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

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Brief Report

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

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**ABSTRACT**

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

**Methods and Results:** We assessed the 1-year outcomes in patients from the PROMIS-HFpEF study, a prospective observational study of patients with chronic stable HFpEF undergoing coronary flow reserve measurements. Outcomes were (1) time to cardiovascular (CV) death/first HF hospitalization, (2) CV death/recurrent HF hospitalizations, (3) all-cause death/first HF hospitalization, and (4) first and (5) recurrent all-cause hospitalizations. CMD was defined as coronary flow reserve of <2.5. Time to CV death/first hospitalization was compared by log-rank test and recurrent HF and all-cause hospitalizations by Poisson test. Of 263 patients enrolled, 257 were evaluable at 1 year. Where the coronary flow reserve was interpretable ($n = 201$), CMD was present in 150 (75%). The median follow-up was 388 days (Q1, Q3 365, 418). The outcome of CV death/first HF hospitalization occurred in 15 patients (4 CV deaths). The incidence rate was in CMD 96 per 1000 person-years, 95% confidence interval 54−159, vs non-CMD 0 per1000 person-years, 95% confidence interval 0−68, $P = .023$, and remained significant after accounting for selected clinical variables. In patients with CMD, the incidence rates were significantly higher also for CV death/recurrent HF hospitalizations, all-cause death/first HF, and recurrent but not first all-cause hospitalization.

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

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

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

## Aims

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

## Methods

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

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

Descriptive data are expressed as median and quartiles (Q1, Q3) or number (%), and compared by the Mann−Whitney *U* test and Fisher's exact test. The incidences for outcomes 1−5 are presented as rate per 1000 person-years (see Fig. 2) with Poisson confidence intervals (CIs) provided in text (number of person-years in the recurrent hospitalization calculation excluding time spent in hospital). In addition, the nonrecurrent outcomes were also compared by log-rank test and the recurrent hospitalization was tested between groups by Poisson test. Because there were no events in the non-CMD group, adjustments for covariates using Cox regression were not possible. Therefore, the primary outcome was compared for CMD and adjusted, one at a time, for selected variables (age ≥75 years, female sex, median NT-proBNP [≥988 pg/mL], diabetes, atrial fibrillation, body mass index of ≥30 kg/m$^2$, and estimated glomerular filtration rate of ≥60 mL · min$^{-1}$ · [1.73 m$^2$]$^{-1}$) using a stratified log-rank test. Outcomes were censored at death, loss to follow-up, or last contact. The significance level was set to 5%, 2-sided. Statistical analyses were performed using R version 3.6.1 (2019-07-05) (R Core Team, 2019) and SAS software version 9.3 (SAS Institute, Cary, NC).

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

## Results

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

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

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

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

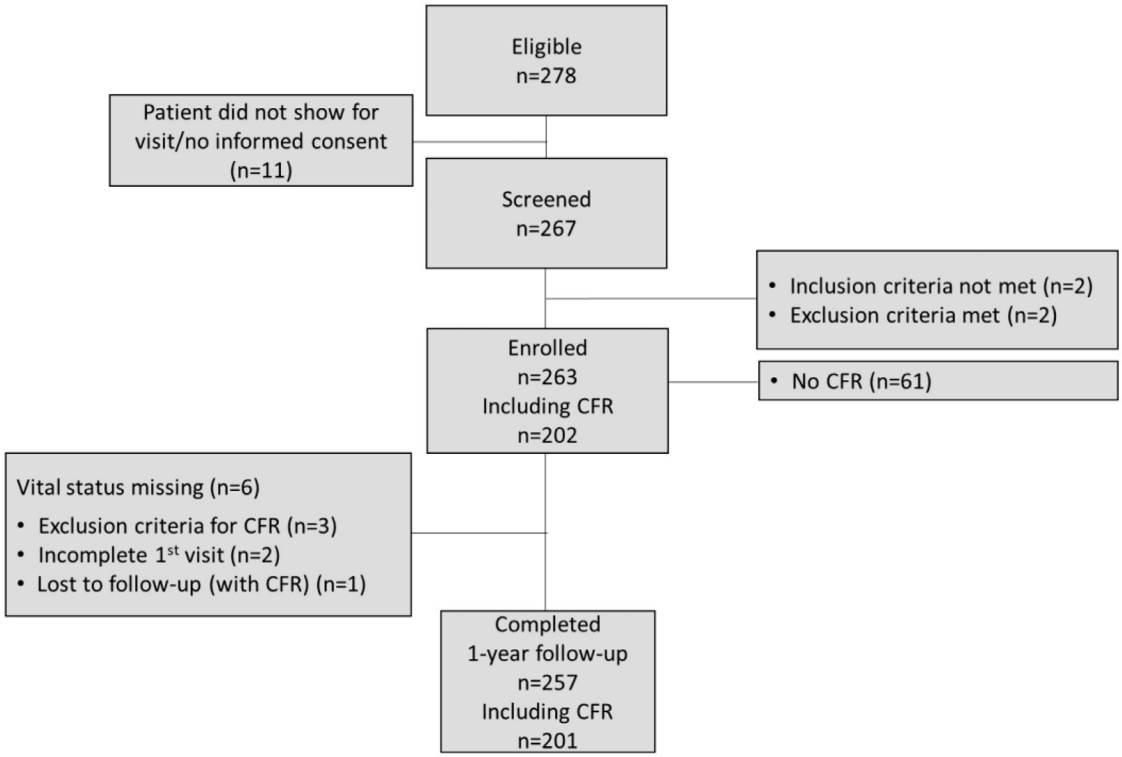


**Fig. 1.** Flow chart of enrolled patients with completed 1-year follow-up. CFR, coronary flow reserve.

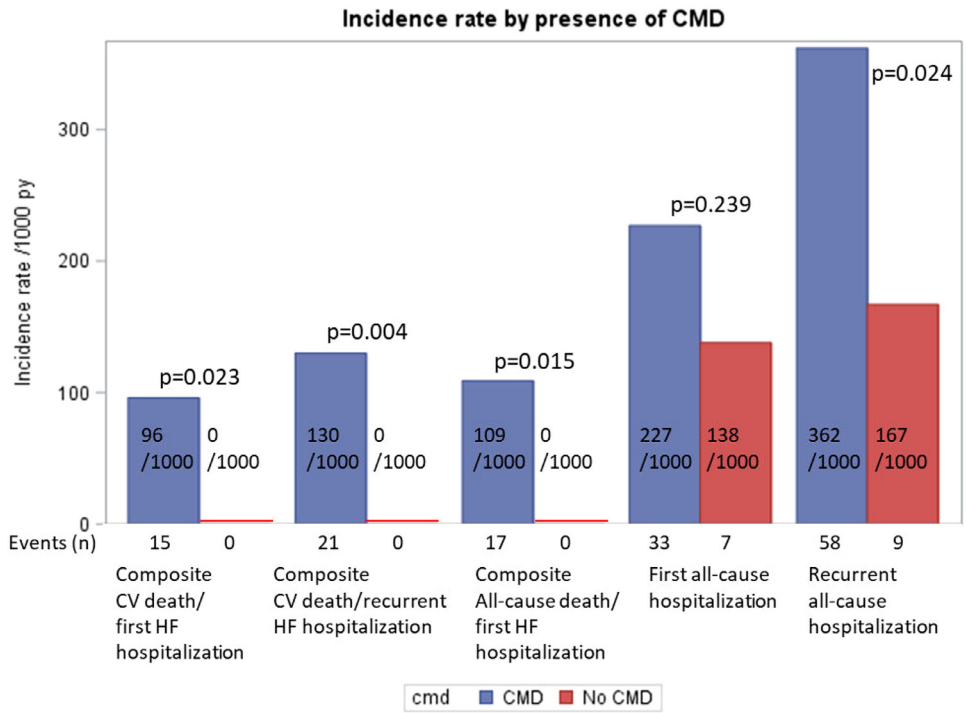


**Fig. 2.** Incidence rates of assessed outcomes in patients with and without coronary microvascular dysfunction. CMD, coronary microvascular dysfunction; CV, cardiovascular; HF, heart failure.

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

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

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

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

## Conclusions

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

Previous reports in HFpEF suggest a relatively greater contribution of non-CV hospitalization and mortality events[11,12] as compared with in HFpEF. In our patients with HFpEF, the majority of deaths were CV (4 of 6), all occurring in the CMD group. Although with few events, these preliminary findings lend support to previous reports in patients with suspected CAD[7] and in HFpEF, correlating CMD with death and/or HF hospitalizations.[8,9] In HFpEF, upregulated inflammation initiating CMD and subclinical atherosclerosis may act as disease drivers impairing outcome.[13−15] Additive information on CMD status may also be more accessible evaluated noninvasively through circulating biomarkers.[13]

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

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