JACC: CARDIOVASCULAR IMAGING VOL. 15, NO. 9, 2022

PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

Association of Sex, Reduced Myocardial Flow Reserve, and Long-Term Mortality Across Spectrum of Atherosclerotic Disease

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ABSTRACT

BACKGROUND Coronary vasomotor dysfunction (defined by reduced myocardial blood flow reserve [MBFR]) is associated with high cardiac risk in both men and women in absence of significant coexisting epicardial disease. Whether there is a sex-specific difference in prognostic value of reduced MBFR in patients with a greater burden of coexisting epicardial atherosclerotic disease is not well understood.

OBJECTIVES The purpose of this study was to examine the association of sex, MBFR, and mortality in consecutive patients with suspected or known coronary artery disease undergoing positron emission tomography myocardial perfusion imaging.

METHODS Unique consecutive patients undergoing rubidium (Rb)-82 rest/stress positron emission tomography myocardial perfusion imaging from 2010-2016 were followed for a median of 3.2 years. Multivariable Cox models were built to describe the interaction of sex and MBFR on all-cause and cardiac death for the overall population and stratified by extent of calcified atherosclerosis (none: coronary artery calcium score = 0, subclinical: coronary artery calcium >0, clinical: prior myocardial infarction/percutaneous coronary intervention) and abnormal perfusion (no significant obstructive disease: summed stress score = 0, 1%-9.9%, and ≥10%) at baseline.

RESULTS Among 12,594 patients, 52.8% were women. Compared with men, women had a lower prevalence of known coronary artery disease (16.5% vs 29.5%; $P < 0.001$) and were less likely to undergo revascularization after myocardial perfusion imaging (4.9% vs 9.7%; $P < 0.001$), but were more likely to have a reduced MBFR of <2 (56.2% vs 50.6%; $P < 0.001$). There were 1,699 (13.5%) all-cause and 490 (3.9%) cardiac deaths. In fully adjusted Cox models, reduced MBFR was independently associated with higher risk of death (HR per 0.1-U decrease: 1.09 [95% CI: 1.08-1.10]; $P < 0.001$), but female sex was not (HR: 0.95 [95% CI: 0.85-1.05]; $P = 0.27$). There was no significant interaction between sex and MBFR on death ($P = 0.22$) and cardiac death ($P = 0.35$) overall or in subgroups of patients with clinical, subclinical, and no atherosclerosis or across categories of perfusion abnormality at baseline.

CONCLUSIONS The association between reduced MBFR and higher risk of all-cause and cardiac death did not differ by sex, regardless of extent of coexisting atherosclerosis or perfusion abnormality.
(J Am Coll Cardiol Img 2022;15:1635-1644) © 2022 by the American College of Cardiology Foundation.

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Marcelo DiCarli, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 30, 2021; revised manuscript received February 14, 2022, accepted March 10, 2022.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2022.03.032

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CFR = coronary flow reserve

MBFR = myocardial blood flow reserve

MI = myocardial infarction

MPI = myocardial perfusion imaging

PET = positron emission tomography

Rb = rubidium

Under-recognition of high-risk markers and subsequent underdiagnosis and inadequate treatment in women are major reasons for disparities in cardiovascular (CV) outcomes between men and women.[1] Coronary microvascular dysfunction is one such high-risk marker, which is commonly present in women with chest pain.[2] Invasively measured coronary flow reserve (CFR) helps identify microvascular dysfunction and has been shown to be associated with higher short- and long-term CV events in women.[3,4] However, these studies enrolled a small and selected population of women, required invasive evaluation, and did not have a comparison arm of men.

Positron emission tomography (PET) myocardial perfusion imaging (MPI) offers the ability to noninvasively measure absolute myocardial blood flow to the myocardium. Myocardial blood flow reserve (MBFR), also known as coronary flow reserve, is the ratio of absolute myocardial blood flow to myocardium at peak hyperemia to rest, which integrates the hemodynamic effects of epicardial focal and diffuse atherosclerosis, as well as microvascular dysfunction, on myocardial perfusion and can help identify CMD. In an earlier study of 1,218 patients with suspected coronary artery disease (CAD) and normal perfusion on PET, reduced MBFR was associated with higher CV risk irrespective of a patient's sex.[5] Subsequently, in a study of 329 patients predominantly with abnormal perfusion referred for coronary angiography, a differential effect between sex and MBFR was noted with a higher rate of CV events in women with very low MBFR compared with men.[6] Men and women often have different profiles of atherosclerotic disease, with men having more obstructive CAD and women more nonobstructive disease, despite similar symptom burden.[7,8] As such, if reduced MBFR in men is more likely to result from obstructive epicardial disease, which can be improved with revascularization, they may be more likely to have better long-term outcomes than women.

We hypothesized that women with reduced MBFR have a different CV risk profile compared with men with low MBFR. To examine this, we first studied the prognostic role of MBFR among men and women undergoing PET MPI. We further examined if the association of sex, MBFR, and long-term cardiac and all-cause mortality would differ based on presence of known clinical, subclinical, or no atherosclerotic disease or presence and severity of perfusion abnormality at the time of the PET MPI test.

METHODS

STUDY POPULATION. A total of 12,594 unique consecutive patients who underwent rest/stress rubidium (Rb)-82 PET MPI at 1 of the 4 nuclear cardiology laboratories with PET capabilities within the Saint Luke's Health System between January 2010 and December 2016 were included in this study, after excluding patients with prior CABG (n = 1,707), cardiomyopathy (EF <40%) (n = 2,854), and missing data on MBFR (n = 2,111). For patients who had multiple tests, the first PET MPI in our system was included. The study protocol was approved by the Institutional Review Board of the Saint Luke's Hospital System. Requirement of informed consent was waived.

STUDY VARIABLES. Demographics, CV risk factors, medical history, symptoms, and baseline medications were collected by trained laboratory personnel at the time of the MPI test from medical chart review and confirmed by patient questioning.

Rb-82 PET AND PET/COMPUTED TOMOGRAPHY MPI IMAGING PROTOCOLS. All patients were studied using a PET (Siemens ECAT ACCEL) or PET/computed tomography (CT) scanner (Siemens Biograph 16 or 64) after fasting for at least 6 hours. Patients were asked to withhold caffeine-containing beverages for 24 hours before the test and beta-blockers, calcium-channel blockers, and nitrates on the morning of the test. One site utilized cardiac PET with line-source attenuation correction for image acquisition during majority of the study period, whereas the remaining 3 sites utilized PET/CT cameras, where a low-dose transmission CT scan was acquired before obtaining rest images for attenuation correction. For the dedicated PET system, a 2.5-minute, 2-dimensional dynamic study (8 × 12-second frames, 2 × 27-second frames) was acquired to measure the quantitative blood flow followed immediately by a 5-minute, 3-dimensional electrocardiography (ECG)-gated perfusion study. For the PET/CT systems, a 3-dimensional, 7-minute ECG-gated list mode study was acquired. Postacquisition, list mode studies were rebinned into 1 dynamic study (8 × 12-second frames, 2 × 27-second frames), and an 8 binned ECG-gate perfusion study (90-330 seconds).

On both PET and PET/CT systems, rest emission image acquisition was started at the same time of beginning the intravenous administration of Rb-82 (10-30 mCi). Regadenoson was used as a stressor in

two-thirds of patients (n = 8,399) and dipyridamole (n = 4,107) was used in the remaining one-third, with 4 patients being stressed with adenosine. At peak stress, another dose of Rb-82 (10-30 mCi) was injected, and stress images were acquired in a similar manner. Patient heart rate, blood pressure, and 12-lead ECG were acquired at baseline and at every 1 minute during and after stress. After acquisition of images, all studies were electronically transmitted to the central nuclear cardiology laboratory where trained nuclear technologists processed and reconstructed the images for interpretation. Perfusion images were reconstructed from the list mode acquisitions starting 90-120 seconds after the beginning of Rb-82 infusions at rest and peak stress using commercial software (Imagen Pro). In patients without known CAD who underwent MPI tests at the sites with a PET/CT camera, a separate CT scan was acquired for purposes of calcium scoring (scored using Siemens Syngo Calcium Scoring software) at the end of the PET study, if no prior calcium score was available in the previous 3 years.

MYOCARDIAL PERFUSION AND LVEF ANALYSIS. Commercial software (Cedars Sinai Cardiac Suite/QPET) was used to display the perfusion images and measure LVEF. All images were semiquantitatively interpreted by experienced observers (T.M.B., A.I.M., and R.C.T.) using a 17-segment model and standard 5-point scoring system.[9] The percentage of myocardium with fixed defect/scar and the percentage of ischemic myocardium were calculated from global summed rest score and summed difference score. Rest and peak stress LVEF were calculated from gated myocardial perfusion images acquired with 8-frame gating using the Cedars Sinai QGS software.

MYOCARDIAL BLOOD FLOW RESERVE. Absolute myocardial blood flow (mL/min/g) was calculated at rest and peak stress using commercially available validated software (Imagen Q).[10,11] The software uses a dynamic net-retention model.[11-13] For every patient, global MBFR was calculated as the ratio of stress to rest absolute myocardial blood flow for the entire left ventricle.

DEFINITIONS OF VARIABLES. Patient sex was based on self-identification as a man or woman at the time of the baseline PET study. Three clinically relevant subgroups were defined based on the presence and extent of atherosclerotic cardiovascular disease (ASCVD) determined by clinical history and coronary artery calcium score. Clinical atherosclerotic event/history of known CAD was defined as having a history of previous myocardial infarction, percutaneous coronary intervention, or presence of prior known obstructive atherosclerotic disease (≥70% epicardial artery stenosis) on a previous coronary angiogram that was not revascularized. As noted in the previous text, patients with prior CABG were excluded; MBFR data may not be reliable in these patients because of severe native vessel disease. Patients with subclinical calcified atherosclerosis were defined as patients with a coronary artery calcium (CAC) >0 without a clinical ASCVD event. Patients with no calcified atherosclerosis were defined as those with a CAC of 0. In a second analysis, the population was divided based on extent of coexisting ischemia on PET into normal perfusion (summed stress score = 0), mildly abnormal perfusion (summed stress score 1%-9.9%) and moderate-severe abnormal perfusion (summed stress score ≥10%). Because coronary anatomy information was not available for all patients, normal perfusion was used as a surrogate to identify patients without any significant obstructive disease.

OUTCOMES. All patients had at least 1 year of follow-up, with the last date of follow-up on December 31, 2017. Data were censored at date of death or last follow-up visit. The primary study endpoint was all-cause mortality, determined from the patient medical record and the National Death Index. The secondary endpoint was cardiac death, determined from cause of death available from National Death Index files.

STATISTICAL ANALYSIS. Patient demographics, risk factors, and clinical and imaging characteristics were compared between men and women using the Student's *t*-test for continuous variables and the chi-square test or Fisher exact test for categorical variables.

Cumulative survival for all-cause and cardiac mortality were compared using Kaplan-Meier survival curves, stratified by patient sex, according to MBFR tertiles for the overall population and by spectrum of CAD risk. Cox proportional hazards analysis was used to assess the association of sex and MBFR with the outcome of all-cause mortality, adjusted for 22 covariates that were chosen a priori based upon previously published literature and clinical judgement. These included demographics (age, sex, body mass index), clinical risk factors (known CAD [prior percutaneous coronary intervention or myocardial infarction (MI)], hypertension, diabetes mellitus, hyperlipidemia, current smoker), inpatient vs outpatient status at the time of PET testing, symptoms (chest pain, dyspnea and syncope), medications (aspirin, beta-blockers, calcium-channel blockers, statins), stress imaging data (resting rate-pressure product, coronary artery calcium score,

TABLE 1 Patient Characteristics

	Women (n = 6,622)	Men (n = 5,927)	*P* Value
Age, y	69.0 ± 11.9	66.9 ± 12.2	<0.001
Body mass index, kg/m^2	29.50 ± 7.35	29.89 ± 5.30	<0.001
Hypertension	5,097 (77.0)	4,716 (79.6)	<0.001
Diabetes	1,722 (26.0)	1,750 (29.5)	<0.001
Prior MI/revascularization	1,094 (16.5)	1,744 (29.5)	<0.001
Dyslipidemia	4,810 (72.6)	4,601 (77.6)	<0.001
Smoker	825 (12.5)	895 (15.1)	<0.001
Prior stroke/TIA	614 (9.3)	457 (7.7)	0.001
Patient status			
Inpatient	2,745 (41.5)	2,114 (35.7)	<0.001
Outpatient	3,877 (58.6)	3,813 (64.3)	
90-d revascularization	325 (4.9)	572 (9.7)	<0.001
Chest pain	4,334 (65.5)	3,126 (52.7)	<0.001
Dyspnea	3,502 (52.9)	2,649 (44.7)	<0.001
Aspirin	4,068 (61.4)	4,066 (68.6)	<0.001
Beta-blocker	2,550 (38.5)	2,623 (44.3)	<0.001
Statin	2,080 (31.4)	2,224 (37.5)	<0.001
ECG response			
Equivocal	132 (2.0)	46 (0.8)	
Ischemic	336 (5.1)	152 (2.6)	<0.001
Nondiagnostic	1,286 (19.4)	953 (16.1)	
Nonischemic	4,868 (73.5)	4,776 (80.6)	
Rest LVEF, %	65.88 ± 11.68	57.33 ± 14.18	<0.001
% scar >0%	799 (12.1)	1,243 (21.0)	<0.001
Ischemia			
None (0%)	4,949 (74.7)	3,549 (59.9)	
Mild-moderate (1%-10%)	1,158 (17.5)	1,480 (25.0)	<0.001
Severe (≥10%)	515 (7.8)	898 (15.2)	
Rest MBF, mL/min/g	0.86 (0.69-1.07)	0.67 (0.55-0.84)	<0.001[a]
Stress MBF, mL/min/g	1.66 (1.33-2.07)	1.36 (1.08-1.71)	0.83[a]
Global MBFR	1.96 ± 0.53	2.04 ± 0.59	<0.001

Values are mean ± SD, n (%), or median (IQR). Continuous variables compared using Student's *t*-test, unless otherwise indicated. Categorical variables compared using chi-square test. [a]Compared using Wilcoxon rank sum test.

ECG = electrocardiography; LVEF = left ventricular ejection fraction; MBF = myocardial blood flow; MBFR = myocardial blood flow reserve; MI = myocardial infarction; TIA = transient ischemic attack.

perfusion data [% total abnormal myocardium], rest LVEF, global MBFR, early revascularization), and an interaction term for MBFR × early revascularization (based on results from previous analysis[14]). To assess if there was a differential effect of patient sex on outcomes in relation to MBFR, an interaction term between sex and MBFR was entered into the Cox models. To account for the change in hazards associated with post-test revascularization, for patients who underwent revascularization within 90-days post-test, prognostic assessment was started from the time of revascularization and not time of index test.

Similar adjusted Cox-proportional hazard regression models were built in a subgroup of patients with known CAD, subclinical CAD, and no CAD defined based on CACS and clinical history, and interaction between sex and MBFR was tested to assess for differential effect of low MBFR on outcomes by sex. Using extent and severity of abnormal perfusion on relative perfusion images as a surrogate for epicardial obstructive disease, a similar approach was used to assess the interaction between sex and MBFR in adjusted Cox regression models across subgroups of normal perfusion and mild and moderate-severely abnormal perfusion. Similar models were used for the outcome of cardiac death. The proportional hazard assumption was checked for all models and was found to be valid. Model fit was tested using likelihood ratio test.

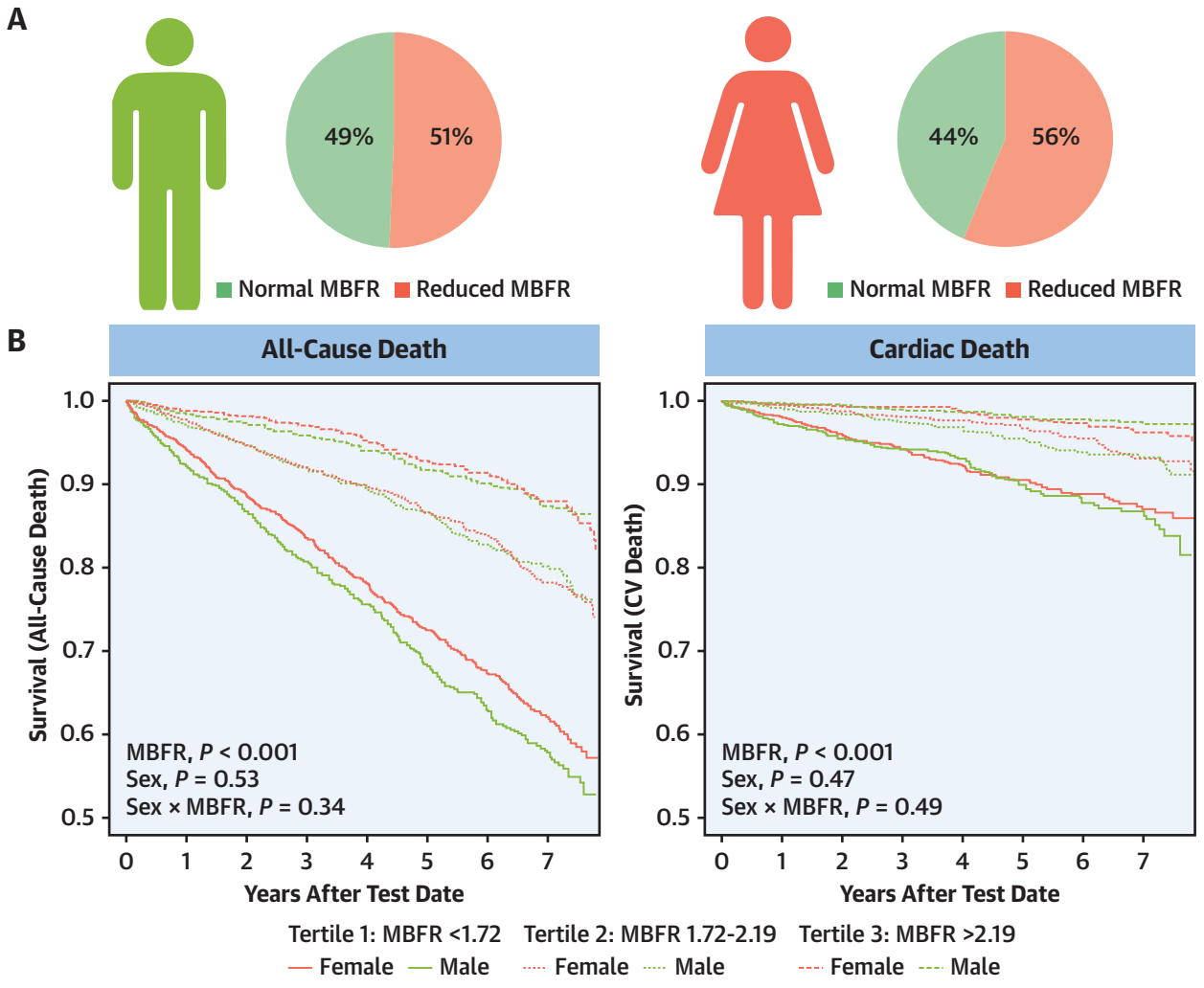
Missing data was rare with most variables missing 0%; age had the most missing data at 3.2%. For these cases, we used a single imputation based on sequential regression methods using the IVEWARE software. Two-sided *P* values <0.05 were considered significant. All analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

Of 12,549 patients in the study cohort, 6,622 (52.8%) were women (Table 1). Women were more likely to be older and to have symptoms of angina and dyspnea compared with men. There was a high prevalence of CV risk factors in the entire population, but women were less likely to have comorbid CV risk factors such as hypertension, diabetes, dyslipidemia, and smoking compared with men. On PET, women were more likely to have an equivocal or ischemic ECG response to vasodilator stress and higher resting LVEF compared with men. On average, women had lower calcium scores and a lower burden of ischemia than men. Significant ischemia (≥10%) was present in 515 (7.8%) women and 898 (15.2%) men. Women had higher absolute resting myocardial blood flows compared with men, but similar stress myocardial blood flows. Mean MBFR was 2.0 ± 1.3, and a MBFR <2 was present in 6,724 (53.6%), with a higher prevalence in women (56.2% vs 50.6%; $P < 0.001$). Compared with men, women had a lower prevalence of known CAD (16.5% vs 29.5%; $P < 0.001$) and were less likely to undergo coronary revascularization after MPI (4.9% vs 9.7%; $P < 0.001$).

During a median study follow-up of 3.2 years (IQR: 1.8-5.0 years), there were 1,699 (13.5%) all-cause deaths and 490 (3.9%) cardiac deaths. Unadjusted survival curves found higher all-cause and CV mortality rates in those with lower baseline MBFR ($P < 0.001$) overall and across different predefined subgroups; however, there was no difference between men and women (Central Illustration, Figure 1).

CENTRAL ILLUSTRATION **Prevalence and Prognosis of Reduced Myocardial Flow Reserve Among Men and Women with Suspected or Known Coronary Artery Disease**



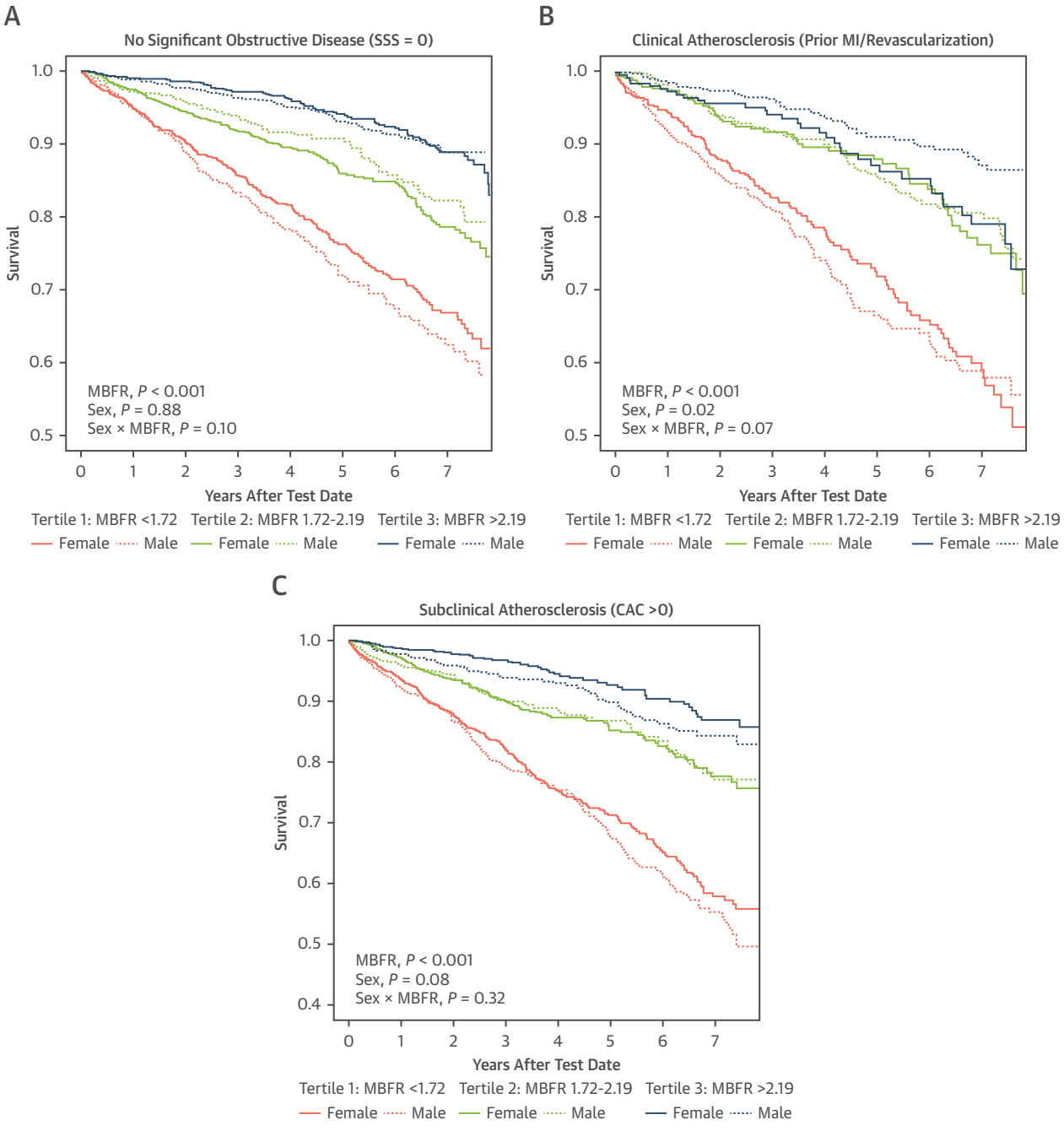
C

	Adjusted Hazard Ratio All-Cause Death (95% CI)	*P* Value	Adjusted Hazard Ratio Cardiac Death (95% CI)	*P* Value
Female	0.94 (0.85-1.05)	0.27	1.08 (0.89-1.31)	0.46
MBFR (per 0.1 ↓)	1.09 (1.08-1.10)	<0.0001	1.10 (1.08-1.12)	<0.0001
Sex × MBFR		0.22		0.35

Patel KK, et al. J Am Coll Cardiol Img. 2022;15(9):1635-1644.

(A) Prevalence of reduced myocardial blood flow reserve (MBFR <2) among men and women. **(B)** Unadjusted Kaplan-Meier survival estimates as a function of baseline myocardial blood flow reserve and patient sex. **(C)** Adjusted HR estimates from Cox proportional hazards analysis for overall population. All models adjusted for age, sex, body mass index, inpatient status, abnormal baseline electrocardiogram, comorbidities (hypertension, diabetes mellitus, hyperlipidemia, smoking, known coronary artery disease), symptoms (chest pain, dyspnea, syncope), medications (acetylsalicylic acid, statin, beta-blockers, calcium-channel blockers), and stress variables (resting rate-pressure product, ischemic electrocardiographic response, peak systolic blood pressure, peak heart rate), rest left ventricular ejection fraction, % abnormal myocardium, 90-day revascularization, and myocardial blood flow reserve × 90-day revascularization. HR estimates from the main effect models without interaction term (as interaction was nonsignificant). CV = cardiovascular.

FIGURE 1 Unadjusted Kaplan-Meier Survival Estimates for All-Cause Death as a Function of Baseline MBFR and Patient Sex, Sub-Stratified by Baseline Coronary Artery Disease Risk



(A) No significant obstructive disease (summed stress score [SSS] = 0), **(B)** clinical atherosclerosis (prior myocardial infarction [MI]/percutaneous coronary intervention [PCI]), and **(C)** subclinical atherosclerosis (coronary artery calcium [CAC] >0). *P* values derived using log-rank test. MBFR = myocardial blood flow reserve.

After adjusting for patient and test characteristics, female sex was not independently associated with all-cause death (HR: 0.94 [95% CI: 0.85-1.05]; $P = 0.27$) or cardiac death (HR: 1.08 [95% CI: 0.89-1.31]; $P = 0.46$). A lower rest LVEF, higher summed stress score, and lower MBFR were significantly independently associated with all-cause death and cardiac death (**Central Illustration,** Supplemental Table 1). Each

TABLE 2 Assessment of the Interaction Between Sex and MBFR on Mortality in Subgroups Across Spectrum of CAD

	With MBFR <2	Characteristic	HR (95% CI) for All-cause Death	*P* Value	HR (95% CI) for Cardiac Death	*P* Value
Clinical CAD (prior MI/PCI, n = 2,838, 39% women)	Women: 64.6%	Female	1.14 (0.93-1.09)	0.20	1.19 (0.84-1.67)	0.33
	Men: 53.3%	MBFR (per 0.1 ↓)	1.07 (1.05-1.09)	<0.001	1.08 (1.04-1.12)	<0.001
		Sex × MBFR		0.13		0.55
Subclinical CAD (CAC >0, n = 5,657, 54.9% women)[a]	Women: 59.3%	Female	0.88 (0.75-1.02)	0.088	1.21 (0.90-1.63)	0.21
	Men: 53.8%	MBFR (per 0.1 ↓)	1.10 (1.07-1.11)	<0.001	1.10 (1.06-1.14)	<0.001
		Sex × MBFR		0.47		0.07
No CAD[a] (CAC = 0, n = 1,395, 73.5% women)[a]	Women: 40.3%	Female	0.83 (0.44-1.60)	0.59	NA[b]	
	Men: 30.5%	MBFR (per 0.1 ↓)	1.08 (1.03-1.14)	0.001	NA	
		Sex × MBFR		0.57	NA	

All estimates derived from adjusted Cox proportional hazards model adjusted for age, sex, body mass index, cardiovascular risk factors, 90-day revascularization, MBFR × early revascularization, resting rate-pressure product, and PET imaging variables. "No CAD" model adjusted for age, sex, body mass index, diabetes, rest left ventricular ejection fraction, % abnormal myocardium, MBFR, sex × MBFR. [a]A total of 7,052/9,711 patients without known CAD (prior MI/PCI) had CAC information available along with PET. HR estimates from the main effect models without interaction term (as interaction was nonsignificant). [b]Adjusted cardiovascular death model for "no CAD" subgroup was not reported because of the small number of events (n = 13).

CAC = coronary artery calcium; CAD = coronary artery disease; NA = not applicable; PCI = percutaneous coronary intervention; PET = positron emission tomography; other abbreviations as in Table 1.

0.1-U decrease in MBFR was associated with a 9% greater hazard of all-cause death (HR: 1.09 [95% CI: 1.08-1.10]; $P < 0.001$) and a 10% greater hazard of cardiac death (HR: 1.10 [95% CI: 1.08-1.12]; $P < 0.001$). There was no difference in the relationship of MBFR with all-cause death between men and women (interaction *P* values of 0.22 for all-cause death and 0.35 for cardiac death).

Coronary vasomotor dysfunction was highly prevalent in both men and women in subgroups of clinical, subclinical, and no calcified atherosclerosis. Prevalence of reduced MBFR (<2) ranged from 41%-67% in women and 31%-62% in men across these subgroups. Similar to the overall population, each 0.1-unit decrease in MBFR was significantly associated with 7%- to 9%-greater hazards of all-cause and CV mortality in each CAD subgroup, but female sex was not, indicating that there was no differential relationship between MBFR and outcomes based on patient sex (**Table 2, Figure 1,** Supplemental Figure 1).

A high prevalence of reduced MBFR was noted in patients with normal perfusion (no significant obstructive disease) affecting 51% of women and 42% of men. As expected, the prevalence of reduced MBFR increased in both sexes with increasing perfusion abnormality on relative perfusion images (**Table 3**). Consistent results similar to the primary analyses were seen across all subgroups of abnormal perfusion for both all-cause and cardiac mortality (**Table 3**). In all subgroups, each 0.1-U decrease in MBFR was associated with a 11%- to 18%-higher hazard of all-cause and cardiac mortality, whereas female sex was not. There was no significant interaction between sex and MBFR, suggesting no differential effect of sex on outcomes based on MBFR in any of the subgroups.

DISCUSSION

In a large cohort of over 12,000 patients undergoing PET MPI, we found that reduced MBFR was independently associated with higher long-term all-cause and cardiac mortality, and this relationship was similar in both men and women. The relationship of lower MBFR and higher mortality between both sexes was consistent regardless of the presence and severity of coexisting burden of atherosclerosis or ischemia.

Prevalence and prognosis of invasively or noninvasively measured CMD with long-term CV risk in men and women has been studied in various settings. In a younger cohort (mean age 55 years) of 224 women with signs and symptoms of ischemia undergoing invasive anatomic and physiological testing in the WISE (Women's Ischemia Syndrome Evaluation) study, 38% had an abnormal CFR, although only 19% had evidence for coronary artery stenosis.[3] In that study, abnormal CFR was associated with a higher risk of major adverse CV events in women both with and without epicardial atherosclerotic CAD.[3] In another cohort of women with nonobstructive CAD, the prevalence of abnormal CFR measured noninvasively with echocardiography was 26%.[15] However, these studies did not include men.[3,15] In a single-center cohort of relatively young (mean age 51 years) symptomatic patients with nonobstructive disease undergoing invasive physiological testing, abnormal CFR was present in two-thirds of all patients, of whom 59.3% were women.[16] In a study of 1,218 patients (67% of whom were women) without known history of CAD and normal perfusion with a mean age of 62 years followed for a median of 1.3

TABLE 3 Assessment of the Interaction Between Sex and MBFR on Mortality in Subgroups Across Spectrum of Perfusion Abnormality

	With MBFR <2	Characteristic	HR (95% CI) for All-cause Death	*P* Value	HR (95% CI) for Cardiac Death	*P* Value
Normal perfusion (no significant obstructive disease) (0%, n = 7,899, 59.2% women)	Women: 50.5%	Female	0.97 (0.84-1.11)	0.66	0.99 (0.74-1.33)	0.96
	Men: 42.2%	MBFR (per 0.1 ↓)	1.13 (1.12-1.15)	<0.001	1.15 (1.11-1.18)	<0.001
		Sex × MBFR		0.77		0.48
Mildly abnormal perfusion (1%-9.9%, n = 2,544, 47.2% women)	Women: 64.7%	Female	0.87 (0.72-1.06)	0.17	1.09 (0.78-1.52)	0.62
	Men: 53.2%	MBFR (per 0.1 ↓)	1.12 (1.10-1.15)	<0.001	1.11 (1.07-1.15)	<0.001
		Sex × MBFR		0.91		0.17
Moderate-severely abnormal perfusion (≥10%, n = 2,106, 35.4% women)	Women: 78.5%	Female	1.04 (0.86-1.26)	0.69	1.18 (0.86-1.64)	0.31
	Men: 70.4%	MBFR (per 0.1 ↓)	1.14 (1.11-1.16)	<0.001	1.17 (1.12-1.21)	<0.001
		Sex × MBFR		0.35		0.33

All estimates derived from adjusted Cox proportional hazards model adjusted for age, sex, body mass index, cardiovascular risk factors, 90-day revascularization, MBFR × early revascularization, resting rate-pressure product, and all PET imaging variables. HR estimates from the main effect models without interaction term (because interaction was nonsignificant).

Abbreviations as in Tables 1 and 2.

years, CMD (MBFR <2) was highly prevalent in both sexes (51% in men and 54% in women) and was associated with worse major adverse CV events in both men and women.[5] In another study of 329 patients from the same center, which included a higher risk population of patients with predominantly abnormal perfusion undergoing angiography post-PET MPI, there was evidence of a differential relationship among sex, MBFR, and CV events on follow-up such that women with very low MBFR were at a higher future CV risk, especially driven by heart failure hospitalizations, compared with men.[6]

Our study expands the findings of these previous studies in several ways. First, the prevalence of coronary vasomotor dysfunction was high in both sexes, ranging from 41%-67% in women and 31%-62% in men across subgroups based on presence and extent of coexisting ASCVD. The larger sample size also allowed us to assess the prognostic importance of CMD across the entire spectrum of CAD from no atherosclerosis to patients with history of clinical ASCVD, improving the generalizability of our findings. The presence of significant ischemia on relative perfusion images on PET suggests the presence of significant obstructive disease, and its associated risk is modified by post-test revascularization. However, we did not find a sex-specific differential effect of reduced MBFR on long-term cardiac and all-cause mortality in patients with normal perfusion or severely abnormal perfusion. We found that presence of coronary vasomotor dysfunction as suggested by a reduced MBFR on PET carries a similar higher risk of future cardiac and all-cause death in both men and women, regardless of the extent or presence of pre-existing subclinical atherosclerosis or presence of ischemia related to epicardial obstructive CAD.

In our study, although women were more likely to have reduced MBFR, they were less likely to undergo post-test revascularization. Reduced MBFR in women may be more likely caused by coexisting microvascular dysfunction with or without diffuse epicardial atherosclerotic disease that does not warrant revascularization, whereas in men, it may be more likely to be secondary to significant epicardial atherosclerotic disease. However, we did not see a difference in the mortality risk associated with reduced MBFR in men and women, even in patients with significant ischemia who are more likely to have epicardial obstructive disease. Women in our cohort also had higher resting myocardial blood flows, which could itself lead to impaired MBFR in presence of normal hyperemic flows. In our cohort, these women with reduced MBFR carried a similar worse long-term prognostic risk, even after adjusting for elevated resting rate-pressure product, as was seen in a study from another center.[17] Although the high cardiac risk associated with reduced MBFR from epicardial obstructive disease can potentially be modified with revascularization,[18] stratified medical therapy for microvascular dysfunction has been shown to improve symptoms, function, and quality of life.[19] Given the high prevalence of coronary vasomotor dysfunction, which helps guide management decision as well as prognosticate events, flow quantitation with PET for patients with multiple CV risk factors and suspected ischemic symptoms can be a useful noninvasive tool for risk stratification and potentially risk mitigation, beyond invasive or noninvasive anatomic testing.

STUDY LIMITATIONS. Our study findings should be interpreted in the context of the following limitations. Even after extensive adjustment for >20

covariates, the possibility of residual confounding from unmeasured variables such as frailty and noncardiac comorbidities remains. We did not have access to coronary artery anatomy information for majority of our cohort, which could have helped us better understand the contribution of obstructive vs nonobstructive disease to the association among sex, MBFR, and outcomes. We instead used surrogate measures such as extent and severity of perfusion defect and calcium score to identify significant obstructive disease and extent of atherosclerosis, as these measures are readily available along with MPI. Noncalcified atherosclerosis may not be captured as we used CAC to define subgroup of subclinical or no known calcified atherosclerosis. All-cause death was used as the primary outcome which is less prone to subjective assessment and misclassification. However, we found similar results with cardiac death as a secondary outcome. Recent data have shown a strong association of reduced MBFR with future risk of heart failure.[20] This outcome of heart failure hospitalization which could have driven some of the discordant results from earlier studies was not available.[3,6]

CONCLUSIONS

This large study of patients undergoing PET MPI demonstrated that although reduced MBFR was more prevalent in women compared with men, there were no sex-specific differences in the prognostic value of reduced MBFR. Reduced MBFR on PET MPI was independently associated with poor long-term survival in both sexes, regardless of presence and severity of coexisting calcified atherosclerosis or perfusion abnormality.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Spertus has served as a consultant to United Healthcare, Bayer, and Novartis; has received research grants from Abbott Vascular and Novartis; is the PI of an analytic center for the American College of Cardiology; and has an equity interest in Health Outcomes Sciences. Dr Bateman has received research grant support from Bracco, GE Healthcare, Jubilant Drax Image, and Spectrum Dynamics; has served as a consultant to GE Healthcare; has an equity interest in Cardiovascular Imaging Technologies; and has intellectual property rights for Imagen PET and SPECT software. All other authors have reported that they have no relationships relevant to the contents of this paper.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a large study of 12,594 patients undergoing PET myocardial perfusion imaging, reduced MBFR was present in more than one-half of all men and women. Reduced MBFR was independently associated with poor long-term survival in both men and women, regardless of presence and severity of coexisting calcified atherosclerosis or perfusion abnormality.

TRANSLATIONAL OUTLOOK: Future studies are needed to assess whether optimal medical management of coexistent microvascular dysfunction (as measured by reduced MBFR) among patients with suspected or known CAD results in improved survival in both sexes.

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KEY WORDS coronary flow reserve, mortality, myocardial perfusion imaging, positron emission tomography, women

APPENDIX For a supplemental table and figure, please see the online version of this paper.