Supplemental Material

Effects of Gender on Coronary Microvascular Dysfunction and Cardiac Outcomes

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Table of Contents

Table of Contents 2

Supplemental Methods 3

Sensitivity Analysis for Incomplete Follow-up 3

Subgroup Analysis without Coronary Calcium 3

Subgroup Analysis with Elevated Coronary Calcium 3

Supplemental Tables 4

Table S1: Multivariate Linear Regression for Corrected Coronary Flow Reserve 4

Table S2: Sensitivity Analysis for Incomplete Follow-Up 5

Table S3: Baseline Characteristics of CAC=0 Subgroup 6

Table S4: Predictors of Corrected CFR for CAC=0 Subgroup 8

Table S5: Clinical Outcomes in CAC=0 Subgroup 9

Table S6: Cox Regression Analysis for MACE among CAC=0 Subgroup 10

Table S7: Baseline Characteristics of CAC>200 Subgroup 11

Table S8: Predictors of Corrected CFR for CAC >200 Subgroup 13

Table S9: Clinical Outcomes in CAC >200 Subgroup 14

Table S10: Cox Regression Analysis for MACE among CAC >200 Subgroup 15

Supplemental Figures 16

Figure S1: Distribution of Overt CAD and CMD by Gender 16

Figure S2: Distribution of CFR by Gender for CAC=0 Subgroup 17

Figure S3: Outcomes by Gender and Coronary Flow Reserve for CAC=0 Subgroup 20

Figure S4: Distribution of CFR by Gender for CAC >200 Subgroup 21

Figure S5: Outcomes by Gender and Coronary Flow Reserve for CAC>200 Subgroup 22

Supplemental Methods

Sensitivity Analysis for Incomplete Follow-up

Because complete follow-up data was only obtained in 94% of patients, we conducted several sensitivity analyses to assess the potential impact of incomplete follow-up. Under multiple imputation, outcome (MACE versus no MACE) and time to event or censoring were imputed 25 times for each of the 74 patients with incomplete follow-up using these data and clinical covariates (age, gender, hypertension, dyslipidemia, diabetes, family history of CAD, tobacco use, history of CAD, referral for chest pain and referral for dyspnea). Prior to imputation, time to first event was transformed with the natural logarithm, after adding 1 day, in order increase normality. After imputation, the inverse transform was applied. The relative efficiency of the multiple imputation was 99.7%. Under right point imputation, each patient without complete follow-up was assumed to have no events through the end of the study period.

Regardless of whether only observed data were used or either of the imputation methods were used, similar results were obtained in survival analysis with Cox regression (Table S2). In no case was gender a significant predictor of outcome. Furthermore, no significant interaction between gender and coronary flow reserve (CFR) could be identified, suggesting the relationship between CFR and MACE is consistent, regardless of gender.

Subgroup Analysis without Coronary Calcium

The primary analysis of this manuscript was on a cohort of patients without clinical history of coronary artery disease (CAD) who had visually normal stress myocardial perfusion imaging (MPI). Due to the limitations of stress MPI, a subset of these patients may have severe subclinical CAD. Consequently, we analyzed the subgroup of the primary cohort without any quantifiable coronary calcium (CAC=0), reflecting populations with minimal to no subclinical atherosclerosis. The baseline characteristics of this subgroup by gender are presented in Table S3. Even in this subgroup, CFR was equivalent across genders (Figure S3). Linear regression was performed to confirm that gender was not a significant predictor of coronary flow reserve (CFR) (Table S4). Clinical outcomes are summarized in Table S5. Cox regression was performed to confirm that CFR but not gender was not a significant predictor of MACE (Table S6). Microvascular dysfunction was associated with higher rates of adverse outcomes in both genders (Figure S4). Interaction terms of gender and CFR were non-significant, suggesting the relationship between CFR and outcomes was consistent across genders.

Subgroup Analysis with Elevated Coronary Calcium

The primary analysis of this manuscript was on a cohort of patients without clinical history of coronary artery disease (CAD) who had visually normal stress myocardial perfusion imaging (MPI). Due to the limitations of stress MPI, a subset of these patients may have significant subclinical CAD. Consequently, we analyzed the subgroup of the primary cohort with significant coronary calcium (CAC>100), reflecting populations with potential for subclinical atherosclerosis. The baseline characteristics of this subgroup by gender are presented in Table S7. Even in this subgroup, CFR was equivalent across genders (Figure S5). Linear regression was performed to confirm that gender was not a significant predictor of coronary flow reserve (CFR) (Table S8). Clinical outcomes are summarized in Table S9. Cox regression was performed to confirm that CFR but not gender was not a significant predictor of MACE (Table S10). Microvascular dysfunction was associated with higher rates of adverse outcomes in both genders (Figure S6). Interaction terms of gender and CFR were non-significant, suggesting the relationship between CFR and outcomes was consistent across genders.

Supplemental Tables

Table S1: Multivariable Predictors of Corrected Coronary Flow Reserve

	Model 1		Model 2	
Parameter	**Estimate**	**P-Value**	**Estimate**	**P-Value**
R2	0.165		0.166	
AIC	870.4	ref	870.8	1.00
SBC	-271.0	ref	-265.5	1.00
Variable	**Beta**	**P-Value**	**Beta**	**P-Value**
Intercept	3.53 [3.17-3.90]	<0.0001	3.50 [3.13-3.87]	<0.0001
Age (y)	-0.01 [-0.02--0.01]	<0.0001	-0.01 [-0.02--0.01]	<0.0001
BMI (kg/m^2)	-0.02 [-0.02--0.01]	<0.0001	-0.02 [-0.02--0.01]	<0.0001
Hypertension	-0.20 [-0.32--0.08]	0.001	-0.20 [-0.32--0.08]	0.002
Diabetes Mellitus	-0.24 [-0.35--0.12]	<0.0001	-0.24 [-0.36--0.12]	<0.0001
Dialysis	-0.55 [-0.79--0.31]	<0.0001	-0.56 [-0.8--0.32]	<0.0001
Preoperative Evaluation	-0.25 [-0.39--0.11]	0.0005	-0.26 [-0.4--0.12]	0.0004
EF Reserve >0	0.03 [0.02-0.04]	<0.0001	0.03 [0.02-0.04]	<0.0001
Male Gender			0.07 [-0.04-0.18]	0.21

Stepwise multivariable linear regression identified seven independent predictors of corrected coronary flow reserve (Model 1). Addition of gender (Model 2) did not improve the model. AIC = Akaike information criterion. SBC = Schwarz-Bayes criterion.

Table S2: Sensitivity Analysis for Incomplete Follow-Up in Cox Regression for MACE

	No Imputation		Multiple Imputation		Right Point Imputation	
	Hazard Ratio	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Model 1						
Clinical Risk Score (per 10% increase)	1.06 [1.03-1.1]	0.0007	1.06 [1.02-1.09]	0.0009	1.06 [1.02-1.09]	0.001
Rest LVEF (per 10% increase)	0.56 [0.44-0.72]	<0.0001	0.57 [0.44-0.73]	<0.0001	0.56 [0.43-0.72]	<0.0001
ln(CFR) (per 10% increase)	0.8 [0.75-0.86]	<0.0001	0.81 [0.76-0.87]	<0.0001	0.81 [0.75-0.86]	<0.0001
Model 2						
Clinical Risk Score (per 10% increase)	1.06 [1.03-1.1]	0.0008	1.06 [1.02-1.09]	0.001	1.06 [1.02-1.09]	0.002
Rest LVEF (per 10% increase)	0.57 [0.44-0.74]	<0.0001	0.58 [0.44-0.75]	<0.0001	0.56 [0.44-0.73]	<0.0001
ln(CFR) (per 10% increase)	0.8 [0.75-0.86]	<0.0001	0.81 [0.76-0.87]	<0.0001	0.81 [0.75-0.86]	<0.0001
Female Gender	0.9 [0.55-1.45]	0.65	0.89 [0.55-1.44]	0.62	0.93 [0.58-1.5]	0.77
Model 3						
Clinical Risk Score (per 10% increase)	1.06 [1.03-1.1]	0.0008	1.06 [1.02-1.09]	0.001	1.06 [1.02-1.09]	0.002
Rest LVEF (per 10% increase)	0.57 [0.45-0.74]	<0.0001	0.58 [0.45-0.75]	<0.0001	0.57 [0.44-0.73]	<0.0001
ln(CFR) (per 10% increase)	0.79 [0.73-0.85]	<0.0001	0.8 [0.74-0.86]	<0.0001	0.8 [0.74-0.86]	<0.0001
ln(CFR)*Gender Interaction		0.42		0.38		0.45
ln(CFR) (per 10% increase) - Men	0.82 [0.76-0.88]		0.83 [0.76-0.89]		0.82 [0.76-0.89]	
ln(CFR) (per 10% increase) - Women	0.79 [0.73-0.85]		0.8 [0.74-0.86]		0.8 [0.74-0.86]	

Table S3: Baseline Characteristics of CAC=0 Subgroup by Gender

	CAC=0		
Variable	**Males (N=97)**	**Females (N=307)**	**P-Value**
Demographics			
Age (y)	53.1 [45.5-59.1]	56.8 [49.2-63.5]	0.001
Hispanic	11 (11.3)	68 (22.2)	0.02
Race			
White	49 (50.5)	133 (43.3)	0.12
Black	29 (29.9)	81 (26.4)	
Other/Unknown	19 (19.6)	93 (30.3)	
Risk Factors			
BMI (kg/m^2)	29.4 [25.1-37.6]	31.9 [26.6-40.4]	0.09
BMI ≥ 30 kg/m^2	44 (45.4)	177 (57.7)	0.04
Hypertension	58 (59.8)	210 (68.4)	0.14
Dyslipidemia	41 (42.3)	157 (51.1)	0.13
Diabetes Mellitus	24 (24.7)	92 (30)	0.37
Family history of CAD	23 (23.7)	100 (32.6)	0.10
Tobacco Use	19 (19.6)	26 (8.5)	0.005
Modified Duke Clinical Risk (%)	17 [10-27]	24 [12-39]	0.004
Dialysis	4 (4.1)	9 (2.9)	0.52
Medications			
Aspirin	47 (48.5)	134 (43.6)	0.41
β-adrenergic Blockers	26 (26.8)	122 (39.7)	0.02
Cholesterol agents	33 (34.0)	129 (42.0)	0.19
Insulin	8 (8.2)	31 (10.1)	0.7
Oral hypoglycemic	10 (10.3)	40 (13.0)	0.6
Ca-channel blockers	15 (15.5)	48 (15.6)	1.00
ACE inhibitors	29 (29.9)	92 (30.0)	1.00
Nitrates	7 (7.2)	14 (4.6)	0.3
Diuretics	16 (16.5)	80 (26.1)	0.06
Symptoms & Test Indications			
Chest Pain	47 (48.5)	212 (69.0)	0.0004
Dyspnea	22 (22.7)	94 (30.6)	0.16
Pre-operative	15 (15.5)	31 (10.1)	0.15
Other	6 (6.2)	30 (9.8)	0.32

Imaging Findings			
Rest LVEF (%)	58 [52-62]	64 [58-71]	<0.0001
LVEF reserve	91 (93.8)	276 (89.9)	0.31
Stress MBF (ml/g/min)	1.93 [1.35-2.53]	2.36 [1.83-3.32]	<0.0001
Rest MBF (ml/g/min)	0.88 [0.68-1.13]	1.15 [0.91-1.53]	<0.0001
Corrected Rest MBF (ml/g/min)	0.86 [0.66-1.23]	1.17 [0.84-1.70]	<0.0001
CFR	2.04 [1.58-2.49]	2.05 [1.64-2.57]	0.98
Corrected CFR	1.98 [1.36-2.77]	1.93 [1.42-2.67]	1.00
Coronary Microvascular Dysfunction (CFR<2.0)	43 (44.3)	147 (47.9)	0.56

Clinical and imaging characteristics of patients by gender among the subgroup with zero coronary artery calcium score (CAC=0). Corrected rest myocardial blood flow (MBF) is computed by multiplying by the rest rate-pressure product/10000. Coronary flow reserve (CFR) is computed as the ratio of stress/rest MBF. Continuous variables are presented as median with inter-quartile range. Binary variables are presented as absolute numbers and percentages. Comparisons across gender were performed using Wilcoxon, Fisher exact and chi-square tests for continuous, binary and categorical variables, respectively.

Table S4: Multivariable Predictors of Corrected CFR for CAC=0 Subgroup

	CAC=0			
	Model 1		Model 2	
Parameter	**Estimate**	**P-Value**	**Estimate**	**P-Value**
R^2	0.114		0.114	
AIC	347.2	ref	349.2	1
SBC	-20.9	ref	-14.9	1
Variable	**Beta**	**P-Value**	**Beta**	**P-Value**
Intercept	3.04 [2.35-3.73]	<0.0001	3.05 [2.34-3.76]	<0.0001
Age (y)	-0.01 [-0.02-0.00]	0.11	-0.01 [-0.02-0.00]	0.11
BMI (kg/m^2)	-0.02 [-0.03--0.01]	0.003	-0.02 [-0.03--0.01]	0.003
Hypertension	-0.13 [-0.34-0.07]	0.21	-0.13 [-0.34-0.07]	0.21
Diabetes Mellitus	-0.2 [-0.42-0.01]	0.07	-0.21 [-0.42-0.01]	0.07
Dialysis	-0.39 [-0.95-0.17]	0.17	-0.39 [-0.95-0.17]	0.17
Preoperative Evaluation	-0.35 [-0.64--0.05]	0.02	-0.34 [-0.64--0.05]	0.02
EF Reserve >0	0.04 [0.02-0.05]	<0.0001	0.04 [0.02-0.05]	<0.0001
Male Gender			-0.02 [-0.24-0.2]	0.88

Multivariable linear regression using the seven independent predictors of corrected coronary flow reserve identified in the overall cohort (Model 1). Addition of gender (Model 2) did not improve the model. AIC = Akaike information criterion. SBC = Schwarz-Bayes criterion.

Table S5: Clinical Outcomes in CAC=0 Subgroup by CFR

	CAC=0			
Outcome	**CFR <2.0 (N=190)**	**CFR ≥2.0 (N=214)**	**All Subjects (N=404)**	**P-Value**
MACE	13 (6.8)	4 (1.9)	17 (4.2)	0.02
Death	6 (3.2)	2 (0.9)	8 (2)	0.16
Cardiac Death	2 (1.1)	0 (0)	2 (0.5)	0.22
Myocardial Infarction	8 (4.2)	0 (0)	8 (2)	0.002
Late Revascularization	1 (0.5)	0 (0)	1 (0.2)	0.47
Heart Failure Admission	5 (2.6)	4 (1.9)	9 (2.2)	0.74

Major adverse cardiac outcomes (MACE) indicates the composite of death resulting from any cardiac cause, myocardial infarction, late revascularization (after 90 days) and admission for congestive heart failure.

Table S6: Multivariable Cox Regression for MACE among CAC=0 Subgroup

	CAC=0							
	Model 1		**Model 2**		**Model 3**		**Model 4**	
Fit Statistic	**Estimate**	**P-Value**	**Estimate**	**P-Value**	**Estimate**	**P-Value**	**Estimate**	**P-Value**
Global χ^2	4.9	ref	15.2	0.0001	15.3	0.69	16.1	0.33
AIC	155.7	ref	147.4	0.0004	149.3	1	148.5	1
SBC	157.4	ref	149.9	0.0006	152.6	1	151.8	1
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Clinical Risk (per 10% increase)	1.04 [0.98-1.10]	0.24	1.03 [0.97-1.09]	0.39	1.03 [0.97-1.09]	0.38	1.03 [0.97-1.09]	0.37
Rest LVEF (per 10% increase)	0.61 [0.37-1.00]	0.05	0.66 [0.41-1.05]	0.08	0.67 [0.42-1.09]	0.11	0.69 [0.43-1.12]	0.13
ln(CFR) (per 10% increase)			0.82 [0.72-0.92]	0.001	0.81 [0.72-0.92]	0.0009	0.80 [0.70-0.91]	0.06
Female Gender					0.78 [0.24-2.59]	0.69		
*Gender*ln(CFR) Interaction*								
Female (per 10% increase in CFR)							0.80 [0.70-0.91]	0.32 (women vs. men)
Male (per 10% increase in CFR)							0.86 [0.74-1.01]	

Values in square brackets indicate 95% confidence intervals. MACE indicates Major Adverse Cardiac Events. SBC indicates Schwarz-Bayes Criteria. AIC indicates Akaike's information criterion. NRI indicates net reclassification improvement. Categorical NRI was computed with threshold rates of 1 and 3% per year to define low, intermediate and high risk categories. IDI indicates integrated discrimination index. NRI, IDI and P-values for fit statistics compare Model 2 vs. Model 1, Model 3 vs. Model 2, Model 4 vs. Model 2, respectively. C-index, NRI and relative IDI are computed at two years. Clinical risk indicates the Duke clinical risk score[21] modified to be gender neutral. CFR indicates coronary flow reserve without correction for rate-pressure product. LVEF indicates left ventricular ejection fraction.

Table S7: Baseline Characteristics of CAC>100 Subgroup by Gender

	CAC>100		
Variable	**Males (N=121)**	**Females (N=159)**	**P-Value**
Demographics			
Age (y)	66 [60.1-73]	69.7 [62.4-77.1]	0.008
Hispanic	8 (6.6)	23 (14.5)	0.05
Race			
White	85 (53.5)	91 (75.2)	0.0002
Black	36 (22.6)	9 (7.4)	
Other/Unknown	38 (23.9)	21 (17.4)	
Risk Factors			
BMI (kg/m^2)	29.4 [25.7-35.9]	30.2 [25.3-35.5]	0.96
BMI ≥ 30 kg/m^2	58 (47.9)	83 (52.2)	0.55
Hypertension	92 (76)	148 (93.1)	0.0001
Dyslipidemia	74 (61.2)	104 (65.4)	0.53
Diabetes Mellitus	43 (35.5)	57 (35.8)	1
Family history of CAD	28 (23.1)	31 (19.5)	0.46
Tobacco Use	16 (13.2)	16 (10.1)	0.45
Modified Duke Clinical Risk (%)	41 [28-55]	48 [34-63]	0.002
Dialysis	11 (9.1)	10 (6.3)	0.49
Medications			
Aspirin	57 (47.1)	81 (50.9)	0.55
β-adrenergic Blockers	60 (49.6)	85 (53.5)	0.55
Cholesterol agents	66 (54.5)	88 (55.3)	0.9
Insulin	14 (11.6)	25 (15.7)	0.38
Oral hypoglycemic	15 (12.4)	16 (10.1)	0.57
Ca-channel blockers	24 (19.8)	52 (32.7)	0.02
ACE inhibitors	46 (38)	68 (42.8)	0.46
Nitrates	6 (5)	9 (5.7)	1
Diuretics	32 (26.4)	68 (42.8)	0.006
Symptoms & Test Indications			
Chest Pain	45 (37.2)	82 (51.6)	0.02
Dyspnea	33 (27.3)	43 (27)	1
Pre-operative	27 (22.3)	30 (18.9)	0.55
Other	10 (8.3)	18 (11.3)	0.43

Imaging Findings			
Rest LVEF (%)	59 [52-64]	65 [59-72]	<0.0001
LVEF reserve	106 (87.6)	141 (88.7)	0.85
CAC	447 [221-1044]	341 [199-618]	0.02
Stress MBF (ml/g/min)	1.68 [1.21-2.44]	2.2 [1.76-2.83]	<0.0001
Rest MBF (ml/g/min)	0.96 [0.79-1.11]	1.23 [0.94-1.52]	<0.0001
Corrected Rest MBF (ml/g/min)	0.93 [0.71-1.19]	1.3 [0.94-1.78]	<0.0001
CFR	1.86 [1.45-2.27]	1.76 [1.49-2.17]	0.65
Corrected CFR	1.86 [1.42-2.44]	1.63 [1.24-2.19]	0.009
Coronary Microvascular Dysfunction (CFR<2.0)	71 (58.7)	100 (62.9)	0.54

Clinical and imaging characteristics of patients by gender among the subgroup with significant coronary artery calcium (CAC >100). Corrected rest myocardial blood flow (MBF) is computed by multiplying by the rest rate-pressure product/10000. Coronary flow reserve (CFR) is computed as the ratio of stress/rest MBF. Continuous variables are presented as median with inter-quartile range. Binary variables are presented as absolute numbers and percentages. Comparisons across gender were performed using Wilcoxon, Fisher exact and chi-square tests for continuous, binary and categorical variables, respectively.

Table S8: Multivariable Predictors of Corrected CFR for CAC >100 Subgroup

	CAC >100			
	Model 1		Model 2	
Parameter	**Estimate**	**P-Value**	**Estimate**	**P-Value**
R^2	0.134		0.158	
AIC	144.7	ref	138.8	0.02
SBC	-99.8	ref	-102	0.14
Variable	**Beta**	**P-Value**	**Beta**	**P-Value**
Intercept	3.06 [2.06-4.06]	<0.0001	2.84 [1.85-3.84]	<0.0001
Age (y)	-0.01 [-0.02-0]	0.04	-0.01 [-0.02-0]	0.13
BMI (kg/m^2)	-0.01 [-0.02-0.01]	0.33	-0.01 [-0.02-0.01]	0.33
Hypertension	-0.18 [-0.44-0.08]	0.18	-0.08 [-0.35-0.19]	0.55
Diabetes Mellitus	-0.23 [-0.43--0.02]	0.03	-0.21 [-0.41--0.02]	0.04
Dialysis	-0.38 [-0.76--0.01]	0.047	-0.36 [-0.73-0.01]	0.06
Preoperative Evaluation	-0.08 [-0.31-0.15]	0.51	-0.1 [-0.33-0.13]	0.40
EF Reserve >0	0.04 [0.02-0.06]	<0.0001	0.04 [0.02-0.06]	<0.0001
ln(CAC)	-0.05 [-0.15-0.06]	0.38	-0.07 [-0.18-0.03]	0.16
Male Gender			0.28 [0.08-0.47]	0.006

Multivariable linear regression using the seven independent predictors of corrected coronary flow reserve identified in the overall cohort plus the natural log of coronary artery calcium (CAC) score (Model 1). Addition of gender (Model 2) did not improve the model. AIC = Akaike information criterion. SBC = Schwarz-Bayes criterion.

Table S9: Clinical Outcomes in CAC >100 Subgroup by CFR

	CAC >100			
Outcome	**CFR <2.0 (N=171)**	**CFR ≥2.0 (N=109)**	**All Subjects (N=280)**	**P-Value**
MACE	25 (14.6)	7 (6.4)	32 (11.4)	0.05
Death	10 (5.8)	2 (1.8)	12 (4.3)	0.14
Cardiac Death	4 (2.3)	0 (0)	4 (1.4)	0.16
Myocardial Infarction	12 (7)	5 (4.6)	17 (6.1)	0.45
Late Revascularization	8 (4.7)	4 (3.7)	12 (4.3)	0.77
Heart Failure Admission	10 (5.8)	2 (1.8)	12 (4.3)	0.14

Major adverse cardiac outcomes (MACE) indicates the composite of death resulting from any cardiac cause, myocardial infarction, late revascularization (after 90 days) and admission for congestive heart failure.

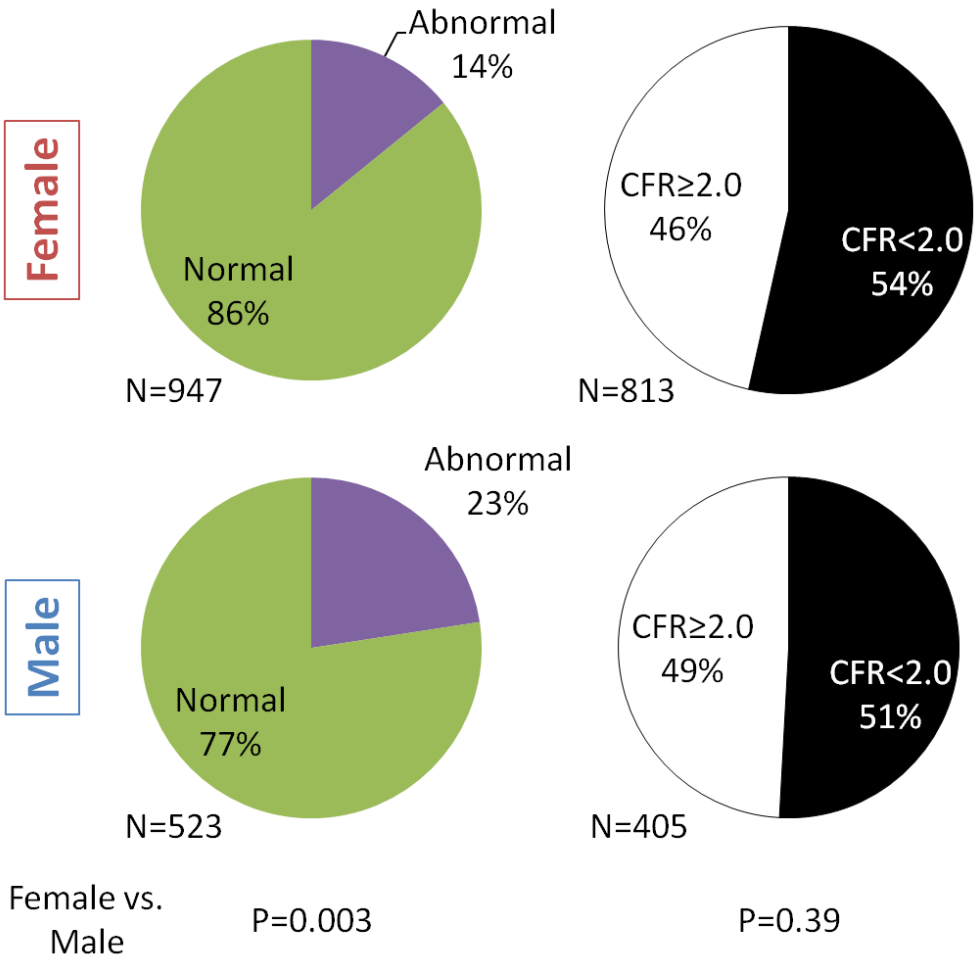
Table S10: Multivariable Cox Regression for MACE among CAC >100 Subgroup

	CAC >100							
	Model 1		Model 2		Model 3		Model 4	
Fit Statistic	**Estimate**	**P-Value**	**Estimate**	**P-Value**	**Estimate**	**P-Value**	**Estimate**	**P-Value**
Global χ^2	6.309	ref	14.716	0.004	14.932	0.64	15.967	0.26
AIC	250.851	ref	244.444	0.01	246.227	1.00	245.193	1.00
SBC	255.248	ref	250.306	0.03	253.556	1.00	252.522	1.00
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Clinical Risk (per 10% increase)	1.05 [0.98-1.13]	0.17	1.06 [0.98-1.14]	0.14	1.06 [0.98-1.15]	0.13	1.07 [0.99-1.15]	0.11
Rest LVEF (per 10% increase)	0.73 [0.5-1.06]	0.10	0.66 [0.45-0.97]	0.04	0.68 [0.46-1.01]	0.06	0.67 [0.46-0.99]	0.046
Ln(CAC) (per 10% increase)	1.02 [0.98-1.06]	0.30	1.02 [0.99-1.06]	0.27	1.02 [0.99-1.06]	0.27	1.02 [0.99-1.06]	0.24
ln(CFR) (per 10% increase)			0.83 [0.74-0.94]	0.004	0.84 [0.74-0.95]	0.006	0.81 [0.7-0.93]	0.04
Female Gender					0.84 [0.39-1.78]	0.64		
*Gender*ln(CFR) Interaction*								
Female (per 10% increase in CFR)							0.81 [0.7-0.93]	0.26 (women vs. men)
Male (per 10% increase in CFR)							0.87 [0.76-0.99]	

Clinical risk indicates the Duke clinical risk score modified to be gender neutral. CFR indicates coronary flow reserve without correction for rate-pressure product. LVEF indicated left ventricular ejection fraction. P-values for fit statistics compare Model 1 vs. Model 0, Model 2 vs. Model 1 and Model 3 vs. Model 1, respectively.

Supplemental Figures

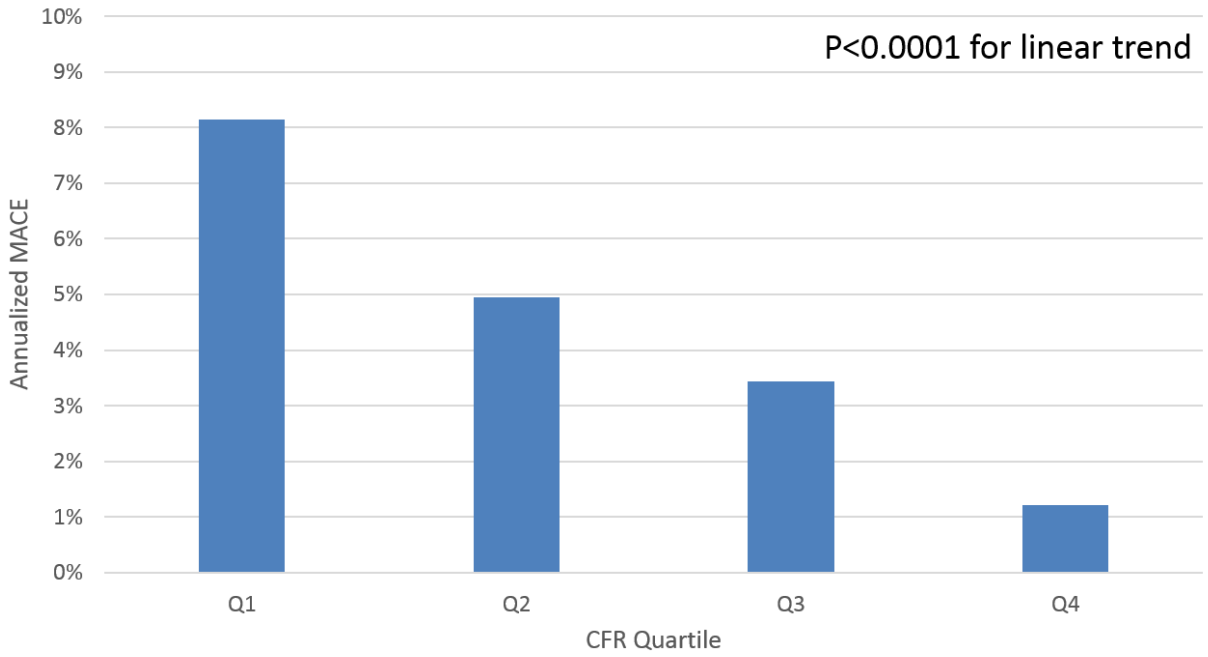
Figure S1: Proportions of Men and Women with Overt CAD and CMD



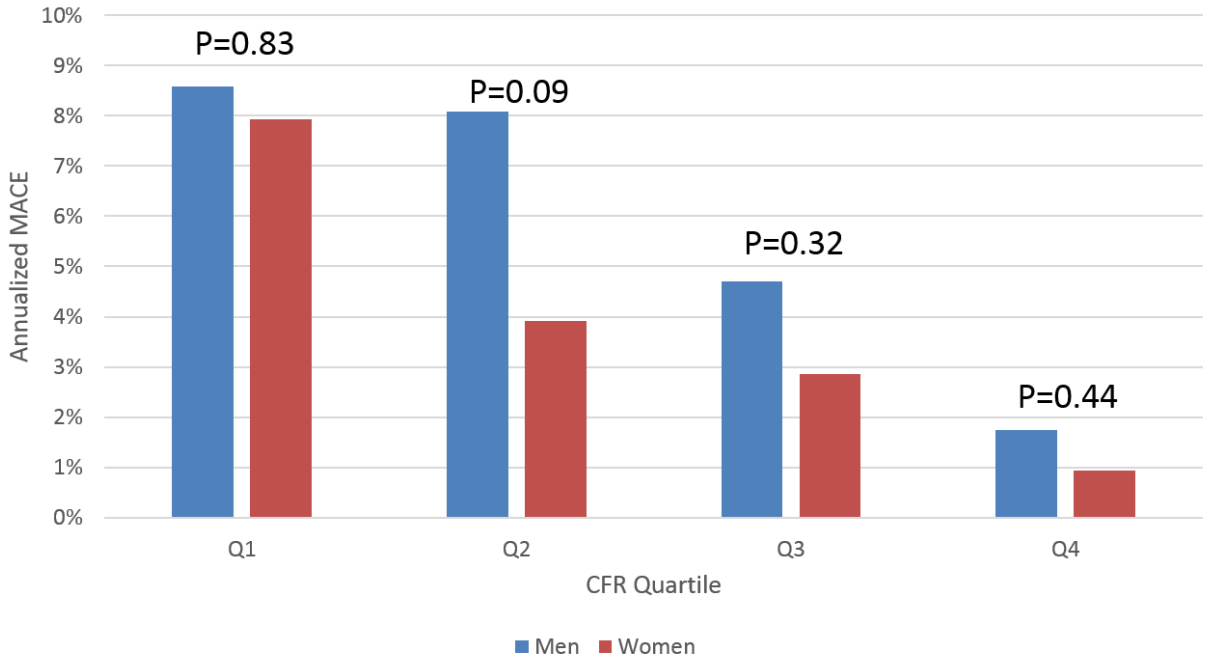
Among patients referred to our laboratory, more women (N=947) than men (N=523) were free of history of coronary artery disease (CAD), myocardial infarction or coronary revascularization. Furthermore, abnormal stress myocardial perfusion imaging (purple) was more common among men (23%) than women (14%, P=0.003). These factors combined to result in a study population dominated by women (N=813 of 1218). Among these patients without history of CAD or visual evidence of myocardial infarction or ischemia, approximately half of both men and women had coronary microvascular dysfunction (CMD), indicated by diminished coronary flow reserve (CFR<2.0, black) (P(Fisher exact test)=0.39; P(equivalence)=0.0002).

Figure S2: Annualized Rate of MACE across Quartiles of CFR

A



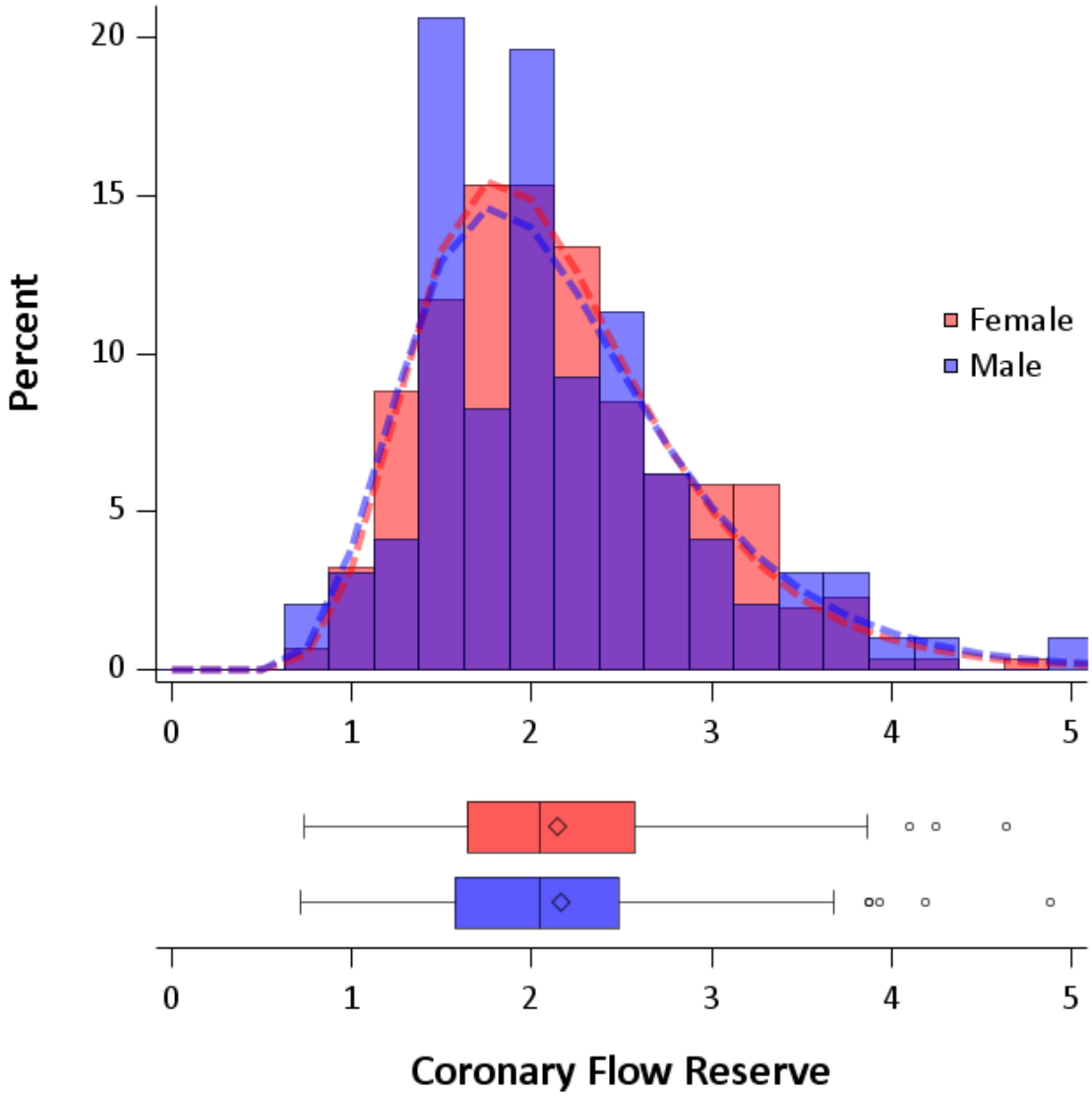
B



Unadjusted annualized rate of major adverse cardiac events (MACE) across quartiles of coronary flow reserve (CFR) (panel A) showing a monotonic trend towards higher rates of adverse events with decreasing CFR. In each quartile

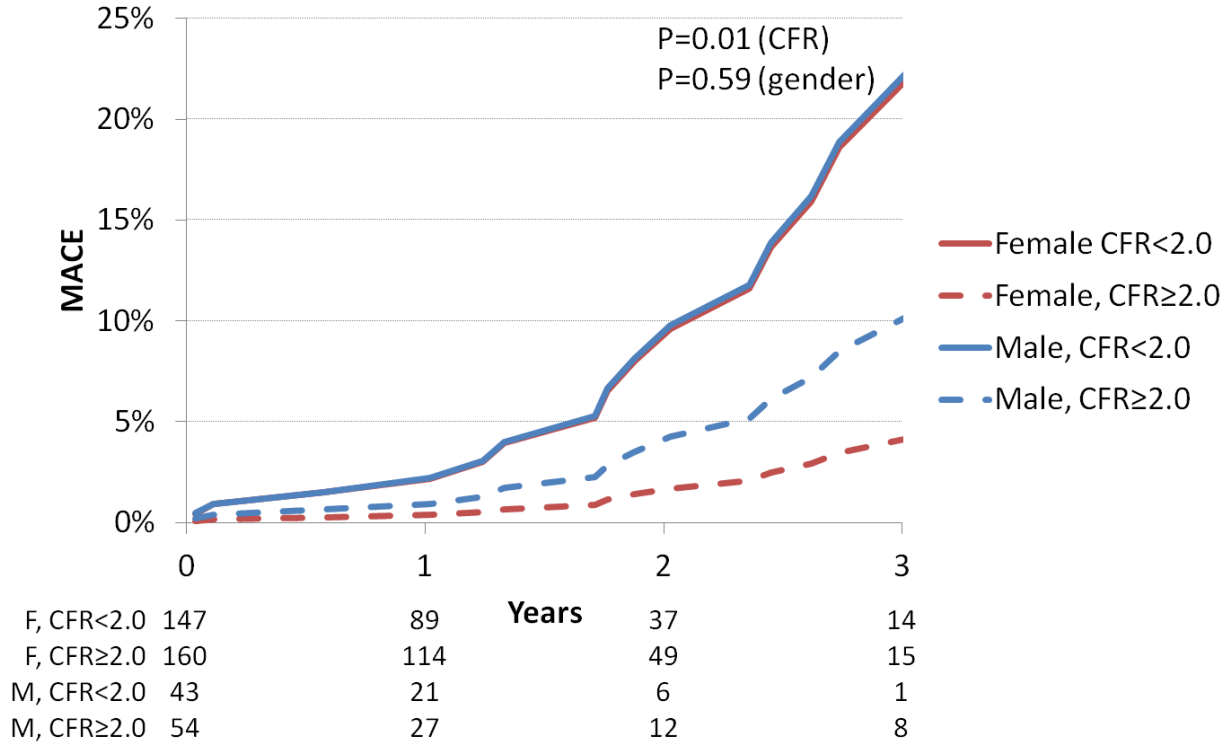
of CFR, no significant differences in annualized MACE were seen across genders (panel B), with only a trend towards worse outcomes in men than women in Quartile 2. Comparisons were performed with Poisson regression.

Figure S3: Distribution of CFR by Gender for CAC=0 Subgroup



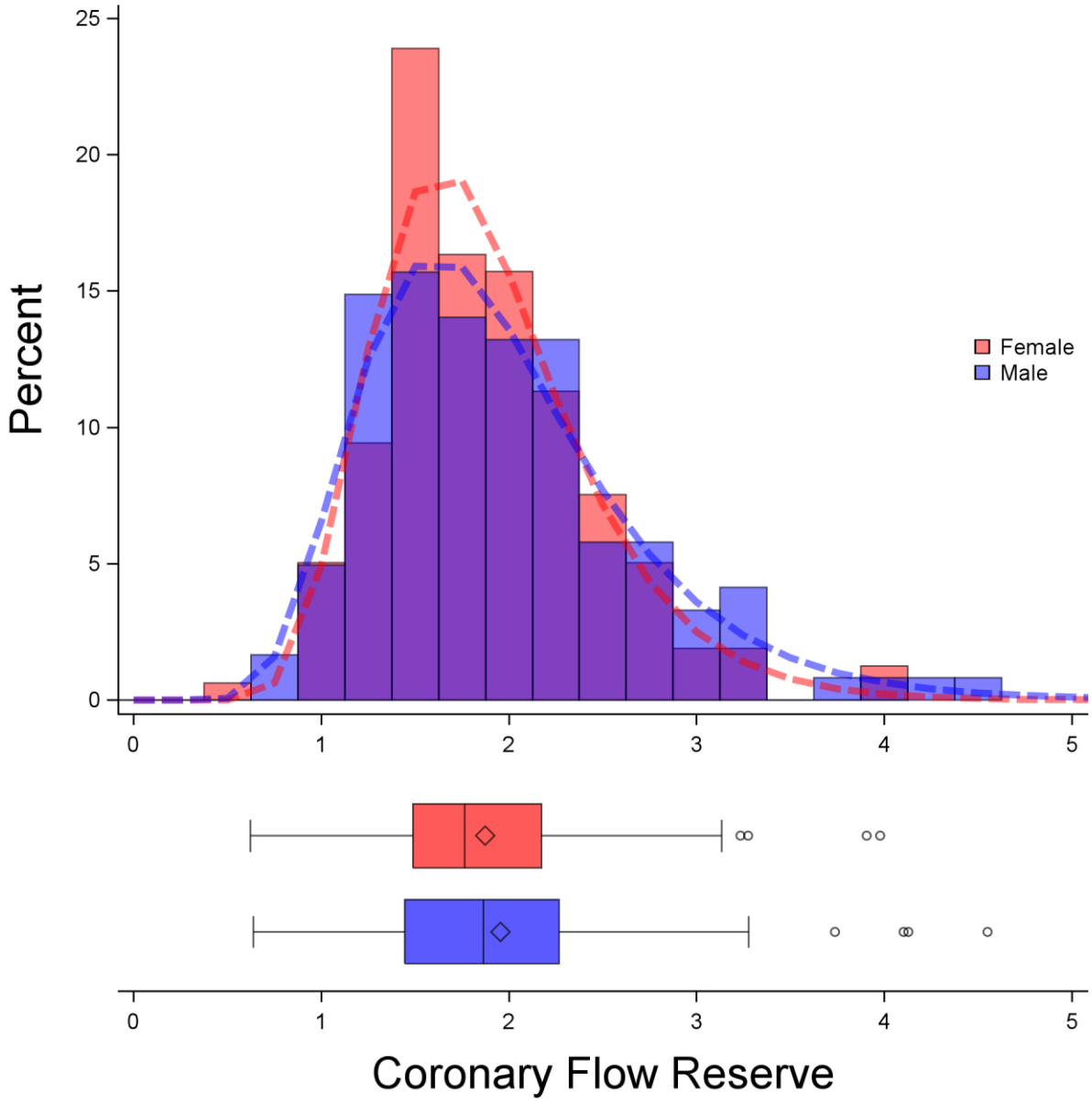
Histograms (top) showing the distribution of coronary flow reserve (CFR) for men (blue) and women (red) among the subgroup with zero coronary artery calcium score (CAC =0). Areas of overlap are shown in purple. Fitted log-normal distribution for men (dashed blue line) and women (dashed red line) are also displayed. Similar data are also shown in box plots (bottom). No statistically significant difference was seen between genders using t-test with log-normal distribution (P=0.93). CFR was equivalent between the genders (P=0.01 for <10% difference) using two one-sided tests and log-normal distribution.

Figure S4: Cumulative Incidence of MACE by Gender and Coronary Flow Reserve for CAC=0 Subgroup



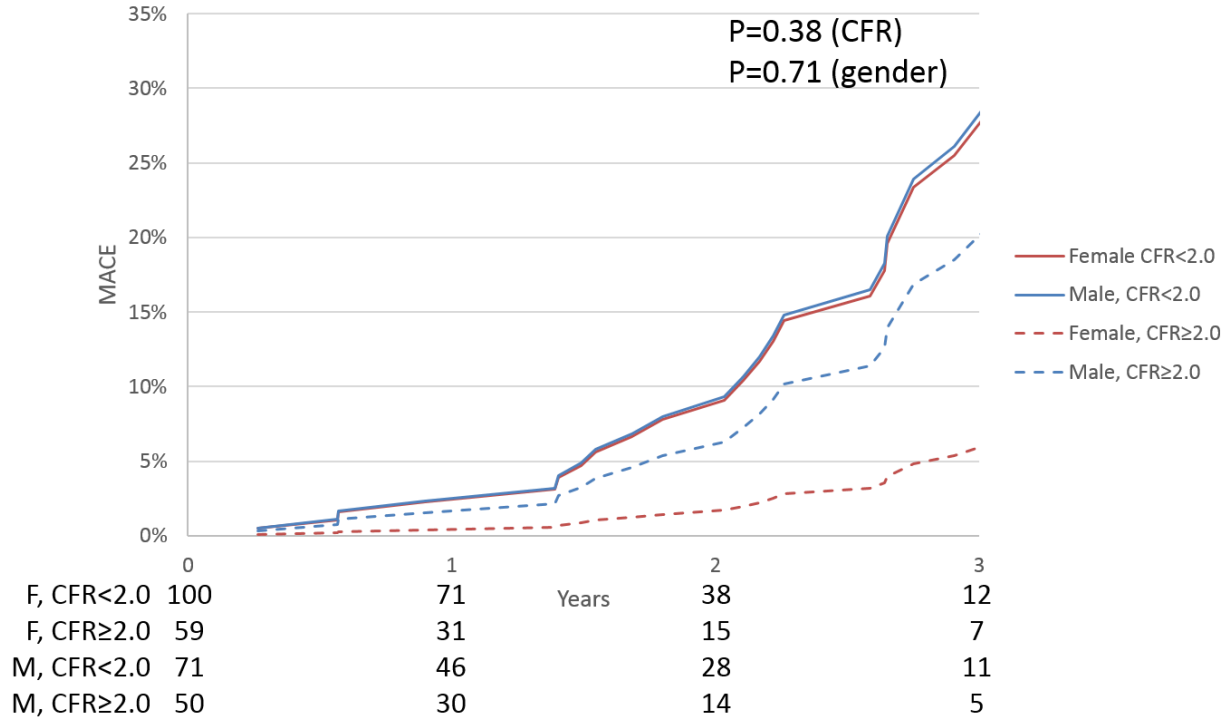
Adjusted cumulative rate of major adverse cardiac events (MACE) by gender and coronary flow reserve (CFR) among subjects with zero coronary artery calcium score (CAC=0). Data are adjusted for the modified Duke clinical risk score and rest LVEF. The curves for women with CFR<2.0 (solid red) and men with CFR<2.0 (solid blue) are nearly overlapping.

Figure S5: Distribution of CFR by Gender for CAC >100 Subgroup



Histograms (top) showing the distribution of coronary flow reserve (CFR) for men (blue) and women (red) among the subgroup with significant coronary artery calcium (CAC >100). Areas of overlap are shown in purple. Fitted log-normal distribution for men (dashed blue line) and women (dashed red line) are also displayed. Similar data are also shown in box plots (bottom). No statistically significant difference was seen between genders using t-test with log-normal distribution (P=0.56). CFR was equivalent between the genders (P=0.037 for <10% difference) using two one-sided tests and log-normal distribution..

Figure S6: Cumulative Incidence of MACE by Gender and Coronary Flow Reserve for CAC>100 Subgroup



Adjusted cumulative rate of major adverse cardiac events (MACE) by gender and coronary flow reserve (CFR) among subjects with significant coronary artery calcium score (CAC>100). Data are adjusted for the modified Duke clinical risk score and rest LVEF. The curves for women with CFR<2.0 (solid red) and men with CFR<2.0 (solid blue) are nearly overlapping.