Excess Cardiovascular Risk in Women Relative to Men Referred for Coronary Angiography Is Associated With Severely Impaired Coronary Flow Reserve, Not Obstructive Disease

BACKGROUND: Cardiovascular disease (CVD) fatality rates are higher for women than for men, yet obstructive coronary artery disease (CAD) is less prevalent in women. Coronary flow reserve (CFR), an integrated measure of large- and small-vessel CAD and myocardial ischemia, identifies patients at risk for CVD death, but is not routinely measured in clinical practice. We sought to investigate the impact of sex, CFR, and angiographic CAD severity on adverse cardiovascular events.

METHODS: Consecutive patients (n=329, 43% women) referred for invasive coronary angiography after stress testing with myocardial perfusion positron emission tomography and with left ventricular ejection fraction >40% were followed (median, 3.0 years) for a composite end point of major adverse cardiovascular events, including cardiovascular death and hospitalization for nonfatal myocardial infarction or heart failure. The extent and severity of angiographic CAD were estimated by using the CAD prognostic index, and CFR was quantified by using positron emission tomography.

RESULTS: Although women in comparison with men had lower pretest clinical scores, rates of prior myocardial infarction, and burden of angiographic CAD ($P<0.001$), they demonstrated greater risk of CVD events, even after adjustment for traditional risk factors, imaging findings, and early revascularization (adjusted hazard ratio, 2.05; 95% confidence interval, 1.05–4.02; $P=0.03$). Impaired CFR was similarly present among women and men, but in patients with low CFR (<1.6, n=163), women showed a higher frequency of nonobstructive CAD, whereas men showed a higher frequency of severely obstructive CAD ($P=0.002$). After also adjusting for CFR, the effect of sex on outcomes was no longer significant. When stratified by sex and CFR, only women with severely impaired CFR demonstrated significantly increased adjusted risk of CVD events ($P<0.0001$, P for interaction=0.04).

CONCLUSIONS: Women referred for coronary angiography had a significantly lower burden of obstructive CAD in comparison with men but were not protected from CVD events. Excess cardiovascular risk in women was independently associated with impaired CFR, representing a hidden biological risk, and a phenotype less amenable to revascularization. Impaired CFR, particularly absent severely obstructive CAD, may represent a novel target for CVD risk reduction.

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Clinical Perspective

What Is New?

- In comparison with men, women referred for invasive evaluation of coronary artery disease demonstrated less obstructive coronary artery disease by angiography, but greater adjusted risk of cardiovascular disease events.
- Impaired coronary flow reserve (CFR) mediated a substantial proportion (40%) of this excess risk in women, representing a hidden biological risk of ischemic heart disease.
- The differential effect of sex on outcomes was amplified for patients with very low CFR (<1.6), and not apparent in patients with preserved CFR (>2). Thus, only women with severely impaired CFR demonstrated increased risk in comparison with men.

What Are the Clinical Implications?

- The effect of sex on outcomes is mediated in part by a hidden biological risk of ischemic heart disease, which may be better diagnosed using CFR.
- In patients with very low CFR (<1.6), more men than women had multivessel obstructive coronary artery disease and underwent surgical revascularization, possibly mitigating their risk. Closing the "gender gap" in ischemic heart disease will likely require more than equitable application of current guidelines.
- CFR as a biomarker of ischemic heart disease risk should be evaluated not only in prospective studies investigating the role of ischemia and revascularization, but also of emerging anti-inflammatory, lipid-lowering, and neurohormonal-modulating agents on cardiovascular disease outcomes, especially in women.

In the past 3 decades, case fatality rates for cardiovascular disease (CVD) in the United States have been higher for women than for men,[1] yet obstructive coronary artery disease (CAD) is less prevalent in women.[2–6] Luminal coronary angiography is the gold standard for diagnosis of obstructive CAD and remains a cornerstone of modern CVD care, but it has limited ability to identify diffuse atherosclerosis and small-vessel disease, which may contribute to adverse cardiovascular events, including acute coronary syndromes, heart failure, and CVD death from plaque erosion, impaired coronary vasoreactivity, and microvascular dysfunction with resultant myocardial ischemia.[2,7–9]

Coronary flow reserve (CFR) provides a combined physiological measure of large- and small-vessel CAD and myocardial ischemia, and identifies patients at risk for cardiovascular death. CFR, calculated as the ratio of hyperemic to rest myocardial blood flow, evaluates the integrated hemodynamic effects of epicardial CAD, diffuse atherosclerosis, vessel remodeling, and microvascular dysfunction on myocardial perfusion. Emerging data have demonstrated that CFR measurements by noninvasive positron emission tomography (PET) can distinguish patients at highest risk for serious cardiovascular events independently of the traditional measures of stress-induced ischemia or left ventricular ejection fraction (LVEF).[10–14] We recently showed that impaired CFR is associated with adverse cardiovascular events independently of angiographic stenosis severity, and that baseline CFR may modify the outcomes of revascularization, especially with coronary artery bypass grafting (CABG).[15]

Because symptomatic women are less likely than men to manifest obstructive CAD on angiography (and thus less likely to partake in any beneficial effect of revascularization), we sought to investigate the relative contributions of sex and CFR on CVD outcomes in a clinical cohort of patients referred for coronary angiography for the evaluation of CAD. We hypothesized that women in comparison with men would have less obstructive CAD, but not less impaired CFR as quantified by PET myocardial perfusion, and that this would be associated with a significant hidden risk of CVD events despite access to revascularization.

METHODS

Study Population

Study participants were consecutive patients clinically referred for invasive coronary angiography within 90 days after stress myocardial perfusion PET at Brigham and Women's Hospital between 2006 and 2012. Indications for testing most commonly included evaluation for chest pain, dyspnea, or their combination. Patient history and medication use were ascertained at the time of PET imaging. From a cohort of 841 patients, those with prior CABG, LVEF <40%, or a clinical diagnosis of heart failure were excluded, leaving a final cohort of 329 individuals. The median time from PET to invasive angiography was 2.6 (Q1–Q3, 0.3–13.5) days. No patients had an intervening cardiovascular event or revascularization between PET and angiography. A pretest clinical score integrating age, sex, type of chest pain, history of myocardial infarction, presence of diabetes mellitus, hyperlipidemia, current smoking, and electrocardiographic abnormalities into a pretest probability of obstructive angiographic CAD was calculated as described previously.[16] Early revascularization, considered to be triggered by imaging results, was defined as occurring within 90 days of PET.[14] The study was approved by the Partners Healthcare Institutional Review Board and conducted in accordance with institutional guidelines.

PET Imaging

Patients were imaged with a whole-body PET–computed tomography scanner (Discovery RX or STE LightSpeed 64, GE Healthcare) using ^{82}Rubidium (1480–2200 MBq) or ^{13}N-ammonia (700–900 MBq) as a flow tracer at rest and pharmacological stress, as described previously.[17] Computed tomography was used to correct for photon attenuation by soft tissues. For

semiquantitative assessment of myocardial scarring and ischemia, 17-segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard 5-point scoring system.[18] Summed rest and difference (stress – rest) scores were converted to percentage of myocardium by dividing by the maximum score of 68.[19] For each of these variables, higher scores reflect larger areas of myocardial scar or ischemia, respectively. Rest LVEFs were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM).

Absolute global myocardial blood flow (in $mL \cdot min^{-1} \cdot g^{-1}$) was quantified at rest and at peak hyperemia by using automated factor analysis and a validated 2-compartment kinetic model, as described previously.[17] Per-patient global CFR was calculated as the ratio of stress to rest absolute myocardial blood flow for the whole left ventricle. Myocardial blood flow and CFR values were not clinically available to referring physicians. Radiation exposure per study was ≤4.6 mSV. Quantitative measures of CFR were obtained in patients undergoing PET myocardial perfusion at no additional clinical cost, imaging time, or radiation exposure.

Coronary Angiography

All patients underwent selective coronary angiography by using standard clinical techniques, with ≥2 projections obtained per vessel distribution, and angles of projection optimized for cardiac position. In each patient, the CAD prognostic index (CADPI) was quantified as described previously.[15,20] The CADPI classification is a hierarchical index (0–100) that assigns prognostic weights to increasing percent stenoses (50%–100%) in 1-, 2-, or 3-vessel classification, with higher weights for proximal left anterior descending or left main artery involvement. Luminal diameter stenoses of the major epicardial coronary arteries were clinically graded by subjective visual consensus of experienced operators on an ordinal scale and applied to the CADPI classification in blinded fashion.

Outcomes

Subjects were followed for a median of 3.0 years (Q1–Q3, 1.7–4.4) for the occurrence of major adverse cardiovascular events, including cardiovascular death and hospitalization for nonfatal myocardial infarction or heart failure. Time to first event was analyzed. Heart failure rather than repeat revascularization was selected a priori for the composite end point because of its emerging clinical significance and associated severe prognosis.[21] Ascertainment of clinical end points was determined by blinded expert adjudication of the longitudinal medical record, Partners Healthcare Research Patient Data Registry, and the National Death Index. For an event to be classified as admission for nonfatal myocardial infarction or heart failure, discharge with a primary hospitalization diagnosis of myocardial infarction or heart failure, respectively, was required. The date of the last consultation was used to determine follow-up. All patients not meeting a clinical end point had >30 days of follow-up.

Statistical Analysis

Baseline characteristics are reported as rates with percentages (%) for categorical variables and medians with interquartile ranges (Q1–Q3) for continuous variables. We used the Fisher exact test and the Wilcoxon rank sum test to assess differences in categorical and continuous baseline characteristics.

Cumulative event-free survival curves for the composite end point were compared using the log-rank test across dichotomous categories of sex, sex and CADPI clinical cut point of ≥37 versus <37, and sex and CFR median (<1.6 versus ≥1.6). The CADPI cut point was selected to reflect a >70% stenosis in >1 major epicardial coronary artery, a clinically actionable threshold for revascularization; this is also the cut point at which a survival benefit has been demonstrated previously for revascularization.[20] The median CFR of 1.6 was selected as a cut point for simplicity in the descriptive display. This value, lower than the all-comer median cut point of 2,[14] is consistent with the more comorbid population referred for coronary angiography.[22] Where indicated (and for modeling), we report values of CADPI and CFR as continuous variables. Similar results were obtained after logarithmic transformation, and results are presented untransformed for ready clinical applicability.

Cox proportional-hazards models were used to examine the association between sex and events after controlling for the effects of clinically important covariates, sequentially adding traditional clinical risk factors, noninvasive and invasive imaging factors, and finally CFR. Data were censored at the time of the last visit. Univariate associations were tested, and Cox models sequentially added sex, age, race, medical history, medications, pretest clinical score, imaging, and angiography variables, with a collinearity index used to check for linear combinations among covariates, and the Akaike information criterion assessed to avoid overfitting. Final covariates were included based on clinical knowledge. To avoid overfitting, demographic and medical history variables (age, type of chest pain, history of myocardial infarction, presence of diabetes mellitus, hyperlipidemia, current smoking, and electrocardiographic abnormalities) were incorporated into a validated, aforementioned pretest clinical score[16] in nested models, which were compared by using the likelihood ratio test. The proportional-hazards assumption was confirmed using martingale residuals, and time-dependent variables were included as appropriate. A linear interaction term for sex and CFR was tested for significance in the final adjusted model. The final model with sex was adjusted for nonwhite race, pretest clinical score, history of percutaneous coronary intervention (PCI), hypertension and insulin use; body mass index >27 kg/m^2, LVEF <50%, left ventricular (LV) ischemia >10%, CADPI, time-dependent variables of early revascularization with PCI or CABG, and CFR. Dichotomous variables were used for body mass index, %LVEF, and %LV ischemia to reflect clinically relevant thresholds. Adjusted event-free survival was plotted using survival probabilities from the Cox model and stratified by categories of sex, sex and CADPI, or sex and CFR. Causal mediation analysis, as recently described with survival data,[23] was used to estimate the proportion of the adjusted effect of sex on outcomes that was mediated by CFR, allowing for their interaction.

In additional analysis, we stratified invasive angiographic severity by sex subgroups across medians of CFR, and used the Mantel-Haenszel χ^2 test to assess differences across categories. We displayed data across categories of CADPI grouped for clinical significance. A P value of <0.05 was considered to indicate statistical significance, and all tests were 2-sided. No adjustment for multiple comparisons was performed. The SAS analysis system, version 9.4, was used for all analyses (SAS Institute).

Table 1. Baseline Characteristics of Patients, by Sex

Characteristic	Overall (N=329)	Sex		*P* Value*
		Women (n=140)	Men (n=189)	
Demographics				
Age,† y (Q1–Q3)	67 (59–75)	68 (59–76)	66 (59–75)	0.34
Nonwhite race (%)	79 (24.0)	44 (31.4)	35 (18.5)	0.009
Body mass index,† kg/m^2	29.9 (26.3–34.5)	31.0 (27.2–37.6)	28.9 (25.9–32.9)	0.002
Pretest clinical score,†‡ %	58.2 (28.4–84.8)	27.1 (13.1–45.7)	78.4 (59.3–91.4)	<0.001
Medical history				
Myocardial infarction, n (%)	108 (32.8)	37 (26.4)	71 (37.6)	0.04
Percutaneous coronary intervention, n (%)	105 (31.9)	35 (25.0)	70 (37.0)	0.02
Peripheral arterial disease, n (%)	48 (14.6)	22 (15.7)	26 (13.8)	0.64
Diabetes mellitus, n (%)	132 (40.1)	70 (50.0)	62 (32.8)	0.002
Hypertension, n (%)	290 (88.2)	129 (92.1)	161 (85.2)	0.06
Dyslipidemia, n (%)	241 (73.3)	105 (75.0)	136 (72.0)	0.61
Current smoker, n (%)	29 (8.8)	10 (7.1)	19 (10.1)	0.43
Renal hemodialysis, n (%)	11 (3.3)	3 (2.1)	8 (4.2)	0.37
Medications				
Antiplatelet therapy, n (%)	253 (76.9)	114 (81.4)	139 (73.5)	0.11
Statin, n (%)	231 (70.2)	99 (70.7)	132 (69.8)	0.90
β-Blocker, n (%)	229 (69.6)	98 (70.0)	131 (69.3)	0.90
Angiotensin inhibitor, n (%)	149 (45.3)	68 (48.6)	81 (42.9)	0.32
Nitroglycerin, n (%)	58 (17.6)	25 (17.9)	33 (17.5)	0.99
Diuretic, n (%)	108 (32.8)	51 (36.4)	57 (30.2)	0.24
Insulin, n (%)	62 (18.8)	38 (27.1)	24 (12.7)	0.002
Noninvasive imaging parameters				
Left ventricular ejection fraction,† %	57 (50–65)	62 (55–68)	54 (49–61)	<0.001
Left ventricular scar,† %	0 (0–2.9)	0 (0–2.9)	0 (0–4.4)	0.82
Left ventricular ischemia,† %	10.3 (5.9–16.2)	10.3 (5.1–17.7)	10.3 (5.9–16.2)	0.92
Stress global myocardial blood flow,† mL·g^{-1}·min^{-1}	1.6 (1.1–2.0)	1.7 (1.2–2.3)	1.5 (1.0–1.9)	<0.001
Rest myocardial blood flow,† mL·g^{-1}·min^{-1}	1.0 (0.8–1.2)	1.1 (0.9–1.3)	0.9 (0.7–1.1)	<0.001
Coronary flow reserve†	1.6 (1.2–2.0)	1.5 (1.2–1.9)	1.6 (1.2–2.0)	0.30
Impaired coronary flow reserve (<1.6)	163 (49.5)	76 (54.3)	87 (46.0)	0.15
Rubidium-82 radiopharmaceutical, %	293 (89.1)	127 (90.7)	166 (87.8)	0.48
Invasive angiography				
Coronary artery disease prognostic index†,§	32 (23–48)	32 (19–37)	37 (23–48)	<0.001
Nonobstructive disease (CADPI 0–19)	77 (23.4)	43 (30.7)	34 (18.0)	0.008
Any early revascularization¶ (%)	193 (58.7)	73 (52.1)	120 (63.5)	0.04
Percutaneous coronary intervention (%)	157 (47.7)	62 (44.3)	95 (50.3)	0.32
Coronary artery bypass surgery (%)	39 (11.9)	12 (8.6)	27 (14.3)	0.12

*P value is for comparison between sex groups, and is based on the Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

†Continuous variables are presented as medians (Q1–Q3).

‡Pretest clinical score is the pretest probability of >70% stenosis in ≥1 major coronary artery on angiography.[16]

§Coronary artery disease prognostic index (CADPI) is a hierarchical index (0–100) assigning prognostic weights to increasing percent stenosis (50%–100%) in 1-, 2-, or 3-vessel classification, with higher weights for proximal left anterior descending or left main artery involvement. CADPI 0 (<50% stenosis), 37 (>70% stenosis in >1 major epicardial coronary artery).[20]

¶Early revascularization is defined as within 90 days of noninvasive imaging. Three patients underwent both percutaneous coronary intervention and coronary artery bypass grafting.

RESULTS

Baseline Characteristics

Distribution of baseline characteristics is shown in Table 1. The median (Q1–Q3) age of patients in the overall cohort was 67 (59–75) years, 42.6% were women, 24.0% were nonwhite, and the median pretest clinical score was 58.2% (28.4–84.8). Nearly one-third of patients had prior myocardial infarction, 31.9% had prior PCI, and 58.7% underwent revascularization by either PCI or CABG within 90 days of PET imaging. In comparison with men, women (n=140) were similar in age, use of cardiovascular medications, and extent of LV ischemia and scar on semiquantitative perfusion imaging. Women, however, had lower pretest clinical scores, with lower rates of prior myocardial infarction or PCI and higher LVEF, and they demonstrated significantly lower burden of obstructive angiographic disease by CADPI in comparison with men (median CADPI, 32 versus 37, respectively; $P<0.001$), with lower rates of early revascularization. They were also more likely than men in this angiography cohort to be nonwhite and diabetic, with higher body mass index and rates of insulin use. Nearly one-third of women demonstrated nonobstructive CAD (CADPI ≤19), in comparison with 18% of men ($P<0.01$). Baseline CFR was similarly impaired among women and men (median CFR, 1.5 versus 1.6, respectively; $P=0.30$).

Sex and Clinical Events

During follow-up, 74 patients met the composite end point of cardiovascular death or admission for nonfatal myocardial infarction or heart failure, including 31 deaths (Table 2). Although women in comparison with men had lower pretest clinical scores, rates of prior myocardial infarction, and burden of angiographic CAD, they demonstrated similar or greater risk of CVD events (unadjusted hazard ratio [HR], 1.95; 95% confidence interval [CI], 1.01–2.52; $P=0.047$), which persisted after adjustment for traditional clinical risk factors, including pretest clinical score; nonwhite race; history of PCI, hypertension, and insulin use; body mass index >27 kg/m^2; LVEF <50%; and LV ischemia >10% (adjusted HR, 2.21; 95% CI, 1.13–4.31; $P=0.02$) (Table 3). Accordingly, women experienced reduced event-free survival in comparison with men (Figure 1A and 1B).

Table 2. Patients Meeting Cardiovascular End Point

Outcome	No. (%) of Patients (N=329)
Total cardiovascular events	74 (22.5)
Cardiovascular death	31 (9.4)
Hospitalization for nonfatal myocardial infarction	19 (5.8)
Hospitalization for heart failure	36 (10.9)

Median (Q1–Q3) follow-up time was 3.0 (1.68–4.42) years. Time to first event was analyzed.

Sex, Angiographic Disease, and Clinical Events

Addition of invasive angiographic variables into the Cox proportional-hazards model to adjust for the effect of angiographic severity and time-dependent revascularization outcomes led to improved model statistics (Table 3). However, despite manifesting a lower burden of obstructive angiographic CAD, women continued to show elevated risk of CVD events (adjusted HR, 2.05; 95% CI, 1.05–4.02; $P=0.03$) (Table 3). When survival probability was stratified by sex and CADPI, women independently of angiographic disease severity experienced higher rates of major adverse cardiovascular events, whereas men with less angiographic disease experienced the highest adjusted freedom from events (Figure 1C and 1D). Whereas outcomes for men were more closely associated with the presence or absence of severely obstructive CAD, in women, even those with less severe CAD appeared to fare as poorly as those with severely obstructive CAD.

Sex, Angiographic Disease, CFR, and Clinical Events

To investigate whether CAD severity as defined by coronary angiography may be insufficient to optimally risk stratify symptomatic, intermediate- to high-risk women, we next examined the effect of CFR on cardiovascular events. Subsequent addition of CFR into the Cox proportional-hazards model to adjust for the hemodynamic burden associated with not only the effect of obstructive CAD but also that of nonobstructive CAD and microvascular dysfunction, led to incremental improvements in model statistics (Table 3). After adjusting for CFR (adjusted HR for unit decrease in CFR, 1.69; 95% CI, 1.04–2.76; $P=0.03$), the effect of sex on outcomes decreased and was no longer statistically significant (adjusted HR, 1.81; 95% CI, 0.91–3.59; $P=0.10$). There was also a significant interaction between CFR and sex on major adverse cardiovascular events (P for interaction=0.04) such that not all women, but only those with impaired CFR demonstrated a significantly increased risk of CVD events (unadjusted $P=0.01$, adjusted $P<0.0001$) (Figure 1E and 1F). This differential effect of sex on outcomes was amplified for patients with very low CFR (Table 3, Figure 2), and not apparent in patients with CFR >2. Allowing for this interaction, CFR was estimated to mediate 40% of the observed differential effect of sex on outcomes in the adjusted model (online-only Data Supplement Table).

To better understand the mechanism for this effect modification, we then explored the influence of patient sex on angiographic disease score across categories

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Table 3. Multivariable-Adjusted Associations of Sex and Coronary Flow Reserve With Cardiovascular Events

	Female Sex		Coronary Flow Reserve*		Model Statistics	
Sequential Models for Total Cardiovascular Events	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Likelihood Ratio χ^2	*P* Value†
Multivariable model 1 Traditional clinical factors	2.21 (1.13–4.31)	0.02			34.45	<0.001
Multivariable model 2 +Invasive factors	2.05 (1.05–4.02)	0.03			47.58	0.02
Multivariable model 3 +Coronary flow reserve	1.81 (0.91–3.59)	0.10	1.69 (1.04–2.76)	0.03	52.45	0.03
+Interaction (CFR* × Sex)		0.04‡			112.07	<0.001
for CFR = 2.0	1.14 (0.49–2.72)					
for CFR = 1.6	1.69 (0.81–3.50)					
for CFR = 1.2	2.49 (1.16–5.38)					

Model 1: adjusted for nonwhite race; pretest clinical score (includes age); history of percutaneous coronary intervention, hypertension, and insulin use; BMI >27 kg/m^2; LVEF <50%; and LV ischemia >10%.

Model 2: adjusted for nonwhite race; pretest clinical score (includes age); history of percutaneous coronary intervention, hypertension, and insulin use; BMI >27 kg/m^2; LVEF <50%; and LV ischemia >10%; coronary artery disease prognostic index; and time-dependent revascularization with percutaneous coronary intervention or coronary artery bypass grafting within 90 days of noninvasive imaging.

Model 3: adjusted for nonwhite race; pretest clinical score (includes age); history of percutaneous coronary intervention, hypertension, and insulin use; BMI >27 kg/m^2; LVEF <50%; and LV ischemia >10%; coronary artery disease prognostic index; time-dependent revascularization with percutaneous coronary intervention or coronary artery bypass grafting within 90 days of noninvasive imaging; and CFR.

BMI indicates body mass index; CFR, coronary flow reserve; CI, confidence interval; LV, left ventricle; and LVEF, left ventricular ejection fraction.

*Indicates coronary flow reserve (CFR, per −1 U).

†Indicates *P* value for likelihood ratio test between sequential models. First value is for comparison of multivariable Model 1 to univariate analysis of female sex.

‡Indicates *P* value for interaction. Estimated effects by level of CFR were obtained from the linear interaction of CFR and sex.

of CFR. CFR was similarly impaired among women and men. In patients with low CFR (<1.6, n=163), however, men had a higher frequency of severely obstructive CAD (CADPI ≥37, 62.9% male), whereas women had higher frequency of nonobstructive CAD (CADPI ≤19, 70.4% female, *P* for trend=0.002) (Figure 3). Thus, fewer women with low CFR were eligible for revascularization, especially by CABG. There was a significant interaction between CFR and revascularization by CABG (*P*=0.01) such that patients with low CFR who underwent CABG experienced low event rates comparable to those with preserved CFR, whether or not they underwent revascularization.

DISCUSSION

In comparison with men, women referred for coronary angiography for the evaluation of CAD had lower pretest clinical risk scores, lower rates of prior myocardial infarction/PCI, and lower burden of obstructive CAD by invasive angiography, but demonstrated similar if not greater adjusted risk of cardiovascular events. Here, for the first time, we show that this excess risk in women was mediated in part by impaired CFR, representing a hidden biological risk. In addition to being a partial mediator, CFR also modified the effect of sex on adverse CVD events, especially for patients with very low CFR. Thus, when stratified by sex and CFR, only women with impaired CFR had significantly increased adjusted risk of CVD events.

These findings have several implications (Figure 4). First, although the effect of sex on CVD outcomes is multifactorial,[2,24,25] it is mediated in a substantial manner by a hidden biological risk of ischemic heart disease. This risk may be better diagnosed through functional quantitative measures[26] such as CFR, than with traditional anatomic visualization using coronary angiography. Because CFR is a measure of not only obstructive CAD, but also diffuse nonobstructive CAD and microvascular dysfunction, these findings suggest that women in this angiography cohort, also disproportionately diabetic and taking insulin, exhibited a phenotype of heart disease that may still lead to adverse events[6,27,28] despite being less amenable to focal revascularization. Instead of being interpreted as demonstrating a false-positive (or negative) traditional ischemic evaluation, patients with impaired CFR and less obstructive CAD may be at significantly increased CVD risk despite having access to revascularization, which is fundamentally targeted at management of obstructive CAD. Thus, although providing optimal, equitable guideline-directed medical care

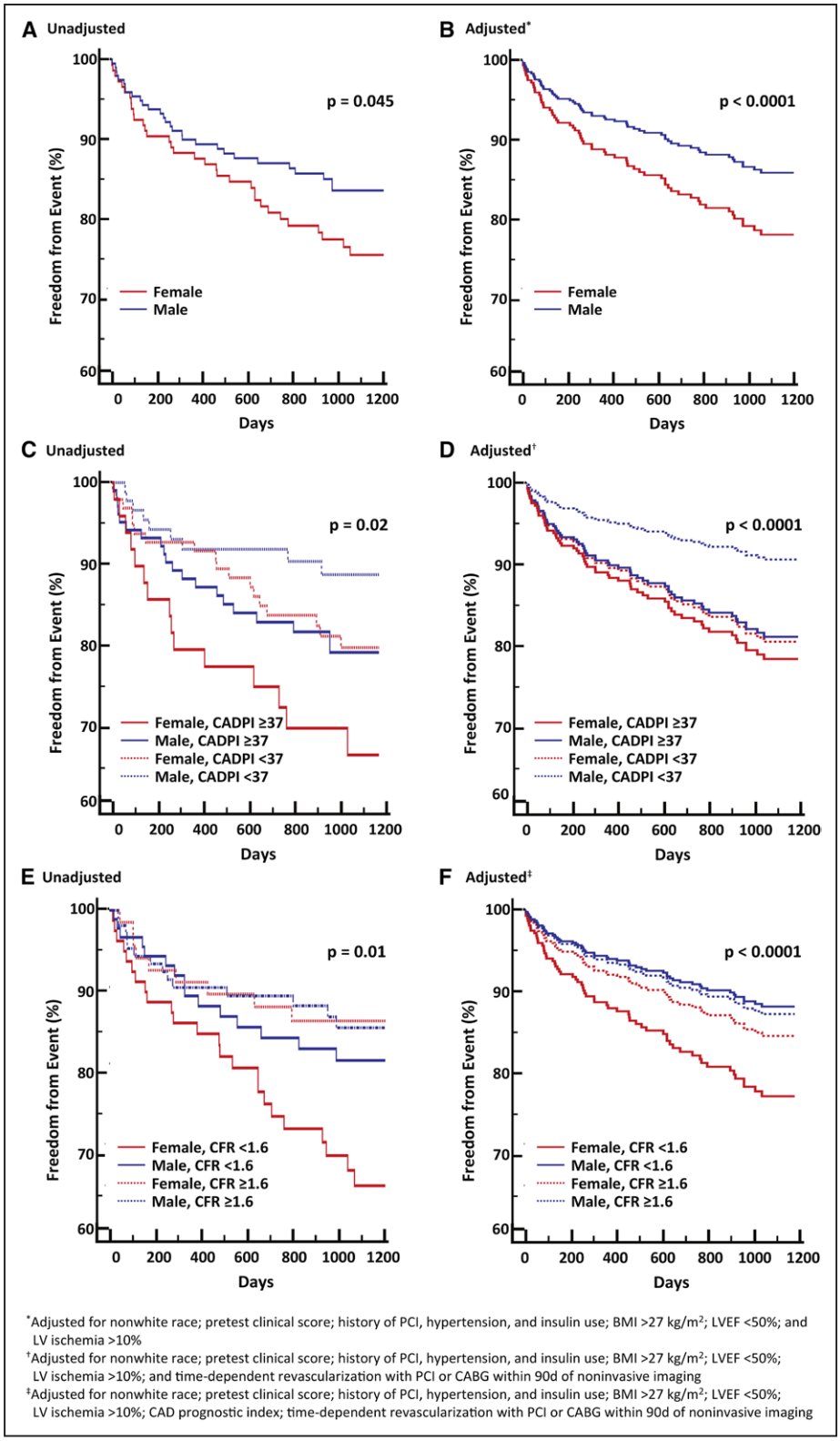

Figure 1. Freedom from major adverse cardiovascular events according to sex (A and B), sex and angiographic disease (C and D), or sex and coronary flow reserve (E and F).
In comparison with men, women experienced similar if not greater risk of cardiovascular events (**A** and **B**). In men but not women, outcomes were associated with the presence or absence of severely obstructive CAD (**C** and **D**). Not all women, but only those with impaired CFR, demonstrated the highest risk of CVD events (**E** and **F**). BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CADPI, CAD prognostic index; CFR, coronary flow reserve; LV, left ventricle; LVEF, left ventricular ejection fraction; and PCI, percutaneous coronary intervention.

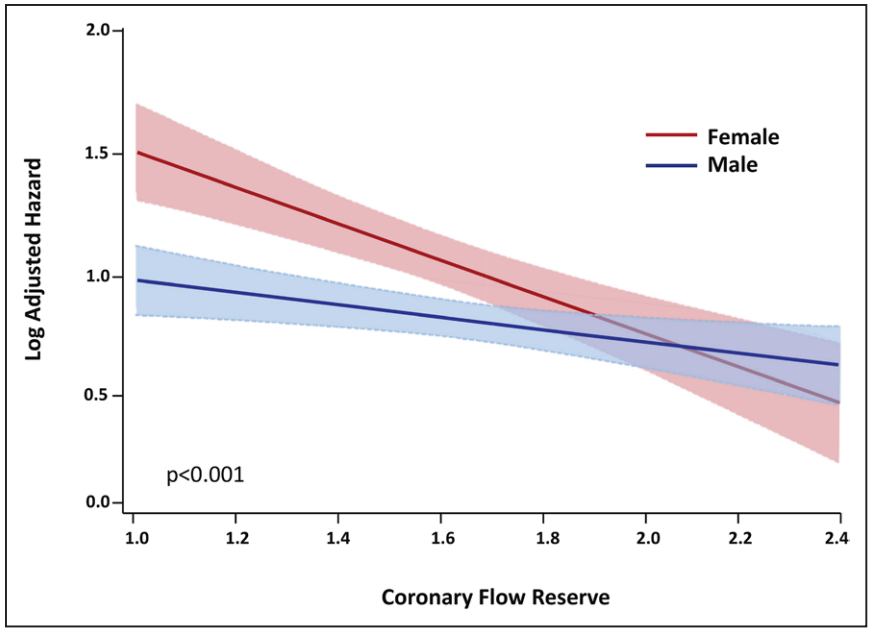

Figure 2. Log adjusted hazard for major adverse cardiovascular events in female versus male sex varies as a function of coronary flow reserve (CFR). The effect of sex on cardiovascular events was modified by CFR such that differences in outcomes between women and men were amplified for patients with very low CFR (hazard estimated from the linear interaction of CFR and sex in the final model, model $P<0.001$, interaction $P=0.04$).

remains a critically necessary goal for managing women with ischemic heart disease,[25] doing so according to current paradigms may be insufficient to address what are likely a combination of biological as well as environmental determinants of their prognosis.

Second, that sex differences on outcomes of CVD vary by CFR and are amplified in those with very low CFR (Figure 2) underscores that revascularization in certain individuals with impaired CFR may be beneficial. Our group previously showed that, in a lower-risk population of symptomatic patients without flow-limiting CAD (and thus, no indication for revascularization), there was no detectable difference between sexes on adverse cardiovascular events, although CFR was still associated with outcomes.[29] In this case, both women and men with microvascular dysfunction (ie, CFR <2 in the presence of normal myocardial perfusion imaging) experienced worse outcomes, although this phenotype was twice as prevalent in women as in men. That in such a lower-risk group (with median CFR ≈2 and most values >1.6), no interaction was seen between sex and CFR is consistent with and now explained by our present findings (Figure 2). In that cohort, there would have been no differential impact of revascularization on outcomes, because neither women nor men were eligible for revascularization. In contrast, in the current study, women fared significantly worse than men as CFR decreased. We hypothesize that this may be partly related to revascularization, and the early hazard for women demonstrated in Figure 1 would be consistent with such an effect. In patients referred for coronary angiography with impaired CFR, women demonstrated less severe angiographic disease than men, and thus were less likely to be referred for more complete revascularization. We previously showed that baseline impaired CFR modified the effect of coronary revascularization on outcomes, especially if revascularization included CABG.[15] Thus, patients with low CFR and severely obstructive CAD (a phenotype more prevalent in men) who were eligible for and underwent revascularization with CABG may have benefited preferentially.[15]

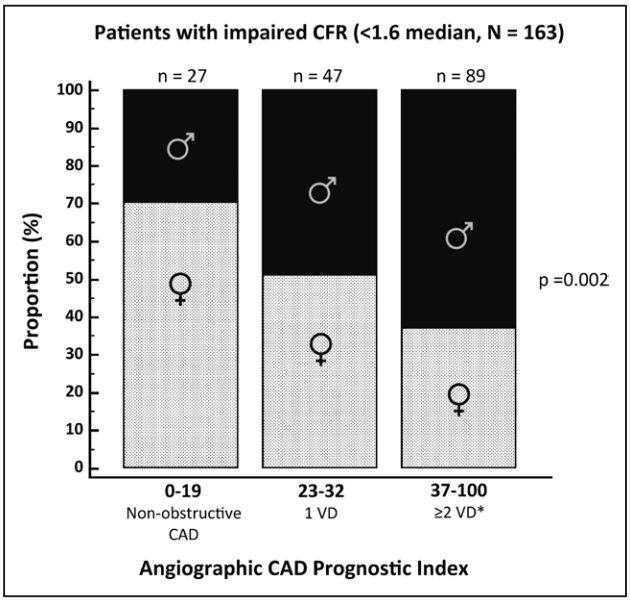

Figure 3. Patients with impaired coronary flow reserve (CFR) by coronary artery disease prognostic index (CADPI) and sex categories. Among patients with impaired CFR (<1.6), men showed higher frequency of severely obstructive CAD (CADPI ≥37, 62.9% male), whereas women showed higher frequency of nonobstructive CAD (CADPI ≤19, 70.4% female, P for trend=0.002). *CADPI 37 to 100 also includes 1 VD with LM or >90% proximal LAD stenosis. CAD indicates coronary artery disease; LAD, left anterior descending artery; LM, left main artery; and VD, vessel disease

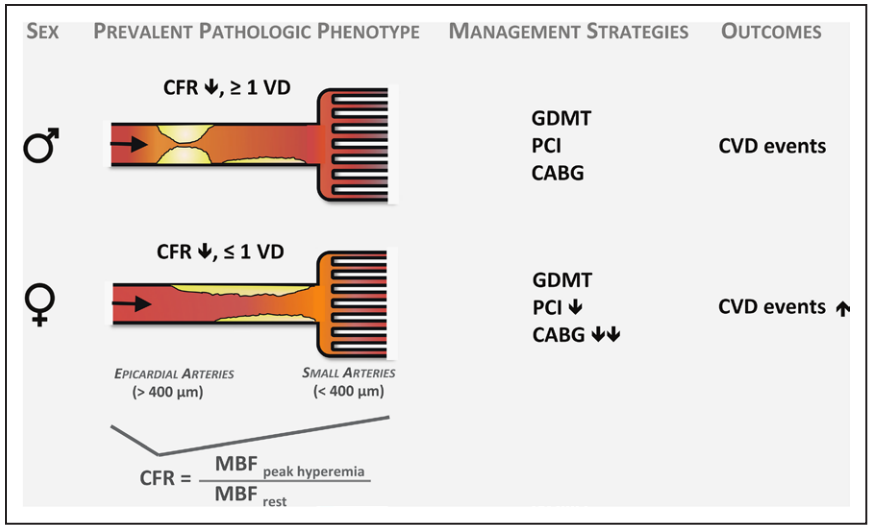

Figure 4. Conceptual model of prevalent pathological phenotypes in women and men with ischemic heart disease and possible impact on cardiovascular management strategies and outcomes.
CABG indicates coronary artery bypass surgery; CFR, coronary flow reserve; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; MBF, myocardial blood flow; PCI, percutaneous coronary intervention; and VD, vessel disease.

That the sex interaction becomes apparent only below a certain CFR threshold may reflect differences in the revascularization options for women versus men with low CFR, as a function of obstructive CAD. This may have far-reaching implications for closing the "gender gap" in cardiovascular morbidity and mortality.

Third, in cases where impaired CFR stems not from obstructive CAD (with no opportunity for revascularization to mitigate CVD risk), a novel therapeutic strategy to systemically target ischemic heart disease may be warranted. That this cohort of symptomatic intermediate- to high-risk women demonstrated high rates of obesity, diabetes mellitus, and hypertension despite less obstructive CAD phenotypes and similar rates of cardiovascular medication use reflects larger epidemiological trends[1,30] that may be contributing to increased prognostic risk among women, especially for subsequent heart failure events, in particular, heart failure with preserved ejection fraction.[21,31–33] Impaired CFR, whether associated with diffuse nonobstructive or obstructive CAD, may provide a clue as to a common mechanism underlying ischemic cardiovascular risk in women and men. Such a mechanism may involve inflammation,[34] endothelial dysfunction,[35] and increased cardiomyocyte oxygen demand with ensuing microvascular ischemia, myocardial injury, and impaired cardiac mechanics.[36,37] CFR, as measured by PET, leads to meaningful risk reclassification of intermediate-risk patients, including those with diabetes mellitus[12] or minimally elevated troponin[36] and no flow-limiting CAD. Thus, clearer understanding of the relationship between coronary vasomotor dysfunction and CAD comorbid conditions, including insulin resistance and heart failure, may guide development of novel systemic therapies to harness the benefit of more complete revascularization[15,38–41] in a manner not defined by anatomy alone. The data presented here suggest that current therapies, possibly in a sex-specific manner, are insufficient to restore coronary vascular function. As such, CFR may represent an important biomarker not only for prospective studies evaluating the role of ischemia and revascularization, but also of emerging anti-inflammatory (ie, interleukin-1 inhibitor,[42] methotrexate[43]), extreme lipid-lowering (ie, proprotein convertase subtilisin kexin 9 inhibitor[44,45]) and neurohormonal-modulating (ie, neprilysin/renin-angiotensin system[46] and sodium-glucose cotransporter 2 inhibitor[47]) agents on cardiovascular outcomes, especially in women.

Study Limitations

Limitations of this study include its single-center observational design, in which subjects were patients clinically referred for PET myocardial perfusion imaging and subsequently referred for invasive coronary angiography. CFR results were not available to referring clinicians and thus did not affect downstream management decisions regarding catheterization or additional therapies. Our modest sample size necessitates the evaluation of outcomes with a composite cardiovascular end point and limits extensive subgroup analysis. As with all observational cohorts, residual confounding may persist despite adjustment for baseline differences and also affect results of mediation analysis.

Recognizing these important limitations, this hypothesis-generating work may help to explain the observed gap between CVD events and CAD diagnosis in women in comparison with men by quantifying the hidden risk of ischemic heart disease in this patient population. As such, these findings may have implications for diagnosis, risk stratification, and development of new management strategies of a clinical problem with a disproportionate impact on women's cardiovascular health.

CONCLUSIONS

Women referred for coronary angiography had significantly lower burden of obstructive CAD than men, but were not protected from CVD events. Excess cardiovas-

cular risk in women was independently associated with severely impaired CFR, representing a hidden biological risk and a phenotype less amenable to revascularization. Impaired CFR, particularly absent severely obstructive CAD, may represent a novel target for CVD risk reduction. Prospective studies are needed to evaluate the ability of CFR to reclassify risk and probe the effects of novel systemic therapies in patients across the anatomic continuum of ischemic heart disease.

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FOOTNOTES

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Excess Cardiovascular Risk in Women Relative to Men Referred for Coronary Angiography Is Associated With Severely Impaired Coronary Flow Reserve, Not Obstructive Disease

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SUPPLEMENTAL MATERIAL

Supplemental Table. Causal Mediation Analysis*

Effect (of female sex on MACE)	Estimate	95% CI
cde	2.01	(0.73-4.27)
nde	1.96	(0.75-4.21)
nie	1.33	(1.02-2.04)
Total effect	2.56	(1.04-5.56)
Proportion mediated (by CFR)	**0.40**	-

*as described with survival data[1]

MACE denotes major adverse cardiovascular events; CI, confidence interval; cde, controlled direct effect; nde, natural direct effect; nie, natural indirect effect; CFR, coronary flow reserve

Supplemental Reference

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