Supplementary Table 1: Summary of key studies of coronary microvascular dysfunction related to heart failure with preserved ejection fraction.

Author, year of publication	Study design/HFpEF LVEF thresholds/presence or absence of CAD	Sample size / key characteristics	MVD assessment methods/measures	Key findings
		Invasive		
Sucato et al.[47] 2015	Single-centre Retrospective Patients presenting with chest pain LVEF >50%	HFpEF n=155 mean age 63 years, females (37%), BMI 25 ± 3, T2D (66%) hypertension (78%) Non-HFpEF controls n=131	**Invasive coronary angiography** TIMI frame count and TIMI myocardial perfusion grade	HFpEF patients had higher TIMI frame count and lower TIMI myocardial perfusion grade in all three major coronary artery territories compared to controls

Dryer et al.[39] 2018	Two-centre Prospective Observational HFpEF patients referred for invasive coronary angiography LVEF ≥50% Controls: no HF, normal LV function and clinical indication for invasive coronary angiography	HFpEF n=30, mean age 65.4 years, females (63%), BMI 38 ± 9, diabetes (60%), hypertension (93%), CAD (30%) Controls n=14 mean age 55.1 years, females (86%), BMI 34 ± 11,	**Invasive coronary Doppler flow wire** MVD defined as: CFR ≤2.0 or IMR ≥23	Overall, HFpEF cohort had lower mean CFR (2.55 ± 1.60 versus. 3.84 ± 1.89, p=0.024) and higher mean IMR (26.7 ± 10.3 versus. 19.7 ± 9.7 units, p=0.037) compared to controls In HFpEF: Overt MVD in 36.7% i.e. abnormal IMR and abnormal CFR; 26.7% had normal CFR and abnormal IMR; 10.0% had abnormal CFR and normal IMR; 26.7% had normal coronary physiology

		diabetes (43%), hypertension (64%), CAD (21%)		
Yang et al.[48] 2020	Single-centre Retrospective Consecutive HFpEF patients referred for invasive coronary haemodynamic assessment LVEF ≥50% Excluded if obstructive CAD i.e. >50% stenosis of any coronary artery or prior acute coronary syndrome Median follow-up 12.5 years	HFpEF n=162 mean age 54 years, females (67%), BMI (31 ± 7), T2D (11%), hypertension (49%)	**Invasive coronary Doppler flow wire** MVD defined as: endothelium-dependent (increase in CBF ≤0% in response to acetylcholine) *and/or* endothelium-independent (CFR ≤2.5)	Overall, MVD present in 72%; endothelium-dependent MVD in 29%; endothelium-independent MVD in 33%; combined MVD in 10% . Endothelium-independent MVD was associated with worse diastolic function: lower diastolic relaxation velocities (7.0 ± 1.8 versus. 8.4 ± 2.9 cm/s, p=0.002) and higher estimated filling pressures (E/e' 13.1 ± 4.1 versus. 9.6 ± 3.4, p<0.001).

				Endothelium-dependent MVD: trend to worse mortality compared to preserved endothelial function (adjusted HR 2.81, 95% CI 0.94-8.34, p=0.06) Endothelium-independent MVD: significant association with mortality compared to preserved endothelial function (adjusted HR 3.56, 95% CI 1.14-11.12, p=0.03)
Non-invasive				
Echocardiography				
Shah et al.[45] 2018	Multi-centre (5) Prospective	HFpEF n=202 mean age 74 years,	**Adenosine stress transthoracic Echocardiography**	MVD present in 75%

	Observational LVEF ≥40% Excluded if significant CAD i.e. known or clinically judged (based on stress testing/invasive angiography) or significant revascularized CAD	females (55%), obesity (35%), T2D (29%), hypertension (84%), revascularized CAD (19%)	**Doppler measurement of LAD flow velocity** MVD defined as: CFR <2.5	Patients with MVD were more likely to have a history of AF and smoking In multivariable regression analyses, CFR was independently associated with systemic measures of endothelial dysfunction (reactive hyperaemia index, urinary albumin to creatinine ratio) and markers of HF severity (NTproBNP, and right ventricular dysfunction [tricuspid annular plane systolic excursion])
Mahfouz et al[43] 2020	Single-centre Prospective Observational LVEF >50%	HFpEF n=77 mean age 52 years, females (40%), mean BMI 25,	**Adenosine stress transthoracic Echocardiography Doppler**	MVD present in 66% In HFpEF, CFR correlated with 6MWTD (r=0.47, p<0.001) and E/e' (r= -0.37, p<0.001)

	Excluded if significant CAD i.e. based on stress testing/invasive angiography	diabetes (34%), hypertension (92%) Controls n=30 (age and sex matched)	**measurement of LAD flow velocity** MVD defined as: CFR < 2.0	In HFpEF, CFR was an independent predictor of 6MWTD
PET				
Srivaratharajah et al.[46] 2016	Single-centre Retrospective LVEF ≥50% Excluded if CAD based on any of: abnormal perfusion summed stress score (≥4); history of MI, angina, coronary revascularisation; angiographic evidence of ≥70%	HFpEF n=78 non-HFpEF controls n=298 (hypertensive: n=186; normotensive n=112)	**Rb-82 PET** MVD defined as: MPR (ratio of myocardial blood flow [MBF] at peak stress versus rest) <2.0	MVD present in 40% of HFpEF HFpEF was associated with a significant reduction in global MPR (2.16 ± 0.69 in HFpEF versus 2.54 ± 0.80 in hypertensive controls; p<0.02 and 2.89 ± 0.70 in normotensive controls; p<0.001)

	luminal obstruction in any coronary artery	HFpEF: mean age 68, female (73%), BMI 34 ± 8, T2D (29%)		HFpEF patients 2.6 times more likely to have MVD compared to controls HFpEF was a significant predictor of MVD, even after adjusting for co-morbidities
Taqueti et al.[32] 2017	Single-centre Retrospective Consecutive patients undergoing evaluation for suspected CAD with PET LVEF ≥40%	Without HFpEF n=201; subsequent incident HFpEF n=36 Overall: mean age 66, females (65%),	**Rb-82 PET** MVD defined as: CFR <2.0	MVD was an independent risk factor for incident HFpEF MVD was independently associated with worse LV diastolic function (E/e′ septal >15, adjusted Odds Ratio 2.58, 95% CI 1.22–5.48, p=0.01)

	Excluded if prior known history of CAD or PET evidence of flow-limiting CAD Median follow-up 4.1 years	BMI 29 (25-34), T2D (33%), hypertension (76%)		Patients with both impaired CFR and diastolic dysfunction (E/e′) demonstrated >five-fold increased risk of HFpEF hospitalisation (p<0.001)
CMR				
Kato et al.[61] 2016	Single-centre Prospective LVEF >50% Excluded if CT evidence of CAD	HFpEF n=25 hypertensive LVH n=13 healthy controls n=18 HFpEF: mean age 73 ± 7, female (68%), diabetes (32%), hypertension (44%)	**CMR** CFR: ratio of coronary sinus blood flow during ATP infusion versus resting flow MVD defined as: CFR <2.5	MVD present in 76% of HFpEF CFR lower in HFpEF compared to hypertensive LVH and controls (2.21 ± 0.55 versus 3.05 ± 0.74 versus 3.83 ± 0.73, p<0.001) CFR independently correlated with BNP levels (β=−68.0; 95% CI, −116.2 to −19.7; p=0.007)

Löffler et al.[42] 2019	Single-centre Prospective Observational LVEF > 45% Excluded: prior known MI	HFpEF n=19 mean age 63, females (42%), BMI 35±7, T2D (58%), hypertension (84%) Controls n=15	**CMR** MVD defined as: MPR <2.5	MVD present in 69% of HFpEF HFpEF patients had reduced global MPR compared to controls (2.29 ± 0.64 versus 3.38 ± 0.76, p=0.002) In HFpEF, MPR and ECV inversely correlated
Kato et al.[40] 2021	Single-centre Retrospective LVEF >50% Excluded if prior MI Median follow-up 4.1 years	HFpEF n=163 mean age 73±9, female (53%), BMI 24 ± 4, diabetes (25%), hypertension (61%)	**CMR** CFR: ratio of coronary sinus blood flow	MVD using a different threshold from the same group was detected in 42% of HFpEF who experienced adverse events compared to 3% in those without

			during ATP infusion versus resting flow MVD defined as: CFR <2.0	The area under curve for predicting adverse events was higher for MVD than: focal fibrosis detected by LGE (0.881 versus. 0.768, p=0.037) and global longitudinal strain (0.881 versus. 0.747, p=0.036) in predicting events
Arnold et al.[38] 2021	Single-centre Prospective Observational LVEF ≥50% Significant CAD excluded on the basis of either: CMR regional stress perfusion defects or MI on LGE Median follow-up 3.1 years	HFpEF n=101, females (51%), mean age 73, BMI 34±7, T2D (49%) Controls n=43 (age and sex matched)	**CMR** MVD defined as: MPR <2.0	MVD present in: 70% of HFpEF; 48% of controls MPR was significantly lower in HFpEF compared to controls (1.74 ± 0.76 versus 2.22 ± 0.76; p=0.001) In HFpEF, there was no significant linear correlation between MPR and diffuse fibrosis (r=-0.10, p=0.473),

				and no difference in MPR in those with and without focal fibrosis (mean difference -0.03, 95% CI -0.37-0.3) MPR weakly correlated with indices of diastolic dysfunction: E/e' (r= -0.34, p=0.002) and BNP (r=-0.22, p=0.038) In adjusted multivariate analyses, allowing for clinical, blood and imaging parameters, MPR independently predicted adverse outcomes in HFpEF
Invasive and non-invasive				

Rush et al.[44] 2021	Multi-centre (3) Prospective Observational Consecutive patients hospitalised with HFpEF LVEF ≥50% Median follow-up 18 months	Total HFpEF n=106 Mean age 72, females (50%) Coronary angiography n=75 Coronary microvascular assessment n=62 Coronary vasoreactivity testing n=41 CMR evaluation n=52	**Invasive coronary Doppler flow wire** MVD defined as: Endothelium-dependent (20-90% coronary luminal constriction and/or ischaemic ECG changes in response to acetylcholine); Endothelium-independent (i.e. CFR <2 and/or IMR≥25	Invasive assessment: Obstructive CAD in 51% Endothelium-independent MVD in 66% Endothelium-dependent MVD in 24% CMR assessment: MVD present in 71% Overall, MVD present in 85% MVD present in 81% of those without obstructive CAD Invasive assessment:

			CMR MVD defined as: MPR ≤1.84	The presence of MVD overall, endothelial-independent MVD and endothelial-dependent MVD showed no association with adverse events CMR: Reduced MPR group (surrogate for MVD) had more adverse events compared to normal MPR group

ATP = adenosine triphosphate; BMI = body mass index; CAD = coronary artery disease; CBF = coronary blood flow; CFR = coronary flow reserve; CI = confidence interval; CMR = cardiac magnetic resonance imaging; CT = computed tomography; ECV = extracellular volume; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; IMR = index of microvascular resistance; LAD = left anterior descending coronary artery; LGE = late gadolinium enhancement imaging; LVEF = left ventricular ejection fraction; LVH=left ventricular hypertrophy; MI = myocardial infarction; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; MVD=coronary microvascular dysfunction; NTproBNP = N-terminal pro-brain natriuretic peptide; PET =positron emission tomography; TIMI = thrombolysis in myocardial infarction; T2D = type 2 diabetes; 6MWTD = six minute walk test distance