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ORIGINAL RESEARCH

Sex Differences in Modifiable Risk Factors and Severity of Coronary Artery Disease

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BACKGROUND: It is still unknown whether traditional risk factors may have a sex-specific impact on coronary artery disease (CAD) burden.

METHODS AND RESULTS: We identified 14 793 patients who underwent coronary angiography for acute coronary syndromes in the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries; ClinicalTrials.gov, NCT01218776) registry from 2010 to 2019. The main outcome measure was the association between traditional risk factors and severity of CAD and its relationship with 30-day mortality. Relative risk (RR) ratios and 95% CIs were calculated from the ratio of the absolute risks of women versus men using inverse probability of weighting. Estimates were compared by test of interaction on the log scale. Severity of CAD was categorized as obstructive (≥50% stenosis) versus nonobstructive CAD. The RR ratio for obstructive CAD in women versus men among people without diabetes mellitus was 0.49 (95% CI, 0.41–0.60) and among those with diabetes mellitus was 0.89 (95% CI, 0.62–1.29), with an interaction by diabetes mellitus status of *P* =0.002. Exposure to smoking shifted the RR ratios from 0.50 (95% CI, 0.41–0.61) in nonsmokers to 0.75 (95% CI, 0.54–1.03) in current smokers, with an interaction by smoking status of *P*=0.018. There were no significant sex-related interactions with hypercholesterolemia and hypertension. Women with obstructive CAD had higher 30-day mortality rates than men (RR, 1.75; 95% CI, 1.48–2.07). No sex differences in mortality were observed in patients with nonobstructive CAD.

CONCLUSIONS: Obstructive CAD in women signifies a higher risk for mortality compared with men. Current smoking and diabetes mellitus disproportionally increase the risk of obstructive CAD in women. Achieving the goal of improving cardiovascular health in women still requires intensive efforts toward further implementation of lifestyle and treatment interventions.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01218776.

Key Words: conventional risk factors ■ diabetes mellitus ■ obstructive coronary artery disease ■ sex differences ■ smoking

Although the relationship between traditional cardiovascular risk factors and clinical event rates is well established in both women and men,[1] it remains unclear whether the presence of risk factors correlate with the extent of atherosclerosis and mortality, especially in women. Accordingly, acute coronary syndromes (ACS) may be caused by ruptures of small insignificant rather than severely narrowed plaques,[2] and women present more often with nonobstructive coronary lesions than men at cardiac catheterization.[3,4]

These observations attest that there is a substantial void in current understanding of the pathogenesis of coronary heart disease (CHD) in women. This perceived void has led to considerable research on nontraditional risk factors as a cause of ischemia in women.[5] Yet, data to support these new pathogenetic hypotheses are scarce,[6] and some epidemiologic studies have suggested that traditional risk factors may confer a greater proportional excess cardiovascular risk to women than to men.[7–9]

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CLINICAL PERSPECTIVE

What Is New?

- Little is currently known about the sex-specific associations between traditional risk factors and the degree of coronary artery disease (CAD) with related outcomes.
- We approached this issue by reviewing the presence of traditional risk factors in 14 793 patients who were referred to coronary angiography for an acute coronary syndrome. Severity of CAD was categorized as obstructive (≥50% stenosis) versus nonobstructive CAD.
- Women with obstructive CAD have a roughly 75% greater excess risk of 30-day mortality compared with men; cigarette smoking and diabetes mellitus disproportionally increase the risk of obstructive CAD in women.

What Are the Clinical Implications?

- Our findings support development of prevention strategies in women at a greater level to those that exist in men.
- Intense efforts to reduce tobacco use and increased screening for prediabetes mellitus combined with more stringent follow-up of women with a history of gestational diabetes mellitus have great potential to decrease the sex lag in cardiovascular disease mortality in women compared with men.

Nonstandard Abbreviations and Acronyms

ESC	European Society of Cardiology
ISACS-TC	International Survey of Acute Coronary Syndromes in Transitional Countries
KNN	k-nearest neighbors
MONICA	Monitoring of Trends and Determinants in Cardiovascular Disease
NHIS	National Health Interview Survey
RoPR	Registry of Patient Registries
RR	relative risk

A source of uncertainty merits attention. Epidemiologic studies often present the relationship between risk factors and incident CHD controlling for only age and sex, but not for concomitant risk factors. Results may be inconsistent because of the inclusion of a larger number of people with multiple traditional risk factors for whom different risks exist as compared with people with a single risk factor. The US Surgeon General report of 2006 suggests that the simultaneous presence of smoking with another major risk factor is estimated to quadruple the risk. The presence of 2 other risk factors with smoking results in ≈8 times the risk of individuals with no risk factors.[10] Given this, different distributions of risk factors in different populations may account for the sex differences in outcome observed in some but not in other studies. Most of the prior studies on this issue are meta-analyses.[7–9] Lack of individual participant data in such investigations has precluded the undertaking of more in-depth analyses.

We sought to investigate at an individual level whether there are sex differences in the 4 modifiable traditional cardiovascular risk factors and how these differences may impact the severity of coronary artery disease (CAD) and outcomes in ACS. According to European Society of Cardiology (ESC) guidelines,[11] the severity of atherosclerosis was dichotomized into obstructive versus nonobstructive CAD. To obtain comparable results between women and men, we used a nonparametric balancing strategy by weighting to adjust for differences between nonobstructive and obstructive CAD and among traditional risk factors. This approach may offer insights on the associations between typical risk factors and anatomical CAD burden, which may help to implement sex-tailored preventive strategies.

METHODS

Setting and Design

The authors declare that all supporting data are available within the article and its supplemental material.

Study participants were recruited from 22 tertiary healthcare services of the ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries; ClinicalTrials.gov, NCT01218776) registry providing advanced medical investigation and treatment including percutaneous coronary intervention (PCI) and/or cardiac surgery.[12,13] The data coordinating center has been established at the University of Bologna. The local research ethics committee from each hospital approved the study. Because patient information was collected anonymously, institutional review boards waived the need for individual informed consent. All data were transferred to the Department of Electrical and Computer Engineering, University of California, Los Angeles, CA, where final statistical analyses were performed.

Patient Population

The initial study population consisted of White patients who underwent coronary angiography for ACS from January 1, 2010, to January 15, 2019, which is consistent with estimates of patients enrolled per year and per center of similar registries according to policies and procedures described by the RoPR (Registry of Patient Registries).[14] All hospitals used the same protocol. There were no differences in treatment strategy based on whether the patients had diabetes mellitus. The designated physician collected the registry data at the time of clinical assessment. All patients presented with chest pain or equivalent symptoms, such as dyspnea and fatigue. Appropriateness of inclusion was adjudicated by a cardiology specialist, considering clinical history, physical examination findings, ECG, and cardiac biomarkers. The use of medications given at hospital admission and before the index event was noted. We defined prior users of aspirin, statins, clopidogrel, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, and β-blockers as those patients who had taken these medications on a regular basis at least for 2 weeks before the onset of the qualifying event. All vessels >1.5 mm in diameter were graded for stenosis severity.[15] Obstructive CAD was defined according to 2013 ESC guidelines on the management of stable CAD as at least 1 main branch of the epicardial coronary artery with a ≥50% stenosis.[11] Because the definition of obstructive CAD varies between different guidelines or studies and traditional understanding of obstructive CAD was 70%,[16] we repeated the analyses on outcomes shifting the cutoff for obstructive CAD at ≥70% stenosis. Patients presenting with coronary artery bypass grafting (n=261) were excluded. We also excluded patients with nonobstructive CAD but prior PCI (n=57) as these patients were previously categorized as having obstructive CAD. The final analysis sample consisted of 14 793 patients with ACS (Figure S1).

Outcome Measures

There were 2 outcome measures. First, we measured the obstructive CAD rates to investigate the relationship between severity of disease and traditional risk factors; second, we measured the 30-day mortality rates to evaluate the relationship between severity of CAD (obstructive versus nonobstructive) and outcomes. As it is difficult to discuss 30-day mortality following primary PCI in patients with obstructive disease and ST-segment–elevation myocardial infarction (STEMI) with no reference to how revascularization rate differences come into play, subsidiary analyses were performed by noting the proportion of patients undergoing primary PCI.

Assessment of Traditional Risk Factors

We defined current smokers as individuals who smoked cigarettes, cigars, and cigarillos at the time of the index event according to recommendations from the National Health Interview Survey (NHIS).[17] Individuals who smoked in their lifetime but who were not active smokers at the time of the index event were classified as former smokers regardless of time since they quit. The remaining individuals were classified as never-smokers. The sex-specific risks of obstructive CAD were estimated for current smokers compared with never-/former smokers, hereafter classified as nonsmokers. The other traditional risk factors were assessed by designation of medical history before admission in the database. Definition, therefore, refers to patients with diagnosis of hypercholesterolemia, hypertension, or diabetes mellitus by a general practitioner.

Statistical Analysis

Baseline demographics, clinical characteristics, and acute (within 24 hours) in-hospital medications and clinical outcomes were compared by sex and CAD status: obstructive versus nonobstructive CAD. Baseline characteristics were reported as percentages for categorical variables and means with SDs for continuous variables. Comparisons between groups were made either by Pearson chi-square test for baseline categorical variables or 2-sample *t* test for continuous variables. A 2-sided *P* value <0.05 was considered statistically significant. We used inverse probability of weighting models to assess the relative risk (RR) ratios with their 95% CIs for the outcomes of interest (Data S1).[18] We had complete data on sex, age, CAD status, and 30-day mortality. Some patients had missing data on other variables. We used k-nearest neighbors (KNN) algorithms as imputation method to treat missing data. The value of "k" in the KNN imputation was=10 (Data S1).[19] Estimates were compared by test of interaction on the log scale (Data S1).[20] We modeled the RR (women versus men) ratio of obstructive CAD for each risk factor. Findings were adjusted for demographics, cardiovascular risk factors, and history of ischemic heart disease or cardiovascular disorders (Table S1). For these analyses, we divided the risk factors into dichotomous variables and grouped the patients into those with and those without the risk factor under consideration. We tested each of the risk factors in a specific model, excluding the tested risk factor and estimated the RR ratios with and without the risk factor under consideration. We calculated the 30-day mortality rates by adding variables to the prior model, specifically ST-segment shifts in anterior leads at ECG, systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline (mg/dL), and Killip class ≥2.

RESULTS

Figure S1 describes patient flow through the ISACS-TC study. Overall, 2.1% of the eligible patients with ACS were excluded as they presented with prior coronary revascularization by coronary artery bypass grafting or with nonobstructive lesions in patients with prior PCI. Of the 14 793 enrolled patients, 96.2% had obstructive CAD.

Patient Baseline Characteristics

Baseline clinical characteristics of the study population are displayed in Table S1. Women, whether they had obstructive or nonobstructive CAD, were older and had more traditional risk factors, except cigarette smoking, compared with their male counterparts. At hospital presentation, women more frequently developed heart failure (Killip class ≥2) than men and had lower initial levels of serum creatinine. Women received on average fewer revascularization procedures and fewer antiplatelet and anticoagulant agents compared with men (Table S2). Sex disparities in treatment were also seen when restricting the analysis to patients with STEMI. Women continued to be less likely than men to undergo reperfusion therapies with fibrinolysis (4.9% versus 6.8%, P=0.0002) However, when women were represented in the catheterization laboratory, they had the same interventional therapy as the men (97% versus 97.3%, respectively; P=0.508) (Table S3). Of note, women received more evidence-based therapies before admission for ACS, namely aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, and statins (Table S4).

Prevalence of Traditional Risk Factors in ACS

Overall, among patients with ACS, the prevalence of those patients with at least 1 of the 4 conventional risk factors was 92.2% in women with obstructive CAD and 89.9% in those with nonobstructive CAD (Figure 1). Similar rates were seen in men. When none of these risk factors were present, 7.7% of women and 9.7% of men had obstructive CAD; when 1 of these factors was present, 27.9% of women and 29.7% of men had obstructive CAD; when 1 or 2 of these factors were present, 65.1% of women and 64.8% of men had obstructive CAD; and when 1 to 3 of these factors were present, 87.8% of women and 86.2% of men had obstructive CAD. When adding a fourth risk factor, the increase was small (92.2% in women and 90.2% in men).

Risk Factors and Obstructive CAD by Sex

The women-to-men RR ratios for obstructive CAD among risk factors are shown in Figure 2. The RR ratio among patients without diabetes mellitus was 0.49 (95% CI, 0.41–0.60) and those with diabetes mellitus was 0.89 (95% CI, 0.62–1.29) (Table 1), with evidence of an interaction by diabetes mellitus status of P=0.002 (Table S5). Exposure to smoking (Table 2) shifted the RR ratios from 0.50 (95% CI, 0.41–0.61) in nonsmokers to 0.75 (95% CI, 0.54–1.03) in current smokers, with an interaction by smoking status of P=0.018 (Table S5). The RR ratios for the absence or presence of hypercholesterolemia were 0.56 (95% CI, 0.45–0.70) and 0.55 (95% CI, 0.42–0.72), respectively (Table 3). The RR ratios for the absence or presence of hypertension were 0.50 (95% CI, 0.35–0.73) and 0.56 (95% CI, 0.47–0.68), respectively (Table 4). There were no significant sex-related interactions for hypercholesterolemia and hypertension (Table S5).

Severity of CAD and Outcomes

After clinical baseline characteristics were well matched between women and men using inverse probability of weighting, female sex was associated with a higher risk of STEMI in patients presenting with obstructive CAD (RR ratio, 1.12; 95% CI, 1.03–1.21). No sex difference in STEMI rates were observed in

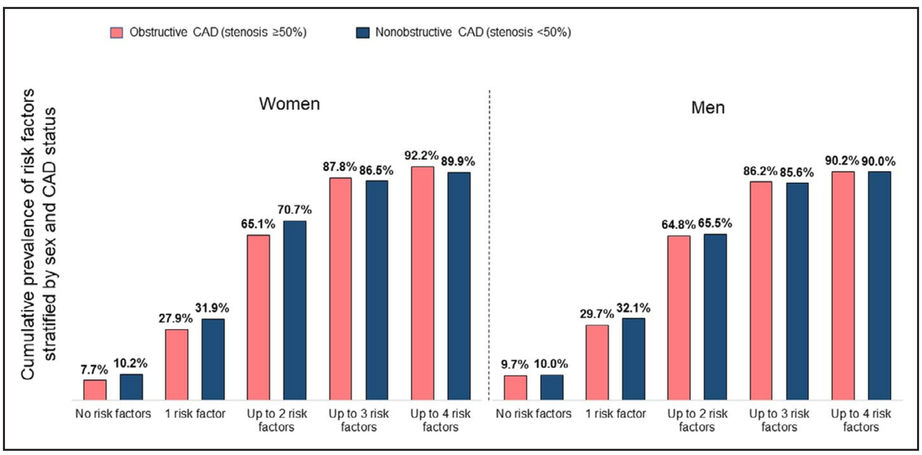

Figure 1. Cumulative prevalence of traditional risk factors in acute coronary syndromes sorted by coronary artery disease (CAD) status and sex.

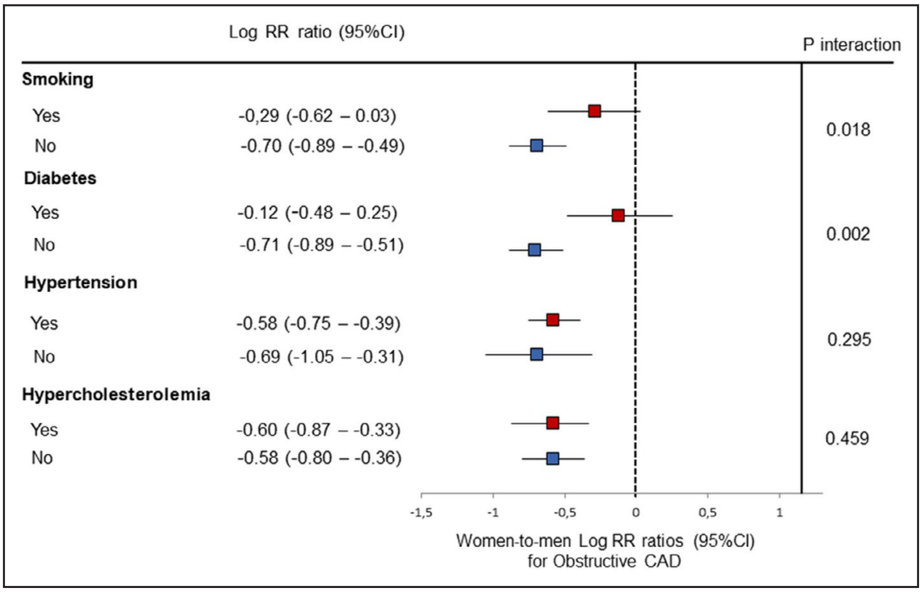

Figure 2. Female sex and obstructive coronary artery disease (CAD) sorted by the presence or absence of traditional risk factors.
Women-to-men relative risk (RR) ratios expressed on a logarithmic scale. Variables used for adjustment are reported in Tables 1 through 4.

patients with nonobstructive CAD (RR ratio, 0.92; 95% CI, 0.60–1.43) (Table 5). However, the RRs from the 2 subgroups did not significantly differ from each other (interaction test, *P*=0.1913) (Table S6). Among patients with obstructive CAD, women had higher 30-day mortality than men (5.8% versus 3.4%, respectively) (RR ratio, 1.75; 95% CI, 1.48–2.07). No sex difference in mortality was observed with patients with nonobstructive CAD (1.5% versus 1.9%, respectively) (RR ratio, 0.79; 95% CI, 0.31–1.74). The interaction test between the outcomes of obstructive versus nonobstructive CAD was highly significant (*P*=0.038) (Table S7). To

Table 1. History of Diabetes Mellitus: Incidence of Obstructive CAD Sorted by Sex (Women Versus Men) Using Inverse Probability of Weighting Analysis

Characteristics	Diabetes Mellitus			No Diabetes Mellitus		
	Women (n=1293)	Men (n=2270)	*P* Value	Women (n=3054)	Men (n=8176)	*P* Value
Age, mean±SD, y	64.1±10.6	64.5±10.4	0.3282	60.3±11.9	60.4±11.8	0.4990
Cardiovascular risk factors, %						
Hypertension	83.5	83.3	0.8775	65.3	65.8	0.6196
Hypercholesterolemia	51.6	51.4	0.9086	41.7	42.4	0.5040
Current smokers	33.7	33.8	0.9516	46.3	46.5	0.8500
Former smokers	10.4	9.7	0.5026	7.7	7.3	0.4712
Clinical history of ischemic heart disease, %						
Previous angina pectoris	20.3	19.6	0.6145	14.3	14.6	0.6882
Previous myocardial infarction	17.1	16.9	0.8785	12.3	12.1	0.7730
Previous heart failure	5.5	5.4	0.8994	3.5	3.3	0.6004
Clinical history of cardiovascular disease, %						
Peripheral artery disease	2.8	2.8	1.0000	1.3	1.4	0.6876
Previous stroke	3.8	3.9	0.8822	2.5	2.4	0.7576
Outcomes, %						
Obstructive CAD, %	96.3	96.7	0.5434	93.9	96.9	<0.0001
RR ratio (95% CI)	0.89 (0.62–1.29)		0.5435	0.49 (0.41–0.60)		<0.0001

CAD indicates coronary artery disease; and RR, relative risk.

Table 2. Smoking Status: Incidence of Obstructive CAD Sorted by Sex (Women Versus Men) Using Inverse Probability of Weighting Analysis

Characteristics	Current Smokers			Nonsmokers		
	Women (n=1394)	Men (n=5026)	*P* Value	Women (n=2953)	Men (n=5420)	*P* Value
Age, mean±SD, y	56.7±10.1	56.8±10.2	0.8585	64.8±11.7	65.0±11.3	0.5535
Cardiovascular risk factors, %						
Diabetes mellitus	18.7	18.7	1.0000	28.1	28.2	0.9226
Hypertension	64.0	64.5	0.7302	73.9	74.3	0.6896
Hypercholesterolemia	48.5	49.2	0.6437	40.3	41.0	0.5334
Clinical history of ischemic heart disease, %						
Previous angina pectoris	12.9	13.3	0.6967	17.4	17.6	0.8182
Previous myocardial infarction	11.8	11.5	0.7567	14.5	14.6	0.9014
Previous heart failure	3.1	2.8	0.5530	4.6	4.6	1.0000
Clinical history of cardiovascular disease, %						
Peripheral artery disease	1.6	1.6	1.0000	1.8	1.8	1.0000
Previous stroke	1.8	1.8	1.0000	3.4	3.4	1.0000
Outcomes						
Obstructive CAD, %	96.3	97.2	0.0778	93.2	96.5	<0.0001
RR ratio (95% CI)	0.75 (0.54–1.03)		0.0788	0.50 (0.41–0.61)		<0.0001

CAD indicates coronary artery disease; and RR, relative risk.

clarify the previously identified excess mortality risk among women with obstructive CAD, we examined mortality rates in patients who underwent primary PCI. Female sex was still associated with higher risk of 30-day mortality compared with men (RR ratio, 1.84; 95% CI, 1.52–2.23) (Table S8).

Confirmatory Analysis on 30-Day Mortality

Results of 30-day mortality were virtually the same in the analysis that restricted the cohort of obstructive CAD to patients with ≥70% stenosis (Tables S9 and S10).

Table 3. History of Hypercholesterolemia: Incidence of Obstructive CAD Sorted by Sex (Women Versus Men) Using Inverse Probability of Weighting Analysis

Characteristics	Hypercholesterolemia			No Hypercholesterolemia		
	Women (n=2025)	Men (n=4584)	*P* Value	Women (n=2322)	Men (n=5862)	*P* Value
Age, mean±SD, y	61.1±11.2	61.2±11.3	0.6409	61.3±12.1	61.6±11.8	0.3712
Cardiovascular risk factors, %						
Diabetes mellitus	27.6	27.7	0.9332	20.6	21.1	0.6162
Hypertension	79.2	79.6	0.7106	61.9	62.3	0.7366
Current smokers	47.9	48.0	0.9402	39.8	39.8	1.0000
Former smokers	10.3	9.7	0.4511	7.1	6.4	0.2502
Clinical history of ischemic heart disease, %						
Previous angina pectoris	21.8	21.7	0.9276	11.0	11.1	0.8967
Previous myocardial infarction	16.0	16.2	0.8385	11.0	10.9	0.8961
Previous heart failure	5.0	5.0	1.0000	3.1	2.9	0.6281
Clinical history of cardiovascular disease, %						
Peripheral artery disease	2.2	2.3	0.8018	1.2	1.3	0.7144
Previous stroke	2.7	2.8	0.8204	2.8	2.7	0.8014
Outcomes						
Obstructive CAD, %	95.3	97.3	<0.0001	93.9	96.5	<0.0001
RR ratio (95% CI)	0.55 (0.42–0.72)		<0.0001	0.56 (0.45–0.70)		<0.0001

CAD indicates coronary artery disease; and RR, relative risk.

Table 4. History of Hypertension: Incidence of Obstructive CAD Sorted by Sex (Women Versus Men) Using Inverse Probability of Weighting Analysis

Characteristics	Hypertension			No Hypertension		
	Women (n=3415)	Men (n=6953)	*P* Value	Women (n=932)	Men (n=3493)	*P* Value
Age, mean±SD, y	62.9±11.1	63.2±11.1	0.4263	57.2±11.9	57.3±11.6	0.7736
Cardiovascular risk factors, %						
Diabetes mellitus	28.5	28.6	0.9156	13.1	13.4	0.8107
Hypercholesterolemia	50.3	50.7	0.7018	30.1	30.4	0.8595
Current smokers	39.7	40.0	0.7694	51.5	51.5	1.0000
Former smokers	9.8	9.1	0.2497	5.2	5.0	0.8034
Clinical history of ischemic heart disease, %						
Previous angina pectoris	18.6	18.6	1.0000	9.7	9.5	0.8535
Previous myocardial infarction	14.7	14.6	0.8923	9.9	10.1	0.8569
Previous heart failure	4.6	4.5	0.8177	2.6	2.2	0.4696
Clinical history of cardiovascular disease, %						
Peripheral artery disease	2.0	2.1	0.7363	0.8	0.9	0.7767
Previous stroke	3.5	3.4	0.7924	1.2	1.3	0.8079
Outcomes						
Obstructive CAD, %	94.0	96.5	<0.0001	95.4	97.6	0.0003
RR ratio (95% CI)	0.56 (0.47–0.68)		<0.0001	0.50 (0.35–0.73)		0.0004

CAD indicates coronary artery disease; and RR, relative risk.

DISCUSSION

This study explored the relationships between risk factors, sex, and obstructive CAD status on 30-day mortality after an ACS. Our results demonstrate that the excess risk of death in women compared with men is limited to patients with obstructive CAD. Obstructive CAD is, therefore, the most life-threatening event in women, and as so, warrants intensified efforts to prevent its occurrence. Our results also shed light on the relationship between traditional risk factors and obstructive CAD in women. Compared with men, obstructive CAD risk in women is increased to a greater extent by current smoking and diabetes mellitus. These data raise potential challenges, which warrant further considerations.

Traditional Risk Factors in ACS

Cigarette smoking, hypertension, diabetes mellitus, and hypercholesteremia are factors of recognized importance in the development of CHD in the general population. Prior epidemiological work focusing on the relationship between risk factors and CHD has required cardiac clinical events as outcomes. However, the term *CHD* holds multiple mechanisms that may contribute to ischemic events. These mechanisms do not necessarily need the presence of obstructive CAD. Abnormal coronary reactivity,[21] microvascular dysfunction,[22,23] and plaque erosion with distal microembolization[23,24] are potential factors able to trigger myocardial ischemia in women even in the absence of obstructive CAD. There is, therefore, a substantial void in current understanding as to whether there are sex differences in the 4 traditional cardiovascular risk factors and how these differences may impact the severity of CAD and its relation with outcomes. We approached this issue by reviewing the presence of traditional risk factors in 14 793 patients who were referred to coronary angiography for an ACS. Our data indicate that conventional risk factors are present at a much higher prevalence than previously thought,[25] with only 8% to 10% of patients lacking any of the conventional risk factors for the disease. This overall pattern was largely independent of sex and severity of CAD. Therefore, in contrast to prior suggestions,[26] we found that only a small minority of patients with nonobstructive CAD lacks conventional risk factors.

Sex Differences in Severity of CAD and Mortality From ACS

The current study challenges the common belief that women with chest pain, whether it be associated with ACS or otherwise, are more likely to have nonobstructive CAD at angiography. The prevalence varies depending on clinical setting and risk profile of the population investigated. Nonobstructive CAD was a relatively uncommon clinical entity in our cohort of patients with ACS. Approximately 5% of women and men undergoing angiography had

Table 5. Outcomes Sorted by Sex (Women Versus Men) and CAD Status in Patients With ACS at Index Event Using Inverse Probability of Weighting Analysis

Characteristics	Obstructive CAD (Stenosis ≥50%)			Nonobstructive CAD (Stenosis <50%)		
	Women (n=4119)	Men (n=10 119)	*P* Value	Women (n=228)	Men (n=327)	*P* Value
Age, mean±SD, y	61.4±11.9	61.4±11.5	0.8232	60.9±11.7	60.8±12.2	0.9484
Cardiovascular risk factors, %						
Diabetes mellitus	24.4	24.1	0.7045	20.2	22.1	0.5914
Hypertension	69.7	69.6	0.9063	78.6	77.5	0.7589
Hypercholesterolemia	44.5	44.7	0.8277	39.3	38.4	0.8308
Current smokers	43.3	43.9	0.5129	35.1	34.3	0.8458
Former smokers	7.4	7.8	0.4157	9.9	10.8	0.7337
Clinical history of ischemic heart disease, %						
Previous angina pectoris	15.3	15.6	0.6541	17.8	18.3	0.8806
Previous myocardial infarction	13.0	13.3	0.6320	12.4	12.1	0.9156
Previous heart failure	3.6	3.8	0.5680	3.8	4.4	0.7279
Clinical history of cardiovascular disorders, %						
Peripheral artery disease	1.6	1.8	0.4067	1.2	1.3	0.9180
Previous stroke	2.7	2.7	1.0000	3.4	2.9	0.7385
Clinical presentation at admission						
ST-segment deviation in anterior leads (at ECG), %	20.6	21.0	0.5945	7.2	7.0	0.9280
Systolic BP at baseline, mean±SD, mm Hg	139.6±28.0	139.6±26.6	0.9856	143.2±25.5	143.7±26.1	0.8476
Heart rate at baseline, mean±SD, beats per min	80.1±17.9	80.2±17.9	0.7351	79.1±18.3	79.0±20.7	0.9650
Serum creatinine at baseline, mean±SD, mg/dL	0.99±0.50	1.05±0.60	0.0001	0.99±0.30	1.03±0.50	0.1501
Killip class ≥2, %	16.5	16.5	1.0000	12.6	14.9	0.4425
Outcomes						
30-d Mortality, %	5.8	3.4	<0.0001	1.5	1.9	0.7236
RR ratio (95% CI)	1.75 (1.48–2.07)		<0.0001	0.79 (0.31–1.74)		0.7237
STEMI, %	70.7	68.4	0.0064	17.8	18.9	0.7243
RR ratio (95% CI)	1.12 (1.03–1.21)		0.0064	0.92 (0.60–1.43)		0.7238

ACS indicates acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; RR, relative risk; and STEMI, ST-segment–elevation myocardial infarction.

nonobstructive disease. This finding is concordant with prior work exploring obstructive CAD status in myocardial infarction.[27,28] Our results also confirm that the excess risk of short-term mortality after ACS in women is restricted to those with obstructive CAD,[29] and demonstrate that women with obstructive CAD present more often with STEMI compared with their male counterparts. Taken together, these findings reinforce the view that women with obstructive CAD are a vulnerable group and the growing demand for development of sex-specific prevention strategies.

Sex-Specific Weights of Risk Factors in CAD

It is difficult to establish the precise sex-specific impact of each of the 4 major risk factors on development of significant CAD. Potential confounding is worth considering. Sex is an important confounder for cardiovascular disease. Each of the traditional risk factors increases the rates of cardiovascular mortality and may represent residual confounding. In addition, associations may increase confounding. Smokers have more adverse cardiovascular risk factors, such as dyslipidemia and hypertension, than never-smokers.[30] Therefore, nonsmokers may have more protection against development of significant CAD compared with smokers, independently of smoking status. This reasoning applies equally well to all risk factors.[31] To try to circumvent this issue we matched patients sorted by sex and each individual risk factor using inverse probability of weighting. The weights created a population where the weighted risk factors and control groups were representative of the patient characteristics in the overall population of women and men.[32] Balanced covariates, including age, could not be confounders anymore, a property that would be expected under randomization. On the other hand, sex and risk factors cannot be randomized.

Current Smoking and Obstructive CAD in Women

Although cigarette smoking is harmful for any sex, there are some discrepancies between studies in demonstrating a different effect of smoking as a risk factor for CHD in women. Some studies have suggested that smoking has a much larger relative detrimental impact on CHD in women.[9] Other studies have shown that smoking has a similar effect on increasing the risk of CHD in both men and women.[8] Conflicting results between studies may be related to many factors including definition of smokers, age with consequent prevalence of oral contraceptive use, and synergistic action of smoking with other conventional risk factors. In the current study, we followed the NHIS[17] definition of smoker and used inverse probability of weighting to mitigate much of the differences in age and other concomitant risk factors. Much more importantly, we investigated whether current smoking has a hazardous effect on the RR ratio of women versus men for the association with significant CAD, which is one of the factors contributing to the pathophysiology of ACS. Compared with nonsmokers, women who were current smokers had a much greater risk of obstructive CAD with statistical evidence of interaction. This clearly indicates that the harm of smoking differs by sex. Our study, therefore, adds to the understanding of the relationship between smoking and CHD events by suggesting an important mechanistic basis: its association with severe atherosclerotic plaques in the coronary arteries. Excess risk of obstructive CAD in female compared with male smokers might have some potential explanations. Women might extract a greater quantity of toxic agents from the same number of cigarettes than men.[33] Plasma levels of estrogen are lower in smoking than in nonsmoking women, which may lead to accelerated progression of CAD.[34] However, in light of the available evidence, no definite answer can be given. Unfortunately, there is an alarming trend toward increased smoking in women and, therefore, better methods leading to prevention and cessation of smoking are needed.

Diabetes Mellitus and Obstructive CAD in Women

There is strong evidence from many studies that women with diabetes mellitus face an increased cardiovascular risk relative to men.[35] Still, it is unclear whether these observed sex differences in CHD risk are real or attributable to differences between men and women with respect to the concomitant presence of other major risk factors for CHD.[7] Several potential interacting factors may contribute to the acceleration of CHD risk in women with diabetes mellitus. Diabetes mellitus is more likely to be associated with elevations in both systolic and diastolic blood pressure in women than in men.[36] Women with diabetes mellitus are more likely to be of low socioeconomic status and as so are quite often cigarette smokers.[37] We tried to circumvent such issues by matching patients with inverse probability of weighting. In our study, concurrent traditional risk factors were all well balanced among women and men with diabetes mellitus. Diabetes mellitus on top of the other risk factors equalized the risk for obstructive CAD by sex at any age. The higher RRof mortality after ACS conferred by obstructive CAD in women compared with men may explain why women with diabetes mellitus have a 2-fold increased risk of myocardial infarction and death compared with their male counterparts.[38,39] Screening for prediabetes mellitus combined with more stringent follow-up of women with a history of gestational diabetes mellitus has the potential to dramatically reduce the burden of CAD and sex differences in outcomes.

Sex Differences in Hypercholesterolemia and Hypertension

Hypercholesterolemia and hypertension are both well-documented primary risk factors. Both factors increased the risk of obstructive CAD without any critical matter to separate risk from women and men. This finding supports the results from the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) study reporting that the increase in CHD events with increasing total cholesterol holds over the entire range of patient characteristics.[40] Although we found no difference in the risk for obstructive CAD by sex, it should be reminded that there is a remarkably higher prevalence of hypertension in women. Thus, women would benefit more from strategies that prevent and treat hypertension at the population not at the individual level.

Limitations

Our study has several potential limitations. First, an observational study is potentially open to confounding. We minimized this factor by using a study design based on matching by inverse probability of weighting to balance covariate distribution among sexes and risk factors.[18] On the other hand, randomized controlled trials are not a viable option as it is unethical to randomly assign women and men to be smokers and nonsmokers. Second, patients who have had coronary angiography do not necessarily represent the general ACS population since those who died before hospital admission are missing. Yet, mortality rates among women and men with ACS are similar to those reported in recent studies, which supports the external validity of the study.[29] Third, some of the risk factors were ascertained by the general practitioner, which might have led to error in some individuals. Although we acknowledge some potential misclassifications, it is unlikely that these misclassifications differentially affect women over men and, thus, are unlikely to modify the sex differences that we found. Fourth, our analysis did not account for potential differences in antidiabetic medication use or medication adherence before index event in women versus men. However, examination of a recent study showing that men have a higher risk of metformin- and sulfonylureas-associated myocardial infarction than women suggests that our model-based estimates are not influenced by antidiabetic drug interactions and are reasonably valid.[41] Fifth, angiographic evaluations were performed at the local level and, hence, the reliability of the observations, especially as it relates to minimal CAD (stenosis <50%) may be difficult to assess. However, such individual characterization of CAD reflects real-world CAD categorization. Further, we repeated the analyses on 30-day mortality shifting the cutoff for nonobstructive CAD at 70% diameter stenosis. Estimates were similar to those seen using a 50% cutoff. As so, misclassification of the severity of CAD in the categories of obstructive and nonobstructive seems unlikely. Defining a cutoff value of 50% or 70% stenosis for obstructive CAD has shed its critical importance in decision-making and may be lumped into a common basket labeled “intermediate” stenosis, now undistinguished and of uncertain importance. Finally, residual confounding from concomitance of nontraditional risk factors such as stress, body mass index, family history of CHD, and adherence to healthy lifestyle behaviors cannot be excluded.

Strengths

Although sometimes used interchangeably, CAD and CHD are not the same condition. CHD may be actually but not necessarily a result of CAD. Little is currently known about the sex-specific associations between traditional risk factors and the degree of CAD. Our angiographic study on CAD represents an advance in furthering our understanding of the mechanisms of vulnerability to traditional risk factors in women and highlights the ongoing need to accurately account for biologic factors specific to women.

Our statistical approach improves on existing studies. Logistic regression ignores the interaction among risk factors. Inverse probability of weighting exhibits balance on the covariates and weights the risk of each type of traditional risk factors equally.

CONCLUSIONS

The current study found greater 30-day mortality related to obstructive CAD in women compared with men. Cigarette smoking and diabetes mellitus disproportionally increase the risk of obstructive CAD in women, and as so they are key factors in explaining sex differences in outcomes from ACS. Intense efforts to reduce tobacco use and increase screening for prediabetes mellitus have potential to decrease the sex lag in cardiovascular disease mortality in women compared with men.

ARTICLE INFORMATION

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None.

Supplementary Materials

Data S1
Tables S1–S10
Figure S1

REFERENCES

1. Mensah GA, Brown DW, Croft JB, Greenlund KJ. Major coronary risk factors and death from coronary heart disease: baseline and follow-up mortality data from the Second National Health and Nutrition Examination Survey (NHANES II). *Am J Prev Med*. 2005;29:68–74.
2. Ambrose JA, Winters SL, Arora RR, Haft JI, Goldstein J, Rentrop KP, Gorlin R, Fuster V. Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. *J Am Coll Cardiol*. 1985;6:1233–1238.
3. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med*. 2006;166:1391–1395.
4. Gulati M. Improving the cardiovascular health of women in the nation. *Circulation*. 2017;135:495–498.
5. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, Humphrey LL. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151:496–507.
6. Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional risk factors in cardiovascular disease risk assessment:

updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;320:281–297.
7. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med*. 2002;162:1737–1745.
8. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
9. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011;378:1297–1305.
10. Office on Smoking and Health (US). *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control and Prevention (US); 2006. Available at: https://www.ncbi.nlm.nih.gov/books/NBK44324/. Accessed January 4, 2020.
11. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
12. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, Kalpak O, Ricci B, Milicic D, Manfrini O, et al. Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern Med*. 2018;178:632–639.
13. Cenko E, van der Schaar M, Yoon J, Manfrini O, Vasiljevic Z, Vavlukis M, Kedev S, Miličić D, Badimon L, Bugiardini R. Sex-related differences in heart failure after ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2019;74:2379–2389.
14. Gliklich RE, Leavy MB, Levy D, Karl J, Campion DM, Taylor T.Registry of Patient Registries (RoPR) Policies and Procedures. Effective Health Care Program Research Report No. 41. (Prepared by Outcome DEcIDE Center under Contract No. HHSA 290-2005-0035-1.) AHRQ Publication No. 12-EHC066-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registry-of-patient-registries_research-2012-2_1.pdf. Accessed January 11, 2020.
15. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, Dill KE, Jacobs JE, Maroules CD, Rubin GD, et al. Coronary Artery Disease—Reporting and Data System (CAD-RADS): an expert consensus document of SCCT, ACR and NASCI: endorsed by the ACC. *JACC Cardiovasc Imaging*. 2016;9:1099–1113.
16. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:2574–2609.
17. National Health Interview Survey-Adult Tobacco Use Information 2017. Available at: https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm. Accessed January 4, 2020.
18. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679.
19. Beretta L, Santaniello A. Nearest neighbor imputation algorithms: a critical evaluation. *BMC Med Inform Decis Mak*. 2016;16(suppl 3):74.
20. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326:219.
21. Hammadah M, Kim JH, Al Mheid I, Samman Tahhan A, Wilmot K, Ramadan R, Alkhoder A, Khayata M, Mekonnen G, Levantsevych O, et al. Coronary and peripheral vasomotor responses to mental stress. *J Am Heart Assoc*. 2018;7:e008532. DOI: 10.1161/JAHA.118.008532.
22. Wong TY, Klein R, Sharrett AR, Duncan BB, Couper DJ, Tielsch JM, Klein BE, Hubbard LD. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA*. 2002;287:1153–1159.
23. Cenko E, van der Schaar M, Yoon J, Kedev S, Valvukis M, Vasiljevic Z, Ašanin M, Miličić D, Manfrini O, Badimon L, et al. Sex-specific treatment effects after primary percutaneous intervention: a study on coronary blood flow and delay to hospital presentation. *J Am Heart Assoc*. 2019;8:e011190. DOI: 10.1161/JAHA.118.011190.
24. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 2011;124:1414–1425.
25. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. *Arch Intern Med*. 2001;161:2657–2660.
26. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv*. 2015;8:1445–1453.
27. Ramanath VS, Armstrong DF, Grzybowski M, Rahnama-Mohagdam S, Tamhane UU, Gordon K, Froehlich JB, Eagle KA, Jackson EA. Receipt of cardiac medications upon discharge among men and women with acute coronary syndrome and nonobstructive coronary artery disease. *Clin Cardiol*. 2010;33:36–41.
28. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, Douglas PS, Krone RJ, McKay CR, Block PC, et al. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation*. 2008;117:1787–1801.
29. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *Circ Cardiovasc Qual Outcomes*. 2017;10:e003443. https://doi.org/10.1161/CIRCOUTCOMES.116.003443.
30. Alkerwi A, Baydarlioglu B, Sauvageot N, Stranges S, Lemmens P, Shivappa N, Hébert JR. Smoking status is inversely associated with overall diet quality: findings from the ORISCAV-LUX study. *Clin Nutr*. 2017;36:1275–1282.
31. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001;37:1053–1059.
32. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol*. 2006;163:262–270.
33. Woodward M, Tunstall-Pedoe H, Smith WC, Tavendale R. Smoking characteristics and inhalation biochemistry in the Scottish population. *J Clin Epidemiol*. 1991;44:1405–1410.
34. Geisler J, Omsjø IH, Helle SI, Ekse D, Silsand T, Lønning PE. Plasma oestrogen fractions in postmenopausal women receiving hormone replacement therapy: influence of route of administration and cigarette smoking. *J Endocrinol*. 1999;162:265–270.
35. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006;332:73–78.
36. Haffner SM, Valdez R, Morales PA, Mitchell BD, Hazuda HP, Stern MP. Greater effect of glycemia on incidence of hypertension in women than in men. *Diabetes Care*. 1992;15:1277–1284.
37. Beckles GLA, Thompson-Reid PE; Centers for Disease Control and Prevention (CDC). Socioeconomic status of women with diabetes—United States, 2000. *MMWR Morb Mortal Wkly Rep*. 2002;51:147–148, 159.
38. Huxley RR, Peters SA, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3:198–206.
39. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia*. 2001;44:S14–S21.
40. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation*. 1999;99:1165–1172.
41. Wang SH, Chen WJ, Hsu LY, Chien KL, Wu CS. Use of spontaneous reporting systems to detect host-medication interactions: sex differences in oral anti-diabetic drug-associated myocardial infarction. *J Am Heart Assoc*. 2018;7:e008959. DOI: 10.1161/JAHA.118.008959.

SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Inverse probability of weighting

We used inverse probability of weighting to balance the distribution of covariates between two patient groups. If *e* denotes the estimated propensity score (i.e. $e=\hat{P}(Z=1 \mid x)$, where the patient x is included in patient group 1; then, $1-e = \hat{P}(Z=0 \mid x)$), then the original sample is weighted by the following weights: $Z/e+(1-Z)/ 1-e$ where Z represents the patient group. For instance, women (Z=1) are assigned a weight equal to the reciprocal of the propensity score (1/e), while men (Z=0) are assigned a weight equal to the reciprocal of one minus the propensity score (1/1-e). The weighting procedure for each sample balances the covariate distributions between two patient groups.[18]

Nearest neighbor imputation algorithms

Nearest neighbor (NN) imputation algorithms are efficient methods to fill in missing data where each missing value on some records is replaced by a value obtained from related cases in the whole set of records. Thus, imputation for clinical features was conducted using the average of measured values from k records (kNN).[19]

NN algorithms are similarity-based methods that rely on distance metrics and results may change in relation to the similarity measure used to evaluate the distance between recipients and donors. In our work, we used the following norm as metric to evaluate distance:

$$(\sum_{i=1}^{n}|x_i-y_i|^p)^{1/p}$$

Before imputation of the recipient X_i, the full set with no missing data C(X) was filtered to select a subset of features relevant to the missing variable to be imputed (X_{i_miss}). To this end, C(X) was considered as a dataset in the context of a regression problem, where the variable with the missing data (Xmiss) was set as the class variable and the other q variables (X1, X2, …, Xq) as predictors. We also applied the RReliefF algorithm. The set was, therefore, filtered to select a subset Cs(X) ⊂ C(X) where (X1, X2, …, Xs) ⊂ (X1, X2, …, Xq) and s < q. In the present context, we set the number of neighbors for RReliefF equal to 10 and set s as 10 %, 20 % or 30 % of q. As C(X) is invariant to Xi, the filtering step was performed only once before the NN imputation step that, on the contrary was performed separately for each Xi.

More specifically, to impute the missing value in i-th column, we find k-nearest neighbor columns from i-th column (in terms of Euclidean distance) and replace the missing value with weighted mean of the k-nearest neighbor columns. Weights are inversely proportional to the Euclidean distance from i-th column.

Interaction test

The comparison of two estimated quantities, each with its standard error, is a general method that can be applied widely.[20] These measures were always analyzed on the log scale because the distributions of the log ratios tend to be those closer to normal than of the ratios themselves. If the estimates are *E*1 and *E*2 with standard errors SE(*E*1) and SE(*E*2), then the difference *d*=*E*1 - *E*2 has standard error SE(*d*)=Ö[SE(*E*1)2 + SE(*E*2)2] i.e., the square root of the sum of the squares of the separate standard errors. The ratio *z*=*d*/SE(*d*) gives a test of the null hypothesis that in the population the difference *d* is zero, by comparing the value of *z* to the standard normal distribution. The 95% confidence interval for the difference is *d*-1.96SE(*d*) to *d*+1.96SE(*d*).

SUPPLEMENTAL RESULTS

Interaction tests

In our study, the estimated women-to-men RR ratio for obstructive CAD among nondiabetics was 0.43 (95%CI 0.36– 0.51) and diabetics was 0.89 (0.43–1.83), but are the relative risks from the subgroups significantly different from each other? We show how to answer this question by using the interaction test based on the summary data quoted. **(Table S4)**. We obtained the logs of the odds ratios (relative risks) and their confidence intervals (rows 2 and 4). As 95% confidence intervals were obtained as 1.96 standard errors either side of the estimate, the SE of each log relative risk was obtained by dividing the width of its confidence interval by 2×1.96 (row 6). The estimated difference in log relative risks was d=E1- E2= 0.5696 (row 7) and its standard error 0.1958 (row 8). From these two values, we tested the interaction and estimated the ratio of the relative risks (with confidence interval). The test of interaction was the ratio of d to its standard error: z= 2.9091, which gives p value=0.0018 when we referred it to a table of the normal distribution (row 10). The estimated interaction effect was exp =1.7676 (row 11). The confidence interval for this effect was 1.2042 to 2.5945 on the log scale (row 9). Transforming back to the relative risk scale, we got 1.2042 to 2.5945 (row 12). There was thus good evidence to support different outcome effects of diabetes on obstructive CAD between sexes. A similar approach was used for comparing any other sex difference. (**Tables S5, S6, and S9**).

Table S1. Baseline characteristics of the overall population sorted by sex and CAD status in patients with acute coronary syndrome at index event.

	Overall			Obstructive CAD (stenosis ≥50%)			Nonobstructive CAD (stenosis <50%)		
Characteristics	**Women (n=4347)**	**Men (n=10446)**	**p value**	**Women (n=4119)**	**Men (n=10119)**	**p value**	**Women (n=228)**	**Men (n=327)**	**p value**
Age, mean ± SD, y	65.2 ± 11.2	59.9 ± 11.4	<0.0001	65.4 ± 11.2	59.9 ± 11.4	<0.0001	62.5 ± 11.5	59.8 ± 12.3	0.0077
Cardiovascular risk factors (overall), n (%)	4020 (92.5)	9543 (91.4)	0.0208	3814 (92.6)	9245 (91.4)	0.0127	206 (90.4)	298 (91.1)	0.7563
Diabetes, n (%)	1293 (29.7)	2270 (21.7)	<0.0001	1247 (30.3)	2196 (21.7)	<0.0001	46 (20.2)	74 (22.6)	0.4872
Hypertension, n (%)	3415 (78.6)	6953 (66.6)	<0.0001	3228 (78.4)	6710 (66.3)	<0.0001	187 (82.0)	243 (74.3)	0.0288
Hypercholesterolemia, n (%)	2025 (46.6)	4584 (43.9)	0.0027	1929 (46.8)	4463 (44.1)	0.0031	96 (42.1)	121 (37.0)	0.2283
Current smokers, n (%)	1394 (32.1)	5026 (48.1)	<0.0001	1344 (32.6)	4889 (48.3)	<0.0001	50 (21.9)	137 (41.9)	<0.0001
Former smokers, n (%)	176 (4.0)	983 (9.4)	<0.0001	162 (3.9)	937 (9.3)	<0.0001	14 (6.1)	46 (14.1)	0.0016
Clinical history of ischemic heart disease (overall), n (%)	1255 (28.9)	2819 (27.0)	0.0205	1176 (28.6)	2729 (27.0)	0.0569	79 (34.6)	90 (27.5)	0.0763
Previous angina pectoris, n (%)	757 (17.4)	1583 (15.2)	0.0008	705 (17.1)	1531 (15.1)	0.0038	52 (22.8)	52 (15.9)	0.0456
Previous MI, n (%)	534 (12.3)	1432 (13.7)	0.0178	504 (12.2)	1398 (13.8)	0.0103	30 (13.2)	34 (10.4)	0.3263
Previous heart failure, n (%)	184 (4.2)	384 (3.7)	0.1185	174 (4.2)	368 (3.6)	0.1070	10 (4.4)	16 (4.9)	0.7795

Clinical history of cardiovascular disorders (overall), n (%)	201 (4.6)	432 (4.1)	0.1909	194 (4.7)	417 (4.1)	0.1259	7 (3.1)	15 (4.6)	0.3521
PAD, n (%)	62 (1.4)	195 (1.9)	0.0486	61 (1.5)	189 (1.9)	0.0946	1 (0.4)	6 (1.8)	0.1063
Previous stroke, n (%)	141 (3.2)	260 (2.5)	0.0146	135 (3.3)	251 (2.5)	0.0121	6 (2.6)	9 (2.8)	0.9311
Clinical presentation at admission									
STEMI, n (%)	2871 (66.0)	7094 (67.9)	0.0284	2833 (68.8)	7027 (69.4)	0.4369	38 (16.7)	67 (20.5)	0.2521
ST-segment shifts in anterior leads (at ECG), n (%)	816 (18.8)	2212 (21.2)	0.0008	800 (19.4)	2189 (21.6)	0.0283	16 (7.0)	23 (7.0)	0.9942
Systolic BP at baseline, mean ± SD, mmHg	140.4 ± 127.7	139.5 ± 26.7	0.0699	140.1 ± 27.8	139.4 ± 26.7	0.1619	145.8±25.4	143 ± 25.9	0.2047
Heart rate at baseline, mean ± SD, bets/min	80.2 ± 18.2	80.2 ± 18.0	0.8447	80.3 ± 18.2	80.2 ± 17.9	0.6824	78.7 ± 17.5	79.8 ± 21.8	0.5134
Serum creatinine at baseline, mean ± SD, mg/dl	1.0 ± 0.5	1.1 ± 0.7	<0.0001	1.0 ± 0.5	1.1 ± 0.7	<0.0001	0.9 ± 0.3	1.1 ± 0.7	0.0009
Killip Class ≥2), n (%)	855 (19.7)	1602 (15.3)	<0.0001	827 (20.1)	1547 (15.3)	<0.0001	28 (12.3)	55 (16.8)	0.1317

BP indicates blood pressure; CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction, PAD, peripheral artery disease, STEMI= ST-segment elevation myocardial infarction.

Table S2. Use of medications and PCI within 24 hours from hospitalization sorted by sex (women versus men) and CAD status in the overall population of patients with acute coronary syndromes.

Characteristics	All Patients			Obstructive CAD (stenosis ≥50%)			Nonobstructive CAD (stenosis <50%)		
	Women (n=4347)	Men (n 10446)	p value	Women (n=4119)	Men (n=10119)	p value	Women (n =228)	Men (n =327)	p value
Aspirin, n (%)	4298 (98.9)	10352 (99.1)	0.2189	4071 (98.8)	10028(99.1)	0.1654	227 (99.6)	324 (99.1)	0.4857
Clopidogrel, n (%)	3908 (89.9)	9291 (88.9)	0.0819	3703 (89.9)	9000 (88.9)	0.0889	205 (89.9)	291 (89.0)	0.7278
Unfractionated heparin, n (%)	2411 (55.5)	6073 (58.1)	0.0028	2309 (56.1)	5905 (58.4)	0.0121	102 (44.7)	168 (51.4)	0.1239
LMWH, n (%)	2091 (48.1)	4769 (45.7)	0.0066	1960 (47.6)	4595 (45.0)	0.0184	131 (57.5)	174 (53.2)	0.3229
Heparins (overall), n (%)	3671 (84.4)	9021 (86.4)	0.0030	3484 (84.6)	8735 (86.3)	0.0083	187 (82.0)	286 (87.5)	0.0837
GP IIb/IIIa inhibitor, n (%)	515 (11.8)	1328 (12.7)	0.1414	511 (12.4)	1326 (13.1)	0.2552	4 (1.8)	2 (0.6)	0.2408
Beta-blockers	3336 (76.7)	8065 (77.2)	0.5421	3132 (76.0)	7773 (76.8)	0.3225	204 (89.5)	292 (89.3)	0.9469
ARBs/ACE-inhibitors, n (%)	3425 (78.8)	8139 (77.9)	0.2378	3235 (78.5)	7873 (77.8)	0.3349	190 (83.3)	266 (81.3)	0.5450
PCI, n (%)	3880 (89.3)	9626 (92.2)	<0.0001	3880 (94.2)	9626 (95.1)	0.0278	0 (0.0%)	0 (0.0%)	-

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CAD, coronary artery disease; GP, glycoprotein; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention.

Table S3. Use of medications and reperfusion therapies within 24 hours from hospitalization sorted by sex (women versus men) and CAD status in patients with STEMI.

	All Patients			Obstructive CAD (stenosis ≥ 50%)			Nonobstructive CAD (stenosis <50%)		
Characteristics	**Women (n=2871)**	**Men (n=7094)**	**p value**	**Women (n=2833)**	**Men (n=7027)**	**p value**	**Women (n=38)**	**Men (n=67)**	**p value**
Aspirin, n (%)	2843 (99.0)	7045 (99.3)	0.1717	2805 (99.0)	6978 (99.3)	0.1673	38 (100.0)	67 (100.0)	1.0000
Clopidogrel, n (%)	2541 (88.5)	6228 (87.7)	0.3158	2508 (88.5)	6170 (87.8)	0.3113	33 (86.8)	58 (86.6)	0.9686
Unfractionated heparin, n (%)	1604 (55.9)	4110 (57.9)	0.0595	1593 (56.2)	4079 (58.0)	0.0993	11 (28.9)	31 (46.3)	0.0765
LMWH, n (%)	1314 (45.8)	3201 (45.1)	0.5581	1290 (45.5)	3168 (45.1)	0.6837	24 (63.2)	33 (49.3)	0.1699
Heparins (overall), n (%)	2424(84.4)	6175 (87.0)	0.0008	2394 (84.5)	6119 (87.1)	0.0011	30 (78.9)	56 (83.6)	0.5693
Beta-blockers, n (%)	2137 (74.4)	5422 (76.4)	0.0371	2104 (74.3)	5366 (76.4)	0.0300	33 (86.8)	56 (83.6)	0.6514
ARBs/ACE-inhibitors, n (%)	2203 (76.7)	5503 (77.6)	0.3673	2173 (76.7)	5449 (77.5)	0.3699	30 (78.9)	54 (80.6)	0.8427
Reperfusion therapies									
Fibrinolysis, n (%)	140 (4.9)	479 (6.8)	0.0001	140 (4.9)	479 (6.8)	0.0002	0 (0.0)	0 (0.0)	-
PCI, n (%)	2749 (95.8)	6836 (96.4)	0.1613	2749 (97.0)	6836 (97.3)	0.5081	0 (0.0)	0 (0.0)	-

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CAD, coronary artery disease; GP, glycoprotein; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

Table S4. Therapy within 15 days before index event.

Characteristics	All Patients			Obstructive CAD			Nonobstructive CAD		
	Women (n=4347)	**Men (n=10446)**	**p value**	**Women (n=4119)**	**Men (n=10119)**	**p value**	**Women (n=228)**	**Men (n=327)**	**p value**
Aspirin, n (%)	1291 (29.7)	2613 (25.0)	<0.0001	1212 (29.4)	2531 (25.0)	<0.0001	79 (34.6)	82 (25.1)	0.0162
Clopidogrel, n (%)	462 (10.6)	928 (8.9)	0.0014	426 (10.3)	896 (8.9)	0.0071	36 (15.8)	32 (9.8)	0.0409
ACE-inhibitors /ARBs, n (%)	2222 (51.1)	3904 (37.4)	<0.0001	2100 (51.0)	3766 (37.2)	<0.0001	122 (53.5)	138 (42.2)	0.0087
Beta-blockers, n (%)	1657 (38.1)	2844 (27.2)	<0.0001	1553 (37.7)	2721 (26.9)	<0.0001	104 (45.6)	123 (37.6)	0.0609
Statins, n (%)	1002 (23.1)	2034 (19.5)	<0.0001	949 (23.0)	1976 (19.5)	<0.0001	53 (23.2)	58 (17.7)	0.1175

ACE indicates angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CAD, coronary artery disease

Table S5. Interaction test calculations for comparing two estimated risk ratios (relative risks of women versus men) by inverse probability of weighting: diabetes, current smoking, hypercholesterolemia, hypertension for obstructive CAD.

		Group 1 [Diabetes] (n = 3563)	Group 2 [No diabetes] (n = 11230)	Group 1 [Current smokers] (n=6420)	Group 2 [Non-smokers] (n=8373)
1	**RR ratio**	0.89	0.49	0.75	0.50
2	**log RR ratio**	-0.1165	-0.7133	-0.2877	-0.6931
3	**95% CI for RR ratio**	0.62 – 1.29	0.41 – 0.60	0.54 – 1.03	0.41 – 0.61
4	**95% CI for log RR ratio**	-0.4780 – 0.2546	-0.8916 – -0.5108	-0.6162 –0.0296	-0.8916 – -0.4943
5	**Width of CI**	0.7326	0.3808	0.6458	0.3973
6	**SE (=width / (2*1.96))**	0.1869	0.0971	0.1647	0.1014
		Difference between log relative risk ratios			
7	**d (=$E_1 - E_2$)**	**0.5968**		**0.4054**	
8	**SE (d)**	**0.2106**		**0.1934**	
9	**CI (d)**	**0.1840 – 1.0096**		**0.0263 – 0.7845**	
10	**Test of Interaction**	**2.8338 (p-value: 0.0023)**		**2.0962 (p-value: 0.0180)**	
		Ratio of relative risk ratios			
11	**RRR ratio (=exp(d))**	1.8163		1.4999	
12	**CI (RRR ratio)**	1.2020 – 2.7445		1.0266 – 2.1913	

		Group 1	Group 2	Group 1	Group 2

		[Hypercholesterolemia] (n=6609)	[No hypercholesterolemia] (n=8184)	[Hypertension] (n=10368)	[No hypertension] (n=4425)
1	**RR ratio**	0.55	0.56	0.56	0.50
2	**log RR ratio**	-0.5978	-0.5798	-0.5798	-0.6931
3	**95% CI for RR ratio**	0.42 – 0.72	0.45 – 0.70	0.47 – 0.68	0.35 – 0.73
4	**95% CI for log RR ratio**	-0.8675 – -0.3285	-0.7985 – -0.3567	-0.7550 – -0.3857	-1.0498 – -0.3147
5	**Width of CI**	0.5390	0.4418	0.3693	0.7351
6	**SE (=width / (2*1.96)**	0.1375	0.1127	0.0942	0.1875
		Difference between log relative risk ratios			
7	**d (=$E_1 - E_2$)**	**-0.0180**		**0.1133**	
8	**SE (d)**	**0.1778**		**0.2098**	
9	**CI (d)**	**-0.3665 – 0.3305**		**-0.2979 – 0.5245**	
10	**Test of Interaction**	**-0.1012 (p-value: 0.4597)**		**0.5400 (p-values: 0.2946)**	
		Ratio of relative risk ratios			
11	**RRR ratio (=exp(d))**	0.9822		1.1200	
12	**CI (RRR ratio)**	0.6932 – 1.3917		0.7424 – 1.6896	

Table S6. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: STEMI in obstructive versus nonobstructive CAD in patients with acute coronary syndrome at index event.

		Group 1 [Obstructive CAD] (n =14238)	Group 2 [Nonobstructive CAD] (n= 555)
1	**RR ratio**	1.12	0.92
2	**log RR ratio**	0.1133	-0.0834
3	**95% CI for RR ratio**	1.03 – 1.21	0.60 – 1.43
4	**95% CI for log RR ratio**	0.0296 – 0.1906	-0.5108 – 0.3577
5	**Width of CI**	0.1611	0.8685
6	**SE (=width / (2*1.96))**	0.0411	0.2216
	Difference between log relative risk ratios		
7	**d (=$E_1 - E_2$)**	**0.1967**	
8	**SE (d)**	**0.2253**	
9	**CI (d)**	**-0.2449 – 0.6384**	
10	**Test of Interaction**	**08730 (p-value: 0.1913)**	
	Ratio of relative risk ratios		
11	**RRR ratio(=exp(d))**	1.2174	
12	**CI (RRR ratio)**	0.7827 – 1.8934	

Table S7. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive versus nonobstructive CAD in patients with acute coronary syndrome at index event.

		Group 1 [Obstructive CAD] (n =14238)	Group 2 [Nonobstructive CAD] (n= 555)
1	**RR ratio**	1.75	0.79
2	**log RR ratio**	0.5596	-0.2357
3	**95% CI for RR ratio**	1.48 – 2.07	0.31 – 1.74
4	**95% CI for log RR ratio**	0.3920 – 0.7275	-1.1712 – 0.5539
5	**Width of CI**	0.3355	1.7251
6	**SE (=width / (2*1.96))**	0.0856	0.4401
	Difference between log relative risk ratios		
7	**d (=$E_1 - E_2$)**	**0.7953**	
8	**SE (d)**	**0.4483**	
9	**CI (d)**	**-0.0834 – 1.6740**	
10	**Test of Interaction**	**1.7740 (p-value: 0.0380)**	
	Ratio of relative risk ratios		
11	**RRR ratio(=exp(d))**	2.2151	
12	**CI (RRR ratio)**	0.9200 – 5.3335	

Table S8. Inverse probability of weighting: outcomes sorted by sex (women versus men) in patients with obstructive CAD who underwent primary PCI.

Characteristics	**Primary PCI**		
	Women (n=2641)	**Men (n=6547)**	**p value**
Cardiovascular risk factors			
Diabetes, %	22.5	22.1	0.6765
Hypertension, %	65.8	66.2	0.7140
Hypercholesterolemia, %	43.1	43.7	0.5996
Current smokers, %	46.6	47.2	0.6021
Former smokers, %	6.7	7.1	0.4957
Clinical history of ischemic heart disease			
Previous angina pectoris, %	10.8	11.1	0.6780
Previous myocardial infarction, %	10.2	10.2	1.0000
Previous heart failure, %	2.6	2.6	1.0000
Clinical history of cardiovascular disorders			
Peripheral artery disease, %	1.7	1.7	1.0000
Previous stroke, %	2.8	2.7	0.7894
Clinical presentation at admission			
ST-segment shifts in anterior leads (at ECG), %	29.1	29.6	0.6342
Systolic BP at baseline, mean ± SD, mmHg	137.5 ± 28.2	137.5 ± 27.1	0.9307
Heart rate at baseline, mean ± SD, beats/min	80.0 ± 17.7	80.3 ± 17.9	0.6048
Serum creatinine at baseline, mean ± SD, mg/dl	0.98 ± 0.50	1.04 ± 0.60	0.0001
Killip Class≥2, %	17.0	17.1	0.9082
Outcomes			
30-day mortality, %	7.1	4.0	<0.0001
Relative Risk Ratio (95% CI)	1.84 (1.52 – 2.23)		<0.0001

BP indicates blood pressure; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Table S9. Inverse probability of weighting: outcomes sorted by sex (women versus men) and CAD status in patients with acute coronary syndrome at index event. Analysis restricted the cohort of obstructive CAD patients having 70% or greater stenosis

Characteristics	Obstructive CAD (stenosis ≥70%)			Nonobstructive CAD (stenosis <70%)		
	Women (n=4037)	**Men (n=10043)**	**p value**	**Women (n=310)**	**Men (n=403)**	**p value**
Age, mean ± SD, y	61.4 ± 11.9	61.4 ± 11.5	0.8643	60.9 ± 11.8	60.8 ± 12.3	0.8409
Cardiovascular risk factors						
Diabetes, %	24.4	24.1	0.7070	20.3	21.7	0.6503
Hypertension, %	69.7	69.6	0.9071	78.9	76.8	0.5048
Hypercholesterolemia, %	44.4	44.6	0.8291	43.1	42.0	0.7687
Current smokers, %	43.4	44.0	0.5165	35.3	35.0	0.9338
Former smokers, %	7.3	7.8	0.3120	10.0	10.3	0.8956
Clinical history of ischemic heart disease						
Previous angina pectoris, %	15.2	15.6	0.5535	17.6	17.7	0.9723
Previous myocardial infarction, %	13.0	13.4	0.5274	11.6	11.4	0.9339
Previous heart failure, %	3.6	3.8	0.5707	4.5	4.6	0.9496
Clinical history of cardiovascular disease						
Peripheral artery disease, %	1.7	1.8	0.6821	0.7	1.2	0.4964
Previous stroke, %	2.8	2.8	1.0000	3.4	2.5	0.4778
Clinical presentation at hospital admission						
ST-segment shifts in anterior leads (at ECG), %	20.7	21.0	0.6922	9.7	9.7	1.0000

Systolic BP at baseline, mean ± SD, mm Hg	139.7±28.0	139.6 ± 26.6	0.8675	142.0±25.5	142.1±26.4	0.9488
Heart rate at baseline, mean ± SD, beats/min	80.0 ± 17.8	80.2 ± 17.9	0.6810	80.1 ± 18.3	79.6 ± 20.9	0.9488
Serum creatinine at baseline, mean ± SD, mg/dl	0.99 ± 0.5	1.06 ± 0.6	<0.0001	0.99 ± 0.4	1.01 ± 0.5	0.4338
Killip Class ≥2, %	16.4	16.4	0.7726	13.4	14.4	0.7029
Outcomes						
30-day mortality, %	5.9	3.4	<0.0001	1.1	1.9	0.3846
Relative Risk Ratio (95% CI)	1.75 (1.48 – 2.08)		<0.0001	0.56 (0.15 – 2.08)		0.3903

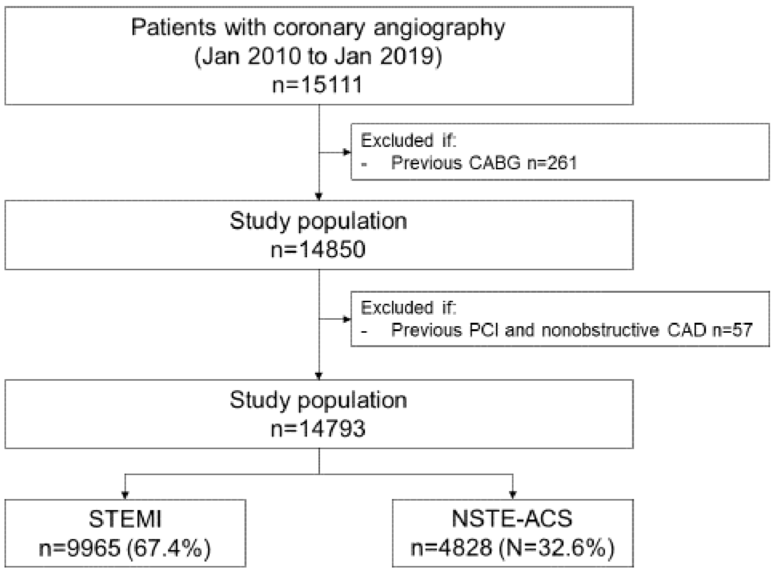
BP indicates blood pressure; CAD, coronary artery disease.

Obstructive CAD was defined as a 70% or more narrowing of the luminal diameter.

Table S10. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive (stenosis ≥70%) versus nonobstructive CAD in patients with acute coronary syndrome at index event.

		Group 1 [Obstructive CAD] (n=14080)	Group 2 [Nonobstructive CAD] (N=713)
1	**RR ratio**	1.75	0.56
2	**log RR ratio**	0.5596	-0.5798
3	**95% CI for RR ratio**	1.48 – 2.08	0.15 – 2.08
4	**95% CI for log RR ratio**	0.3920 – 0.7324	-1.8971 – 0.7324
5	**Width of CI**	0.3404	2.6295
6	**SE (=width / (2*1.96))**	0.0868	0.6708
	Difference between log relative risk ratios		
7	**d (=$E_1 - E_2$)**	**1.1394**	
8	**SE (d)**	**0.6764**	
9	**CI (d)**	**-0.1863 – 2.4651**	
10	**Test of Interaction**	**1.6845 (p-value: 0.0460)**	
	Ratio of relative risk ratios		
11	**RRR ratio (=exp(d))**	3.1249	
12	**CI (RRR ratio)**	0.8300 – 11.7647	

Figure S1. **Study Flow Chart.**



CABG indicates coronary artery bypass graft; CAD, coronary artery disease; NSTE-ACS, non-ST elevation acute coronary syndromes; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.