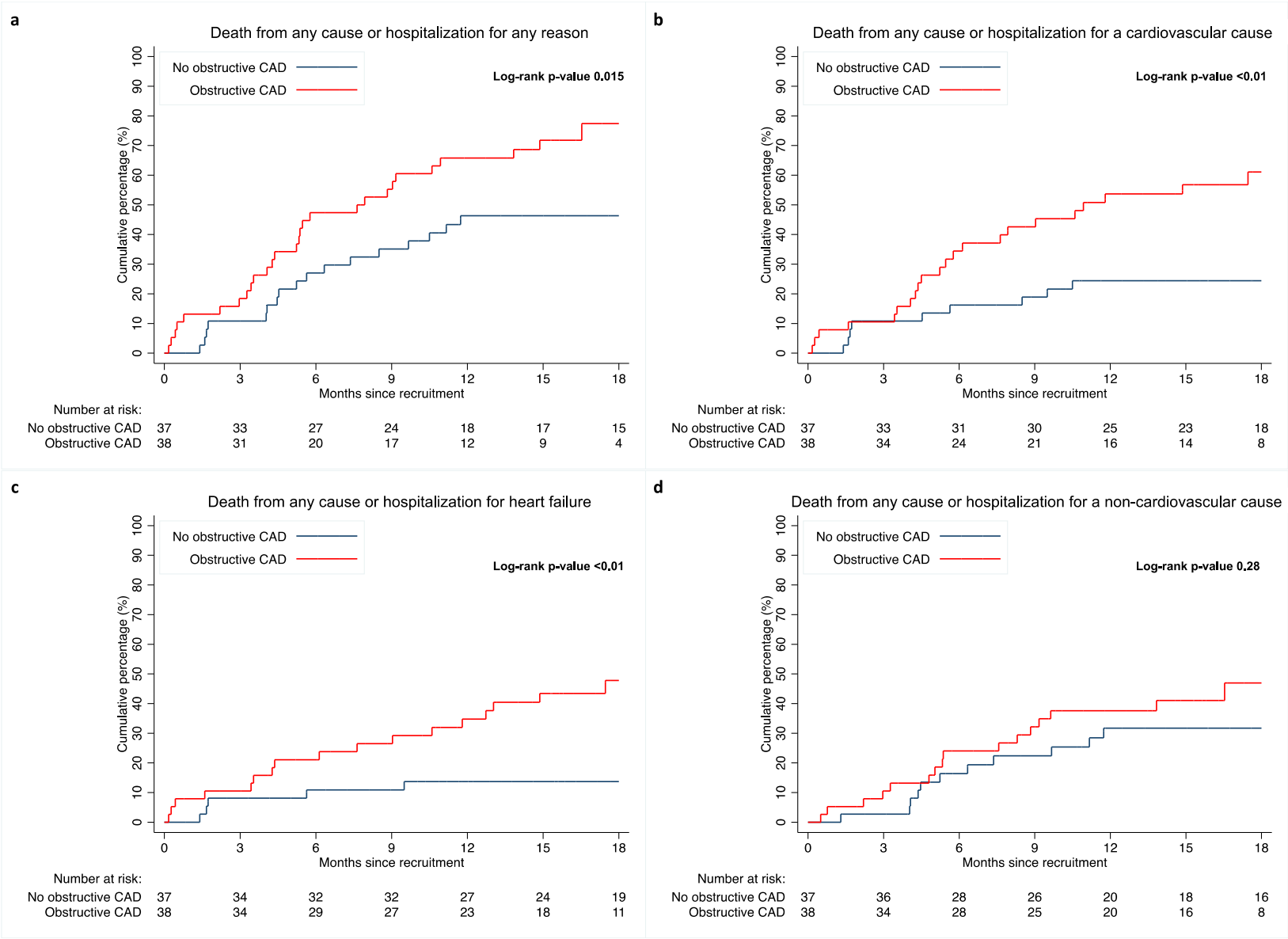
CAD, coronary artery disease; CMD, coronary microvascular dysfunction.

eFigure 5: Venn diagram of cardiac magnetic resonance imaging findings.



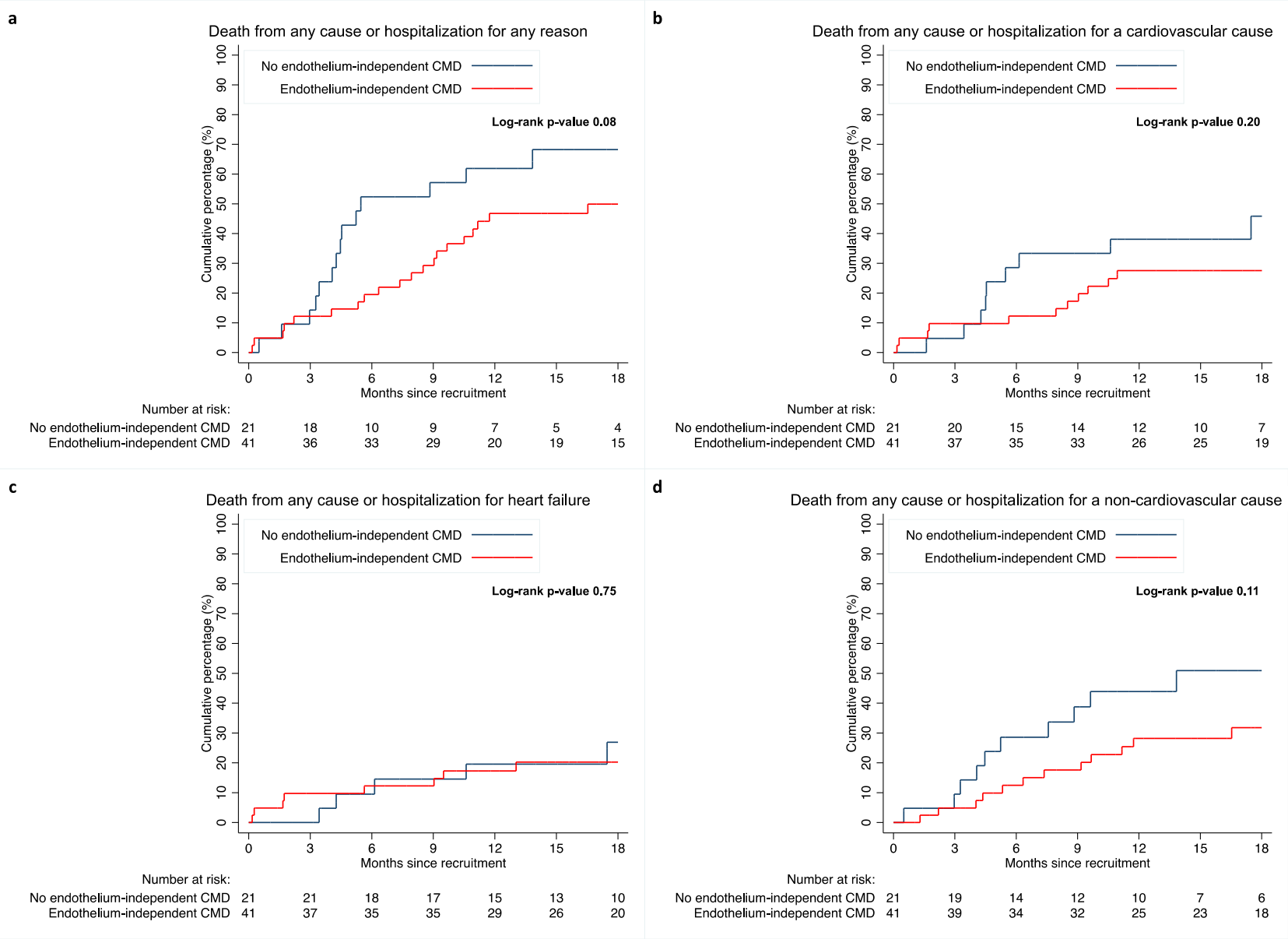
CMR, cardiac magnetic resonance; ECV, extracellular volume; MPRI, myocardial-perfusion reserve index.

eFigure 6: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of obstructive epicardial coronary artery disease.



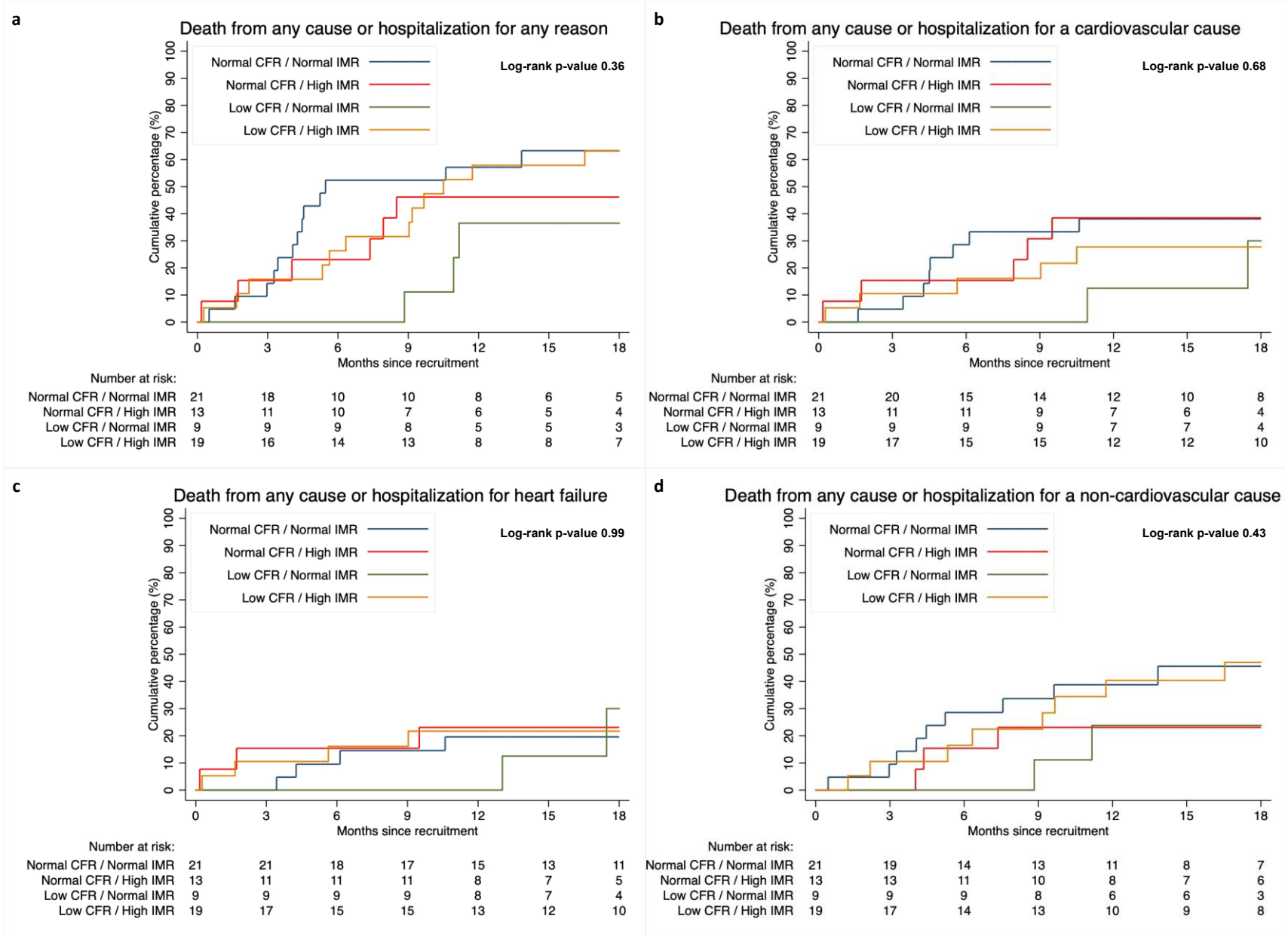
CAD, coronary artery disease.

eFigure 7: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of endothelium-independent coronary microvascular dysfunction.



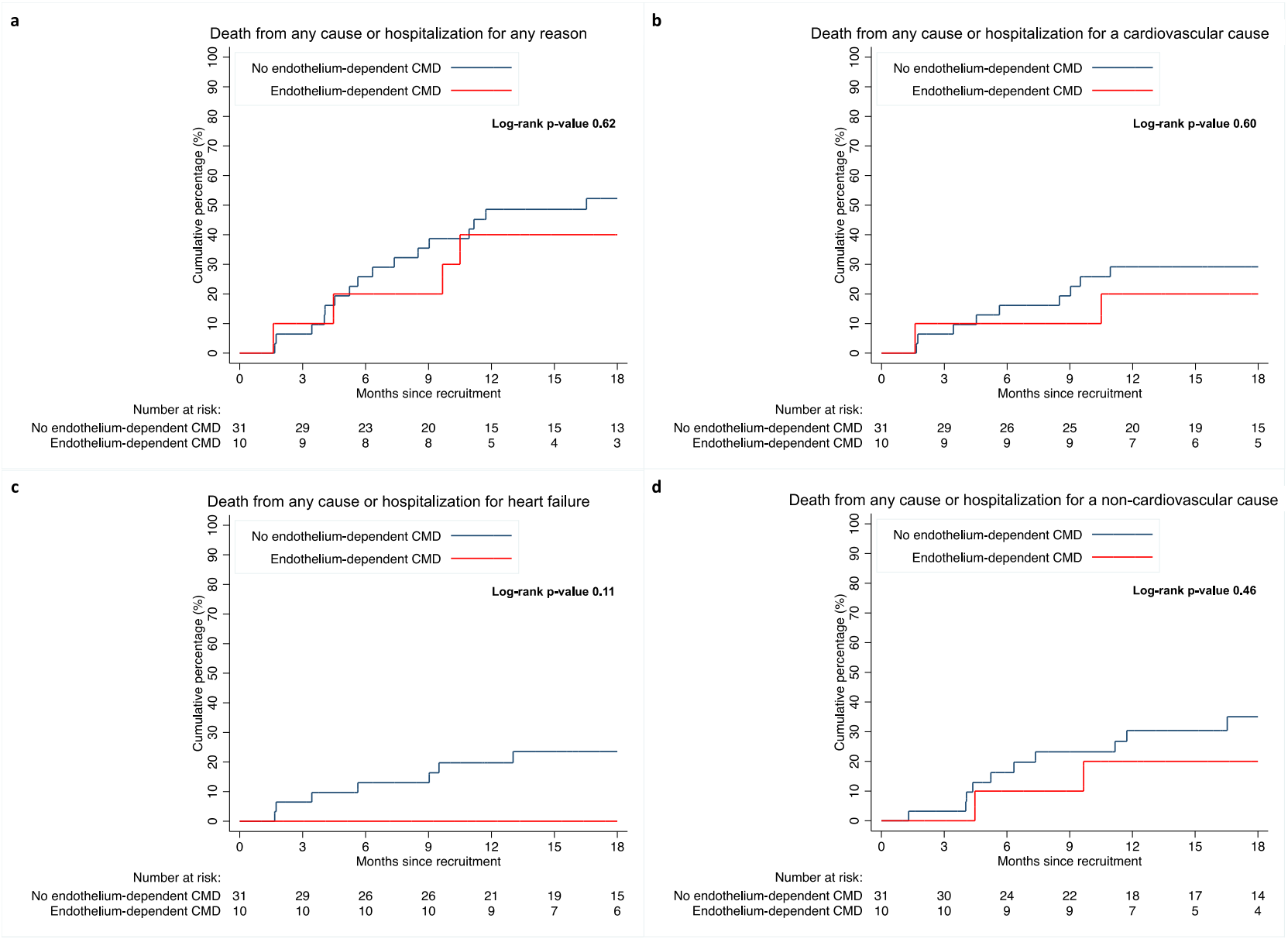
CMD, coronary microvascular dysfunction.

eFigure 8: Kaplan-Meier curves for combined endpoints of death and hospitalizations by microvascular status group.



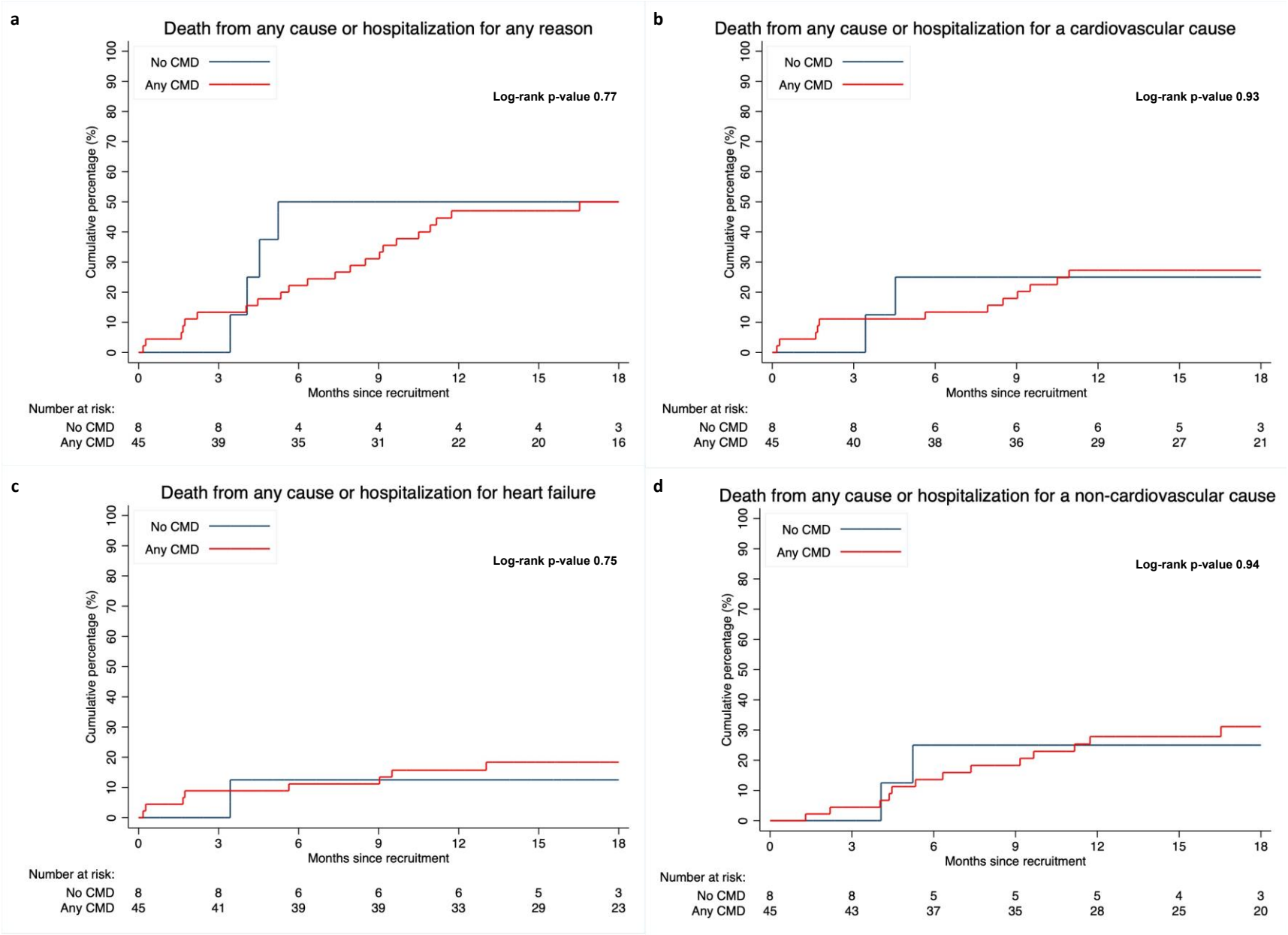
CFR, coronary flow reserve; IMR, index of microcirculatory resistance.

eFigure 9: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of endothelium-dependent coronary microvascular dysfunction.



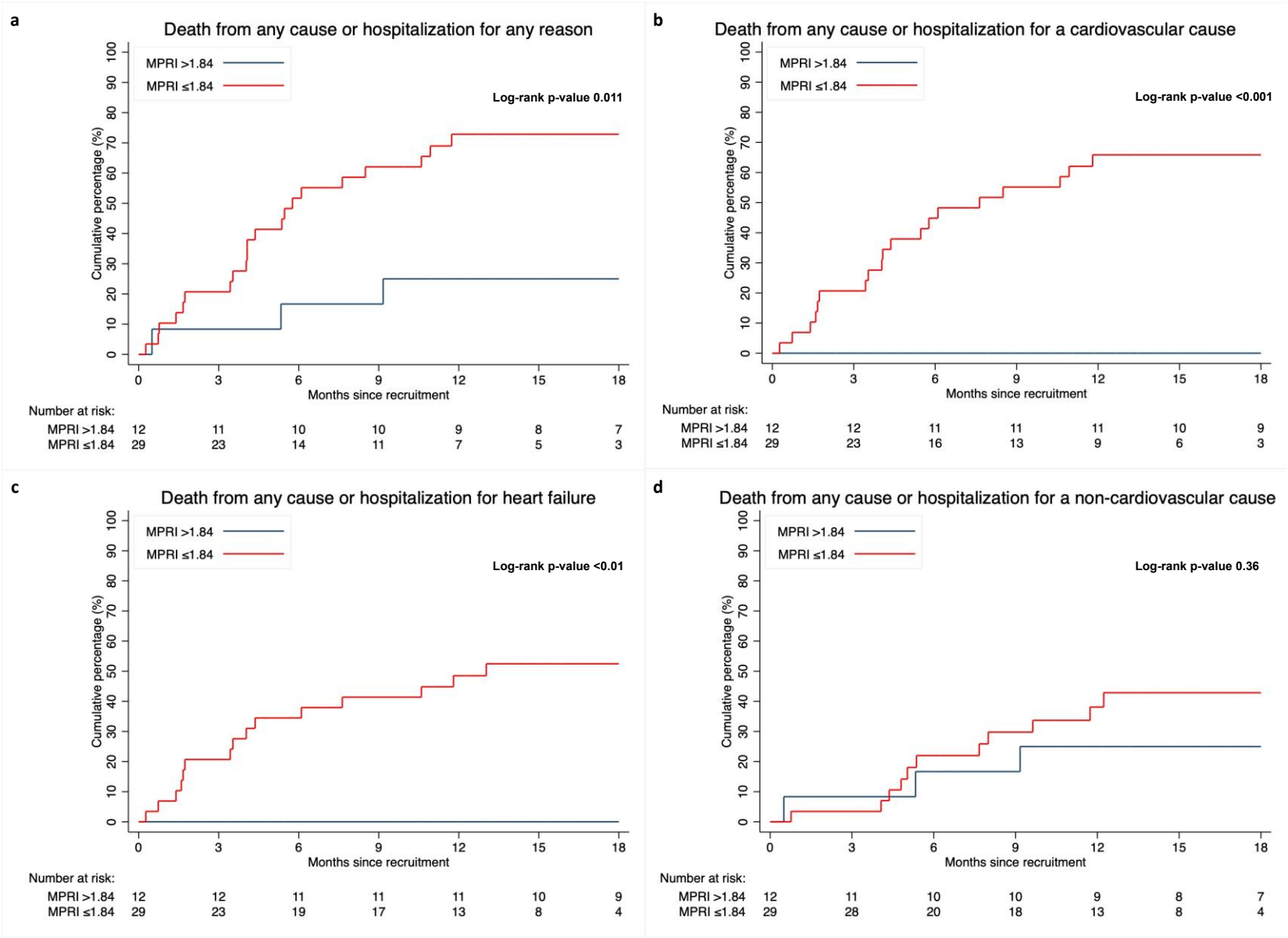
CMD, coronary microvascular dysfunction.

eFigure 10: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of any CMD.



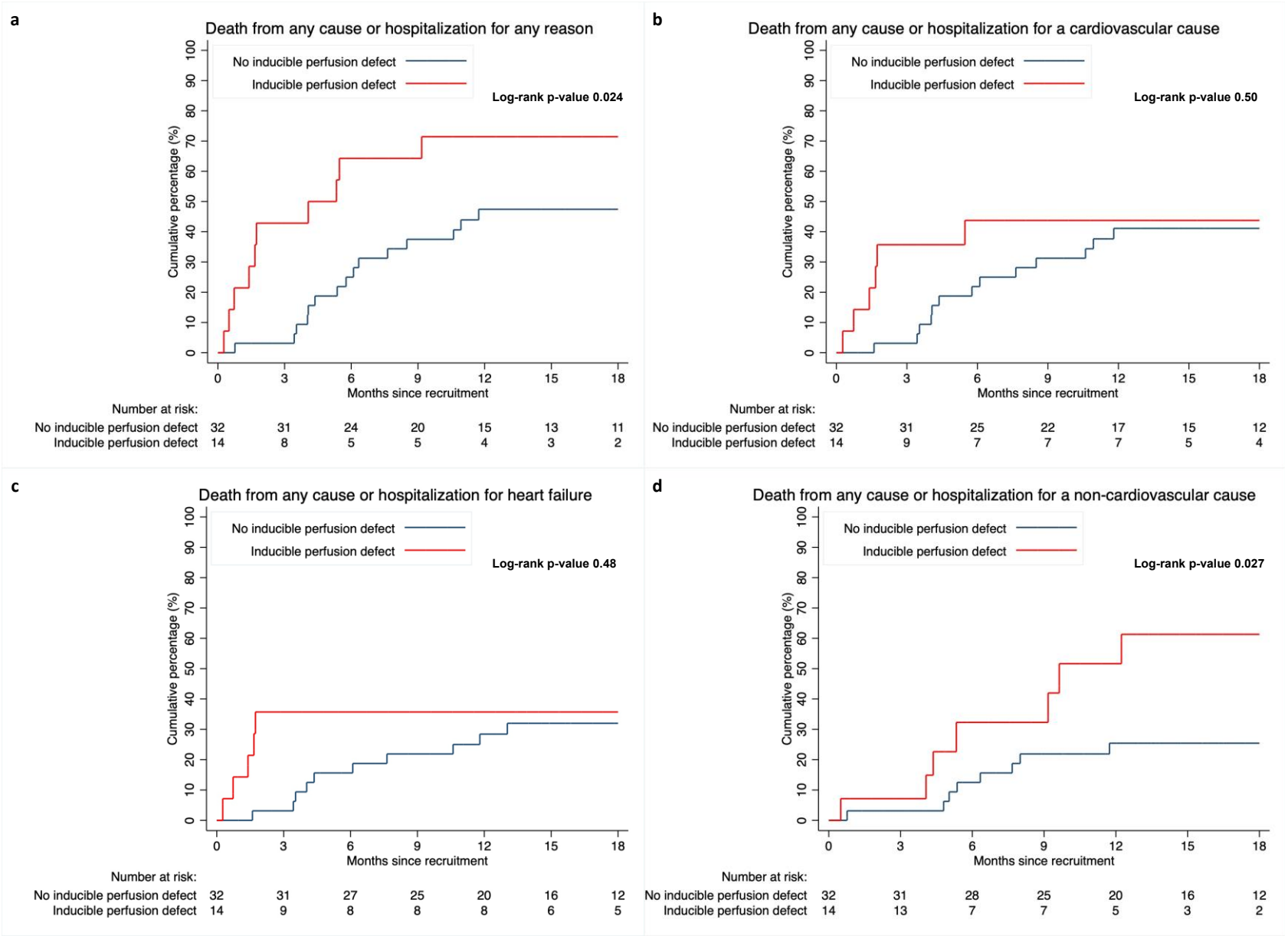
CMD, coronary microvascular dysfunction.

eFigure 11: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of impaired global myocardial-perfusion reserve index.

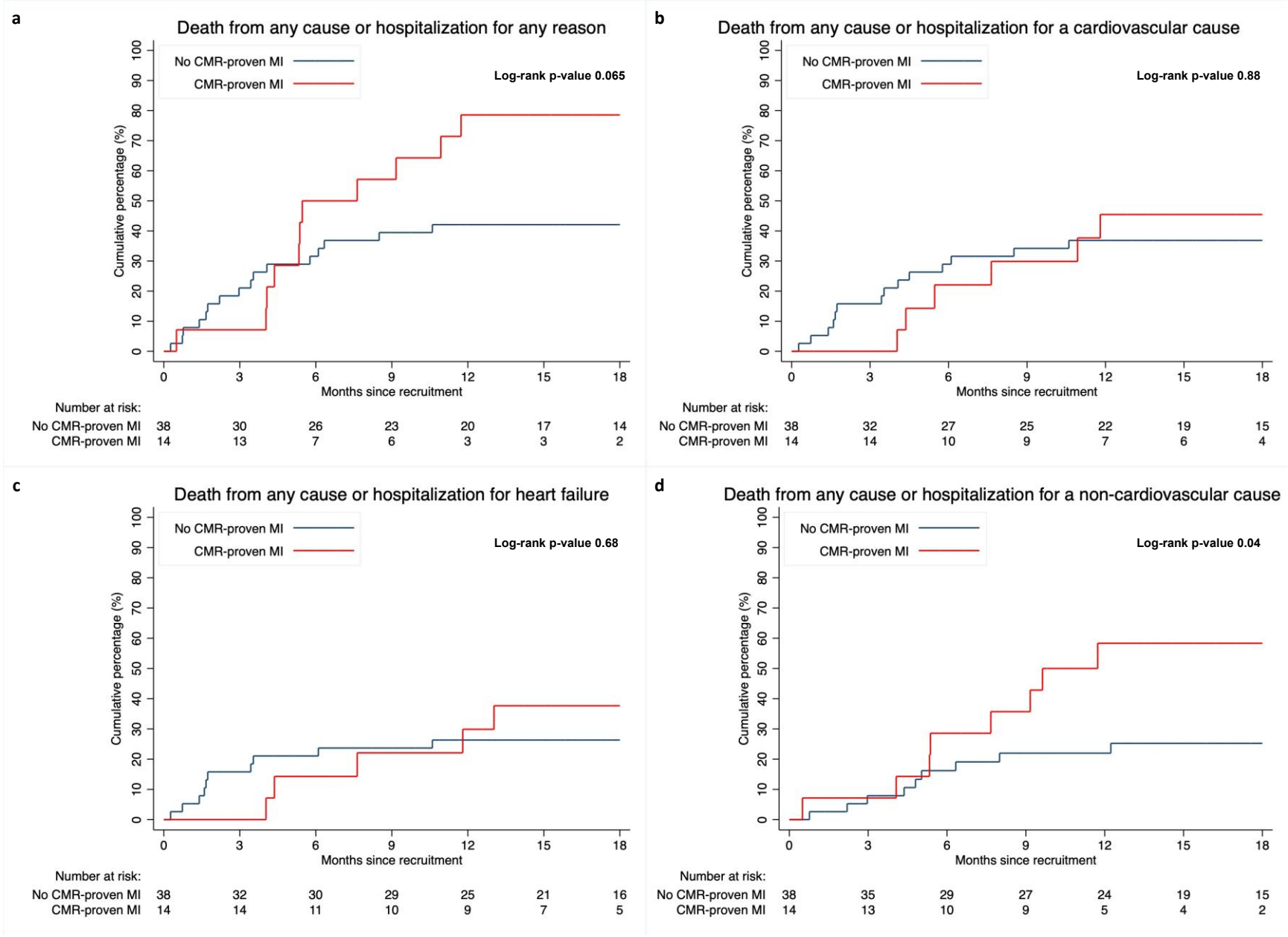


MPRI, myocardial-perfusion reserve index.

eFigure 12: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of a qualitative inducible perfusion defect.

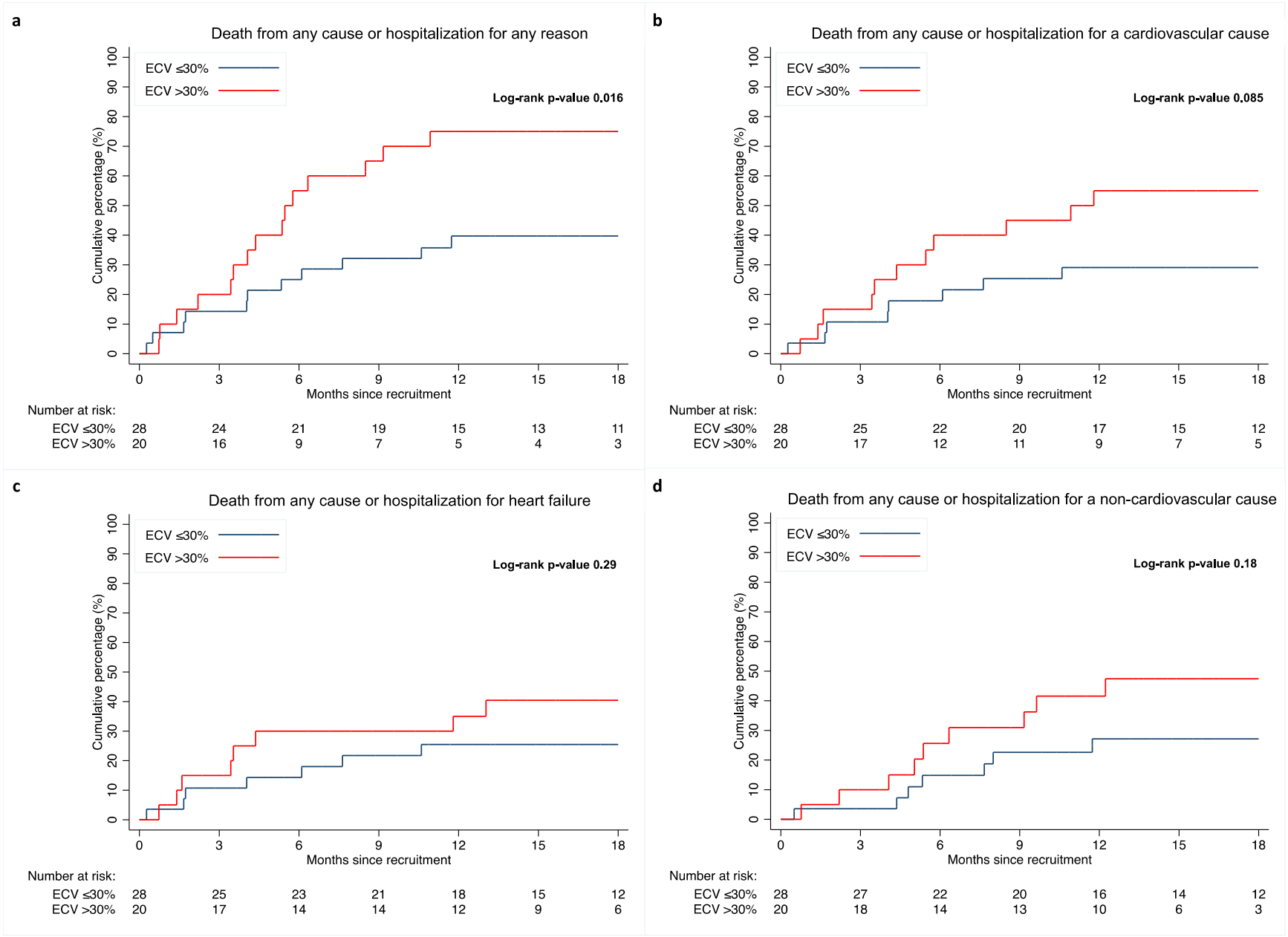


eFigure 13: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of CMR-proven myocardial infarction.



CMR, cardiac magnetic resonance; MI, myocardial infarction.

eFigure 14: Kaplan-Meier curves for combined endpoints of death and hospitalizations by presence or absence of diffuse myocardial fibrosis.



ECV, extracellular volume.

eTable 1: Selected clinical characteristics by microvascular status group.

	Normal CFR / Normal IMR (n= 21)	**Normal CFR / High IMR (n = 13)**	**Low CFR / Normal IMR (n = 9)**	**Low CFR / High IMR (n = 19)**	**p-value**
Age (years)	73 [8]	75 [9]	70 [13]	71 [8]	0.54
Female sex	12 (57)	7 (54)	5 (56)	9 (47)	0.94
Past medical history					
Any CAD	8 (38)	1 (8)	3 (33)	9 (47)	0.25
MI	5 (24)	0 (0)	3 (33)	7 (37)	0.19
Revascularization	2 (10)	0 (0)	3 (33)	5 (26)	0.27
Laboratory					
CRP (mg/L)	9 [4-22]	16 [7-17]	12 [3-15]	11 [5-23]	0.65
hsTnI (ng/L)	21 [14-36]	5 [3-13]	11 [4-25]	18 [10-25]	0.11
	(n = 11)	(n = 6)	(n = 6)	(n = 14)	
BNP (pg/mL)	197 [123-676]	487 [145-1253]	473 [256-1483]	569 [314-1017]	0.39
	(n = 14)	(n = 8)	(n = 4)	(n = 7)	
NT-proBNP (pg/mL)	1454 [414-4535]	1347 [1280-2176]	791 [426-1680]	2108 [1171-5385]	0.24
Echocardiography					
LVEF (%)	60 [6]	56 [5]	57 [7]	59 [6]	0.46
CMR	(n = 12)	(n = 8)	(n = 5)	(n = 10)	
LVEF (%)	58 [7]	60 [6]	56 [8]	59 [8]	0.74
Ischemic LGE	4 (33)	0 (0)	3 (60)	3 (30)	0.12
Non-ischemic LGE	4 (33)	3 (38)	2 (40)	4 (40)	0.99
MPRI	1.60 [1.33-1.87]	1.71 [1.66-1.87]	1.30 [1.16-1.44]	1.72 [1.25-2.01]	0.39
Inducible perfusion defect	5 (45)	1 (17)	1 (25)	4 (50)	0.53
- Ischemic LV segments	*3 [4]*	*2 [5]*	*1 [2]*	*4 [5]*	*0.64*
Invasive assessment					
Obstructive epicardial CAD	10 (48)	3 (23)	5 (56)	8 (42)	0.41
Angiographically normal	3 (14)	3 (23)	2 (22)	3 (16)	0.90
CFR	2.6 [2.4-3.1]	2.7 [2.4-3.2]	1.3 [1.2-1.7]	1.7 [1.2-2.0]	<0.001
IMR	14 [12-18]	39 [28-50]	17 [13-18]	33 [28-63]	<0.001
	(n = 12)	(n = 10)	(n = 6)	(n = 13)	
Endothelium-dependent CMD	4 (33)	1 (10)	2 (33)	3 (23)	0.59
	(n = 21)	(n = 13)	(n = 9)	(n = 16)	
LVEDP (mmHg)	11 [4]	12 [4]	13 [5]	13 [7]	0.75

Values are mean [standard deviation], median [Q1-Q3], or n (%).

BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP; RVEDV, right ventricular end-diastolic volume.

eTable 2: Selected clinical characteristics by presence or absence of any coronary microvascular dysfunction.

	All CMD (n = 53)	**No CMD (n = 8)**	**Any CMD (n = 45)**	**p-value**
Age (years)	72 [9]	72 [10]	72 [9]	0.95
Female sex	31 (58)	5 (62)	26 (58)	0.80
Past medical history				
Previous HF diagnosis	20 (38)	0 (0)	20 (44)	0.017
Any CAD	14 (26)	1 (12)	13 (29)	0.33
MI	10 (19)	1 (12)	9 (20)	0.62
Revascularization	7 (13)	0 (0)	7 (16)	0.23
AF	35 (66)	2 (25)	33 (73)	<0.01
Laboratory				
CRP (mg/L)	13 [5-22]	21 [7-53]	12 [5-21]	0.24
hsTnI (ng/L)	16 [9-34]	64 [21-131]	16 [7-25]	0.015
	(n = 33)	(n = 6)	(n = 27)	
BNP (pg/mL)	355 [185-1017]	228 [177-355]	421 [185-1253]	0.14
	(n = 26)	(n = 3)	(n = 23)	
NT-proBNP (pg/mL)	1459 [1132-3076]	1366 [414-4535]	1532 [1132-3076]	0.75
Echocardiography				
LVEF (%)	58 [6]	63 [5]	58 [6]	0.039
CMR	(n = 31)	(n = 5)	(n = 26)	
LVEF (%)	60 [7]	60 [9]	59 [7]	0.86
Ischemic LGE	8 (26)	1 (20)	7 (27)	0.75
Non-ischemic LGE	12 (39)	3 (60)	9 (35)	0.29
Native T1 (ms)	1280 [70]	1308 [75]	1274 [68]	0.32
ECV (%)	27.9 [4.4]	29.5 [3.1]	27.7 [4.5]	0.45
MPRI	1.68 [1.39-1.93]	1.60 [1.33-1.87]	1.70 [1.44-1.93]	0.56
Inducible perfusion defect	9 (29)	1 (20)	8 (38)	0.44
- Ischemic LV segments	*2 [4]*	*2 [4]*	*3 [4]*	*0.79*
Invasive assessment				
Obstructive epicardial CAD	17 (32)	1 (12)	16 (36)	0.20
Angiographically normal	11 (21)	1 (12)	10 (22)	0.53
CFR	2.0 [1.3-2.7]	2.8 [2.4-3.3]	1.8 [1.3-2.5]	0.006
IMR	26 [18-40]	19 [13-21]	28 [22-43]	0.006
	(n = 50)	(n = 8)	(n = 42)	
LVEDP (mmHg)	13 [6]	11 [4]	13 [6]	0.50

Values are mean [standard deviation], median [Q1-Q3], or n (%).

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP.

eTable 3: Selected clinical characteristics by presence or absence of impaired global myocardial-perfusion reserve index.

	All MPRI (n = 41)	**MPRI >1.84 (n = 12)**	**MPRI ≤1.84 (n = 29)**	**p-value**
Age (years)	74 [8]	71 [8]	75 [8]	0.13
Female sex	18 (44)	6 (50)	12 (41)	0.61
Past medical history				
Any CAD	14 (34)	6 (50)	8 (28)	0.17
MI	7 (17)	6 (50)	1 (3)	<0.01
Revascularization	9 (22)	5 (42)	4 (14)	0.05
Hypertension	32 (78)	7 (58)	25 (86)	0.05
Smoking history	20 (49)	4 (33)	16 (55)	0.20
Laboratory				
CRP (mg/L)	11 [6-22]	9 [7-35]	12 [5-19]	0.86
hsTnI (ng/L)	18 [9-36]	12 [3-38]	19 [13-35]	0.38
	(n = 26)	(n = 17)	(n = 9)	
BNP (pg/mL)	421 [197-856]	327 [182-704]	479 [197-1017]	0.47
	(n = 20)	(n = 15)	(n = 5)	
NT-proBNP (pg/mL)	2079 [912-4960]	1915 [1171-4535]	2242 [845-5385]	0.97
Echocardiography				
LVEF (%)	59 [7]	57 [5]	60 [7]	0.13
LA volume index (mL/m^2)	44 [17]	36 [8]	48 [18]	0.055
CMR				
LVEF (%)	61 [7]	59 [7]	62 [7]	0.18
LV mass index (g/m^2)	70 [22]	60 [17]	74 [23]	0.074
LA volume index (mL/m^2)	69 [23]	58 [18]	73 [24]	0.046
Ischemic LGE	12 (29)	4 (33)	8 (28)	0.71
Non-ischemic LGE	15 (37)	3 (25)	12 (41)	0.32
Native T1 (ms)	1288 [61]	1259 [45]	1300 [64]	0.054
ECV (%)	28.5 [3.7]	26.6 [4.2]	29.2 [3.3]	0.045
Inducible perfusion defect	13 (32)	4 (33)	9 (31)	0.89
- Ischemic LV segments	*2 [4]*	*2 [4]*	*2 [4]*	*0.99*
Invasive assessment				
	(n = 34)	(n = 9)	(n = 25)	
Obstructive epicardial CAD	20 (59)	5 (56)	15 (60)	0.82
Angiographically normal	3 (9)	0 (0)	3 (12)	0.28
	(n = 25)	(n = 9)	(n = 16)	
CFR	2.4 [1.8-2.7]	2.4 [1.8-2.7]	2.3 [1.5-2.7]	0.73
CFR <2.0	8 (32)	3 (33)	5 (31)	0.91
IMR	23 [13-32]	23 [13-25]	22 [15-35]	0.87
IMR ≥25	12 (48)	5 (56)	7 (44)	0.57
Endothelium-independent CMD	15 (60)	6 (67)	9 (56)	0.61
	(n = 15)	(n = 4)	(n = 11)	

Endothelium-dependent CMD	2 (13)	0 (0)	2 (18)	0.36
	(n = 29)	(n = 8)	(n = 21)	
LVEDP (mmHg)	13 [8]	13 [5]	14 [9]	0.80

Values are mean [standard deviation], median [Q1-Q3], or n (%).

BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP.

eTable 4: Selected clinical characteristics by presence or absence of a qualitative inducible perfusion defect.

	All qualitative perfusion imaging (n = 46)	No inducible perfusion defect (n = 32)	Inducible perfusion defect (n = 14)	p-value
Age (years)	73 [9]	75 [8]	69 [11]	0.046
Female sex	21 (46)	13 (41)	8 (57)	0.30
Past medical history				
Any CAD	15 (33)	6 (19)	9 (64)	<0.01
MI	8 (17)	3 (9)	5 (36)	0.03
Revascularization	10 (22)	5 (16)	5 (36)	0.03
AF	31 (67)	26 (81)	5 (36)	<0.01
Smoking history	22 (48)	11 (34)	11 (79)	<0.01
Laboratory				
CRP (mg/L)	11 [6-22]	10 [4-19]	18 [8-32]	0.14
hsTnI (ng/L)	16 [9-34]	16 [7-33]	22 [14-54]	0.39
	(n = 28)	(n = 21)	(n = 7)	
BNP (pg/mL)	421 [204-829]	323 [210-785]	732 [197-2490]	0.28
	(n = 23)	(n = 12)	(n = 11)	
NT-proBNP (pg/mL)	2108 [845-4588]	2301 [1111-4562]	1915 [414-5385]	0.58
Echocardiography				
LVEF (%)	59 [7]	60 [7]	57 [6]	0.12
CMR				
LVEF (%)	61 [7]	62 [6]	58 [7]	0.07
LVEDV index (mL/m^2)	76 [23]	71 [21]	88 [26]	0.026
LVESV index (mL/m^2)	31 [13]	28 [11]	38 [16]	0.014
LV mass index (g/m^2)	68 [22]	64 [17]	78 [27]	0.032
Ischemic LGE	13 (28)	6 (19)	7 (50)	0.03
Non-ischemic LGE	16 (35)	13 (41)	3 (21)	0.21
Native T1 (ms)	1291 [67]	1285 [70]	1305 [58]	0.36
ECV (%)	28.7 [4.1]	28.6 [3.7]	28.9 [5.0]	0.83
MPRI	1.52 [1.37-1.86]	1.54 [1.37-1.86]	1.50 [1.33-1.85]	1.0
Invasive assessment				
	(n = 38)	(n = 25)	(n = 13)	
Obstructive epicardial CAD	21 (55)	13 (52)	8 (62)	0.57
Angiographically normal	4 (11)	3 (12)	1 (8)	0.68
	(n = 29)	(n = 18)	(n = 11)	
CFR	2.3 [1.6-2.7]	2.4 [1.5-2.7]	2.0 [1.6-2.4]	0.43
CFR <2.0	12 (41)	7 (39)	5 (45)	0.73
IMR	23 [13-32]	23 [18-32]	13 [12-42]	0.21
IMR ≥25	14 (48)	9 (50)	5 (45)	0.81
Endothelium-independent CMD	19 (66)	12 (67)	7 (64)	0.87
	(n = 15)	(n = 11)	(n = 4)	

Endothelium-dependent CMD	4 (21)	3 (21)	1 (20)	0.95
	(n = 33)	(n = 22)	(n = 11)	
LVEDP (mmHg)	13 [7]	13 [8]	13 [5]	0.97

Values are mean [standard deviation], median [Q1-Q3], or n (%).

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV LV end-systolic volume; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP.

eTable 5: Selected clinical characteristics by presence or absence of CMR-proven myocardial infarction.

	All CMR (n = 52)	**No CMR-proven MI (n = 38)**	**CMR-proven MI (n = 14)**	**p-value**
Age (years)	72 [9]	73 [9]	69 [10]	0.14
Female sex	24 (46)	17 (45)	7 (50)	0.74
Past medical history				
Any CAD	15 (29)	7 (18)	8 (57)	<0.01
MI	8 (15)	2 (5)	6 (43)	<0.001
Revascularization	10 (19)	4 (11)	6 (43)	<0.01
AF	34 (65)	29 (76)	5 (36)	<0.01
Laboratory				
CRP (mg/L)	12 [7-21]	11 [7-21]	13 [3-32]	0.96
hsTnI (ng/L)	16 [7-34]	19 [5-54]	13 [9-24]	0.34
	(n = 32)	(n = 21)	(n = 11)	
BNP (pg/mL)	399 [204-829]	421 [229-785]	256 [197-1017]	0.83
	(n = 27)	(n = 20)	(n = 7)	
NT-proBNP (pg/mL)	1542 [978-4535]	2175 [1259-4562]	1041 [326-1915]	0.076
Echocardiography				
LVEF (%)	59 [7]	59 [6]	58 [8]	0.79
CMR				
LVEF (%)	60 [7]	60 [7]	59 [8]	0.59
Non-ischemic LGE	20 (38)	18 (47)	2 (14)	0.03
Native T1 (ms)	1287 [67]	1278 [69]	1315 [53]	0.086
ECV (%)	28.6 [4.1]	28.0 [3.9]	30.2 [4.4]	0.096
MPRI	1.52 [1.37-1.86]	1.57 [1.39-1.86]	1.48 [1.29-1.89]	0.69
Inducible perfusion defect	14(27)	7 (21)	7 (54)	0.03
- Ischemic LV segments	*2 [4]*	*2 [4]*	*3 [4]*	*0.17*
Invasive assessment				
	(n = 44)	(n = 31)	(n = 13)	
Obstructive epicardial CAD	24 (55)	13 (42)	11 (85)	<0.01
Angiographically normal	5 (11)	4 (13)	1 (8)	0.62
	(n = 35)	(n = 25)	(n = 10)	
CFR	2.1 [1.3-2.7]	2.4 [1.3-2.8]	1.8 [1.6-2.3]	0.41
CFR <2.0	15 (43)	9 (24)	6 (43)	0.18
IMR	23 [13-39]	28 [18-42]	13 [12-23]	<0.01
IMR ≥25	18 (51)	15 (39)	3 (21)	0.23
Endothelium-independent CMD	24 (69)	17 (68)	7 (70)	0.91
	(n = 22)	(n = 18)	(n = 4)	
Endothelium-dependent CMD	4 (18)	4 (22)	0 (0)	0.30
	(n = 39)	(n = 27)	(n =12)	
LVEDP (mmHg)	12 [7]	13 [8]	12 [69-12]	0.84

Values are mean [standard deviation], median [Q1-Q3], or n (%).

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP.

eTable 6: Clinical characteristics by presence or absence of diffuse myocardial fibrosis.

	All ECV (n = 48)	**ECV ≤30% (n = 28)**	**ECV >30% (n = 20)**	**p-value**
Age (years)	72 [9]	72 [8]	73 [11]	0.83
Female sex	22 (46)	15 (54)	7 (35)	0.20
Past medical history				
Any CAD	15 (31)	8 (29)	7 (35)	0.64
MI	8 (17)	4 (14)	4 (20)	0.60
Revascularization	7 (15)	6 (21)	1 (5)	0.11
Laboratory				
CRP (mg/L)	11 [7-20]	10 [7-17]	16 [5-30]	0.36
hsTnI (ng/L)	16 [7-34]	16 [4-33]	19 [13-34]	0.40
	(n = 29)	(n = 16)	(n = 13)	
BNP (pg/mL)	376 [197-856]	301 [200-725]	785 [197-1684]	0.25
	(n = 25)	(n = 15)	(n = 10)	
NT-proBNP (pg/mL)	1915 [978-4535]	1385 [1171-2819]	3252 [570-9000]	0.51
Echocardiography				
LVEF (%)	59 [7]	60 [7]	58 [7]	0.30
CMR				
LVEF (%)	61 [7]	61 [7]	60 [7]	0.74
LV mass index (g/m^2)	68 [21]	64 [16]	75 [25]	0.061
RVEDV index (mL/m^2)	81 [29]	73 [22]	93 [34]	0.018
Ischemic LGE	13 (27)	5 (18)	8 (40)	0.089
Non-ischemic LGE	18 (38)	9 (32)	9 (45)	0.36
MPRI	1.52 [1.37-1.86]	1.70 [1.47-1.97]	1.37 [1.26-1.55]	0.012
Inducible perfusion defect	14 (29)	7 (27)	7 (37)	0.48
- Ischemic LV segments	*2 [4]*	*2 [4]*	*2 [4]*	*0.84*
Invasive assessment				
	(n = 40)	(n = 22)	(n = 18)	
Obstructive epicardial CAD	22 (55)	8 (36)	14 (78)	<0.01
Angiographically normal	5 (13)	4 (18)	1 (6)	0.23
	(n = 31)	(n = 19)	(n = 12)	
CFR	2.3 [1.6-2.7]	2.3 [1.5-2.8]	2.2 [1.8-2.5]	0.90
CFR <2.0	13 (42)	8 (42)	5 (42)	0.98
IMR	23 [13-40]	28 [14-45]	18 [13-23]	0.096
IMR ≥25	17 (55)	13 (68)	4 (33)	0.056
Endothelium-independent CMD	22 (71)	14 (74)	8 (67)	0.68
	(n = 20)	(n = 14)	(n = 6)	
Endothelium-dependent CMD	4 (20)	3 (21)	1 (17)	0.81
	(n = 35)	(n = 20)	(n = 15)	
LVEDP (mmHg)	12 [7]	12 [5]	14 [10]	0.43

Values are mean [standard deviation], median [Q1-Q3], or n (%).

BNP, B-type natriuretic peptide; CAD, coronary artery disease; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; CRP, C-reactive protein; ECV, extracellular volume; hsTnI, high-sensitivity troponin I; IMR, index of microcirculatory resistance; LGE, late gadolinium enhancement; LV, left ventricular; LVEDP, LV end-diastolic pressure; LVEF, LV ejection fraction; MI, myocardial infarction; MPRI, myocardial-perfusion reserve index; NT-proBNP, N-terminal prohormone BNP; RVEDV, right ventricular end-diastolic volume.

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