

# **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.  $e = \hat{P}(Z=1 | x)$ , where the patient  $x$  is included in patient group 1; then,  $1-e = \hat{P}(Z=0 | x)$ ), 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.<sup>18</sup>

#### 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).<sup>19</sup>

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 ( $X_{\text{miss}}$ ) was set as the class variable and the other  $q$  variables ( $X_1, X_2, \dots, X_q$ ) as predictors.

We also applied the RReliefF algorithm. The set was, therefore, filtered to select a subset

$C_s(X) \subset C(X)$  where  $(X_1, X_2, \dots, X_s) \subset (X_1, X_2, \dots, X_q)$  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  $X_i$ , the filtering step was performed only once before the NN imputation step that, on the contrary was performed separately for each  $X_i$ .

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.<sup>20</sup> 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  $SE(d) = \sqrt{SE(E_1)^2 + SE(E_2)^2}$  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  $2 \times 1.96$  (row 6). The estimated difference in log relative risks was  $d = E_1 - E_2 = 0.5696$  (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  $p \text{ value} = 0.0018$  when we referred it to a table of the normal distribution (row 10). The estimated interaction effect was  $\exp d = 1.7676$  (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.**

Characteristics	Overall			Obstructive CAD (stenosis $\geq$ 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
Age, mean $\pm$ SD, y	65.2 $\pm$ 11.2	59.9 $\pm$ 11.4	<0.0001	65.4 $\pm$ 11.2	59.9 $\pm$ 11.4	<0.0001	62.5 $\pm$ 11.5	59.8 $\pm$ 12.3	0.0077
<b>Cardiovascular risk factors (overall), n (%)</b>	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
<b>Clinical history of ischemic heart disease (overall), n (%)</b>	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

<b>Clinical history of cardiovascular disorders (overall), n (%)</b>	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
<b>Clinical presentation at admission</b>									
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 $\pm$ SD, mmHg	140.4 $\pm$ 127.7	139.5 $\pm$ 26.7	0.0699	140.1 $\pm$ 27.8	139.4 $\pm$ 26.7	0.1619	145.8 $\pm$ 25.4	143 $\pm$ 25.9	0.2047
Heart rate at baseline, mean $\pm$ SD, bets/min	80.2 $\pm$ 18.2	80.2 $\pm$ 18.0	0.8447	80.3 $\pm$ 18.2	80.2 $\pm$ 17.9	0.6824	78.7 $\pm$ 17.5	79.8 $\pm$ 21.8	0.5134
Serum creatinine at baseline, mean $\pm$ SD, mg/dl	1.0 $\pm$ 0.5	1.1 $\pm$ 0.7	<0.0001	1.0 $\pm$ 0.5	1.1 $\pm$ 0.7	<0.0001	0.9 $\pm$ 0.3	1.1 $\pm$ 0.7	0.0009
Killip Class $\geq$ 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.**

Characteristics	All Patients			Obstructive CAD (stenosis $\geq$ 50%)			Nonobstructive CAD (stenosis <50%)		
	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
<b>Reperfusion therapies</b>									
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.**

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

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

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

	<b>Group 1</b>	<b>Group 2</b>
	<b>[Obstructive CAD]</b>	<b>[Nonobstructive CAD]</b>
	<b>(n =14238)</b>	<b>(n= 555)</b>
<b>1 RR ratio</b>	1.75	0.79
<b>2 log RR ratio</b>	0.5596	-0.2357
<b>3 95% CI for RR ratio</b>	1.48 – 2.07	0.31 – 1.74
<b>4 95% CI for log RR ratio</b>	0.3920 – 0.7275	-1.1712 – 0.5539
<b>5 Width of CI</b>	0.3355	1.7251
<b>6 SE (=width / (2*1.96) )</b>	0.0856	0.4401
<b>Difference between log relative risk ratios</b>		
<b>7 d (=E<sub>1</sub> – E<sub>2</sub>)</b>		<b>0.7953</b>
<b>8 SE (d)</b>		<b>0.4483</b>
<b>9 CI (d)</b>		<b>-0.0834 – 1.6740</b>
<b>10 Test of Interaction</b>		<b>1.7740 (p-value: 0.0380)</b>
<b>Ratio of relative risk ratios</b>		
<b>11 RRR ratio( =exp(d) )</b>		2.2151
<b>12 CI (RRR ratio)</b>		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		p value
	Women (n=2641)	Men (n=6547)	
<b>Cardiovascular risk factors</b>			
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
<b>Clinical history of ischemic heart disease</b>			
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
<b>Clinical history of cardiovascular disorders</b>			
Peripheral artery disease, %	1.7	1.7	1.0000
Previous stroke, %	2.8	2.7	0.7894
<b>Clinical presentation at admission</b>			
ST-segment shifts in anterior leads (at ECG), %	29.1	29.6	0.6342
Systolic BP at baseline, mean $\pm$ SD, mmHg	137.5 $\pm$ 28.2	137.5 $\pm$ 27.1	0.9307
Heart rate at baseline, mean $\pm$ SD, beats/min	80.0 $\pm$ 17.7	80.3 $\pm$ 17.9	0.6048
Serum creatinine at baseline, mean $\pm$ SD, mg/dl	0.98 $\pm$ 0.50	1.04 $\pm$ 0.60	0.0001
Killip Class $\geq$ 2, %	17.0	17.1	0.9082
<b>Outcomes</b>			
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 $\geq$ 70%)			Nonobstructive CAD (stenosis <70%)		
	Women (n=4037)	Men (n=10043)	p value	Women (n=310)	Men (n=403)	p value
Age, mean $\pm$ SD, y	61.4 $\pm$ 11.9	61.4 $\pm$ 11.5	0.8643	60.9 $\pm$ 11.8	60.8 $\pm$ 12.3	0.8409
<b>Cardiovascular risk factors</b>						
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
<b>Clinical history of ischemic heart disease</b>						
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
<b>Clinical history of cardiovascular disease</b>						
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
<b>Clinical presentation at hospital admission</b>						
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 $\pm$ SD, mm Hg	139.7 $\pm$ 28.0	139.6 $\pm$ 26.6	0.8675	142.0 $\pm$ 25.5	142.1 $\pm$ 26.4	0.9488
Heart rate at baseline, mean $\pm$ SD, beats/min	80.0 $\pm$ 17.8	80.2 $\pm$ 17.9	0.6810	80.1 $\pm$ 18.3	79.6 $\pm$ 20.9	0.9488
Serum creatinine at baseline, mean $\pm$ SD, mg/dl	0.99 $\pm$ 0.5	1.06 $\pm$ 0.6	<0.0001	0.99 $\pm$ 0.4	1.01 $\pm$ 0.5	0.4338
Killip Class $\geq$ 2, %	16.4	16.4	0.7726	13.4	14.4	0.7029
<b>Outcomes</b>						
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

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BP indicates blood pressure; CAD, coronary artery disease.

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

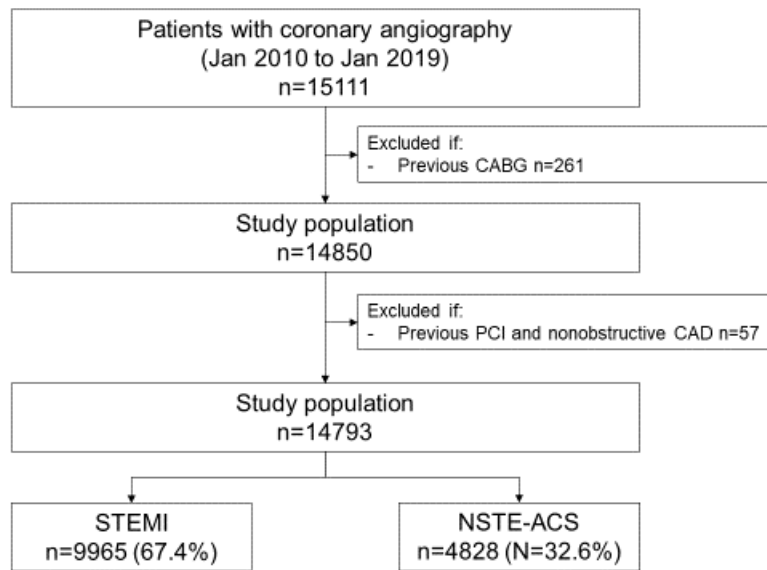
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**Table S10. Interaction test: calculations for comparing two estimated RR ratios (women versus men) by inverse probability of weighting: 30-day mortality in obstructive (stenosis  $\geq 70\%$ ) versus nonobstructive CAD in patients with acute coronary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

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

**Figure S1. Study Flow Chart.**



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