Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

SUPPLEMENTAL MATERIAL

Sex Differences in Outcomes after STEMI: Effect Modification by Treatment Strategy and Age

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SUPPLEMENTAL METHODS

Inverse Probability of Treatment Weighting Analysis

We used Inverse Propensity of Treatment Weighting (IPTW) 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. In this manuscript, for each patient subgroups stratified by age under 60 years, ≥60 to 74 years, and ≥75 years, we reported the results of IPTW analysis between the patient groups stratified by the gender [1].

Interaction test

The comparison of two estimated quantities, each with its standard error, is a general method that can be applied widely. We compared the odds ratios from the following age subgroups: ≤ 60 years versus ≥60 to 74 years, ≤ 60 years versus ≥75 years, and ≥60 to 74 years versus ≥75 years. 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 $E1$ and $E2$ with standard errors SE($E1$) and SE($E2$), then the difference $d=E1 - E2$ has standard error SE(d)=Ö[SE($E1$)2 + SE($E2$)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).

Nearest neighbour imputation algorithms

Nearest neighbour (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, whose missing rate exceeded 10%, was conducted using the average of measured values from k records (kNN) [2,3].

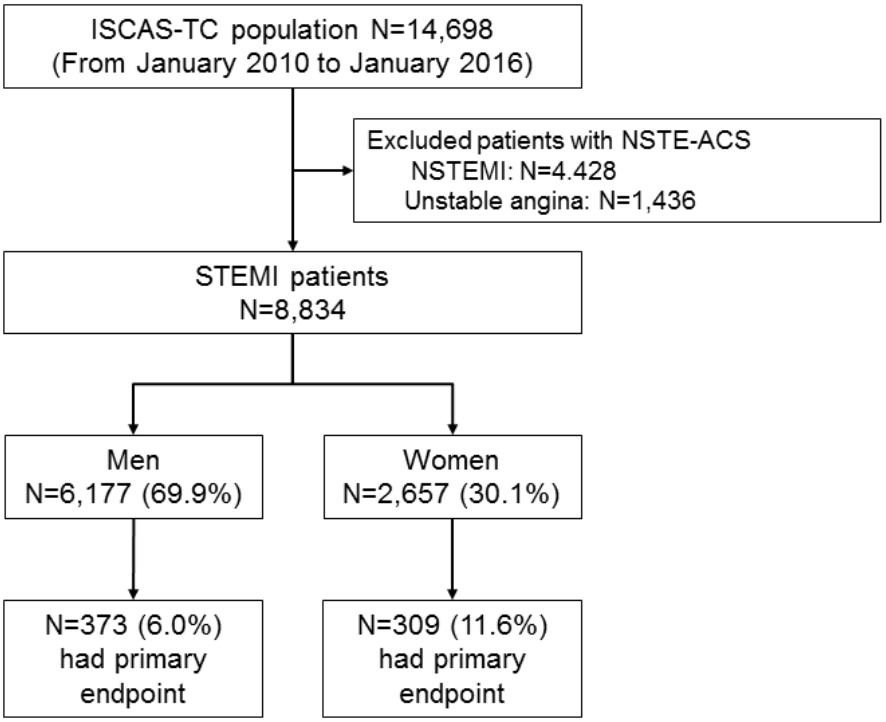
NN algorithms are similarity-based methods that rely on distance metrics and results may change in relation to the similarity measure used to evaluate the distance between recipients and donors. In our work, we used the following norm as metric to evaluate distance:

$(\sum ni=1|xi-yi|p)1/p$

Before imputation of the recipient Xi, 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 (Xi_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 [4] The set was, therefore, filtered to select a subset $Cs(X) \subset C(X)$ where $(X1, X2, \ldots, Xs) \subset (X1, X2, \ldots, Xq)$ and $s < q$. In the present context, we set the number of neighbours 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.

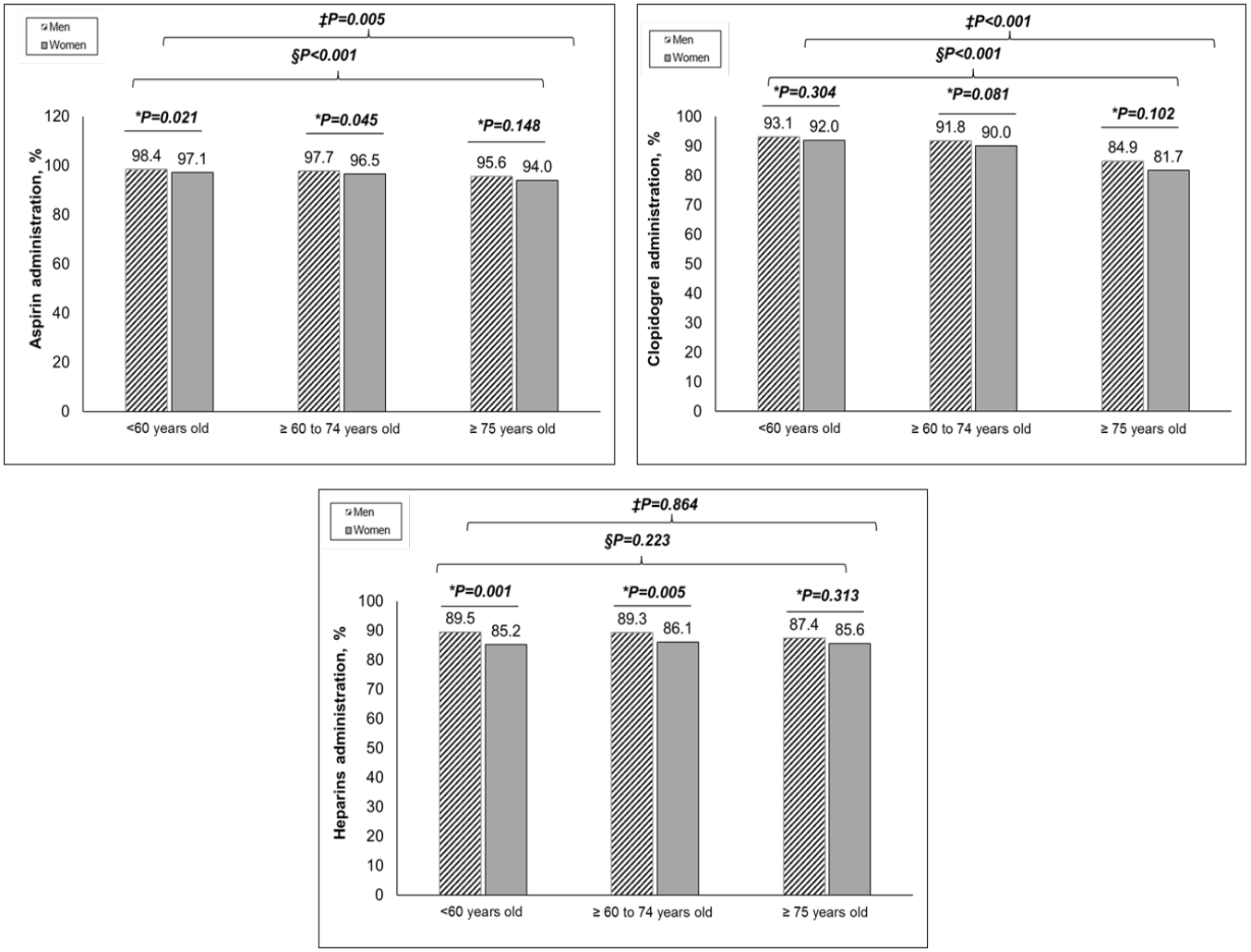
SUPPLEMENTAL RESULTS

Supplemental Figure 1. Study Flow Chart



Abbreviations: NSTE-ACS, non-ST-segment elevation acute coronary syndromes; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction

Supplemental Figure 2. Rates of medications within 24 hours in the selected age categories sorted by sex



*****P value for comparison between women and men in the same age category

‡ P value for comparison between different age categories in women

§ P value for comparison between different age categories in men

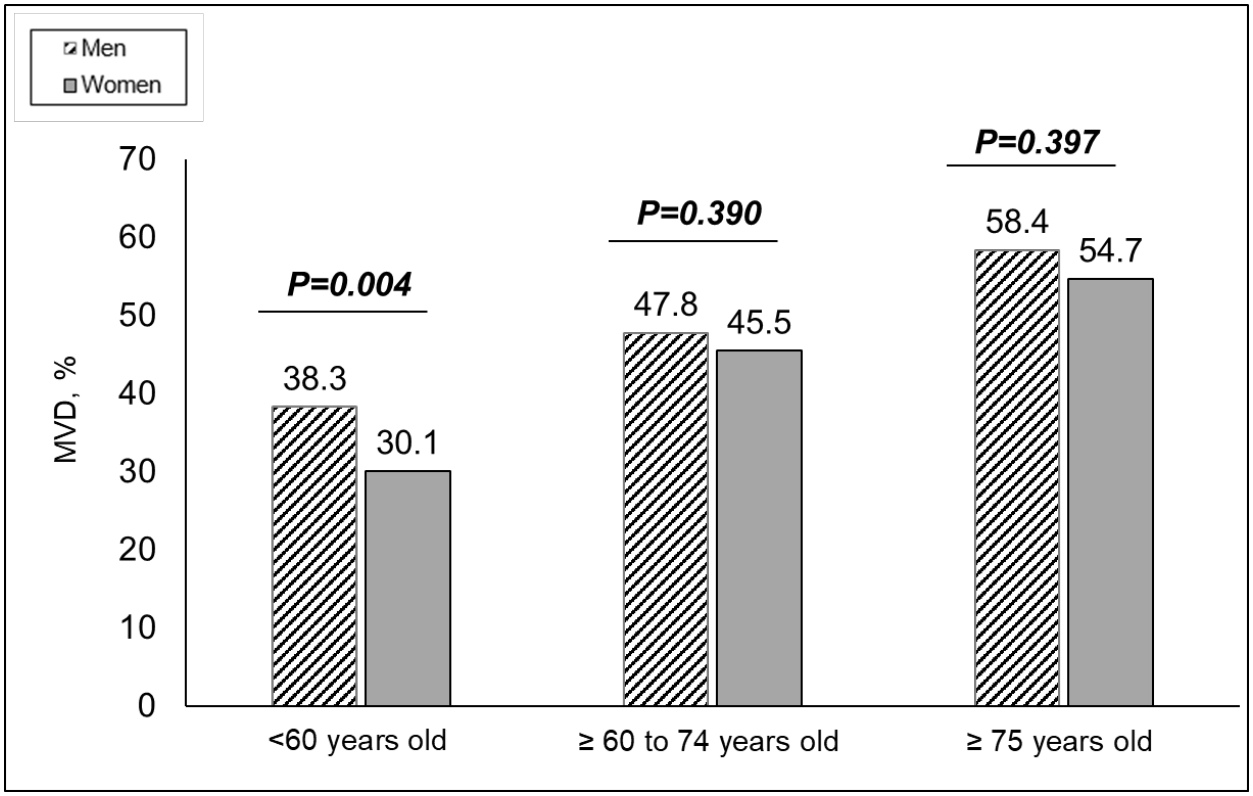
ǂ Heparins were calculated taking into account both Unfractionated Heparin and Enoxaparin

Supplemental Table 1 Angiographic and Procedural Characteristics sorted by sex

	Men N=3132	Women N=1117	P-value
Multivessel disease	42.6	42.0	0.76
Acute vessel closure	0.3	0.3	0.91
Bifurcation lesion	5.4	6.1	0.41
Acute thrombosis	0.6	1.0	0.20
Stent use	94.7	92.8	0.06
PCI anatomical angiographical success	96.1	94.3	0.01

Data are presented as percentages (%)
Abbreviations: PCI, percutaneous coronary intervention

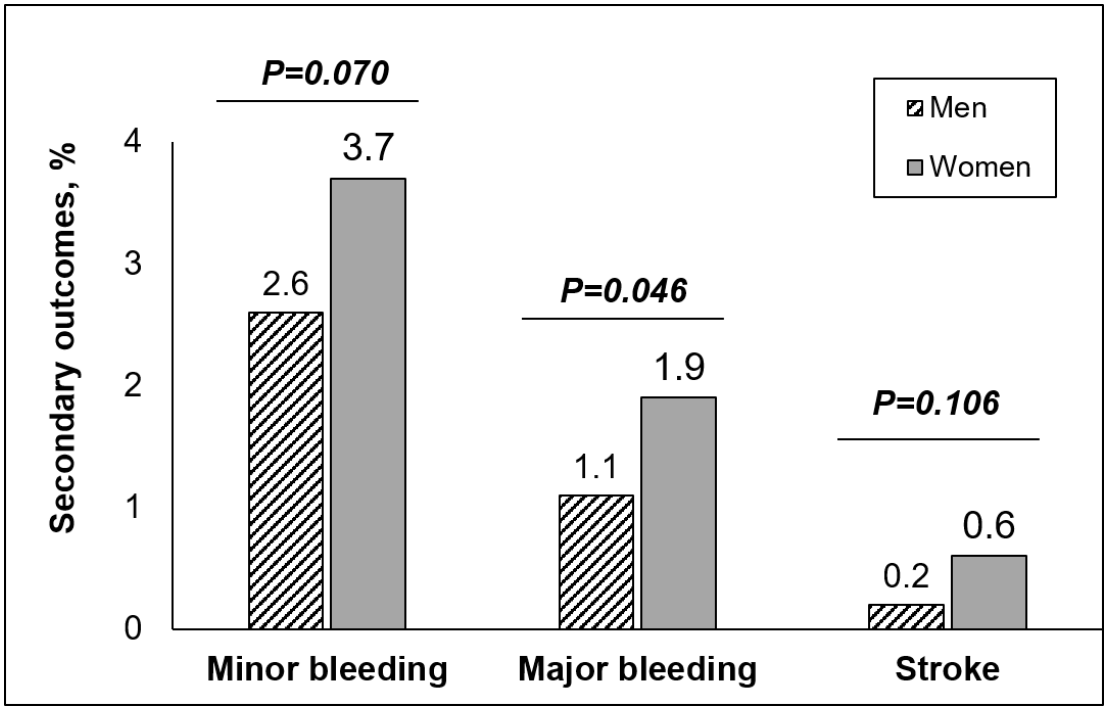
Supplemental Figure 3. Rates of multivessel disease in age categories sorted by sex



P value for comparison between women and men in the same age category

MVD= Multivessel disease

Supplemental Figure 4. Rates of secondary outcomes among patients who underwent primary PCI



Abbreviations: PCI, percutaneous coronary interventions

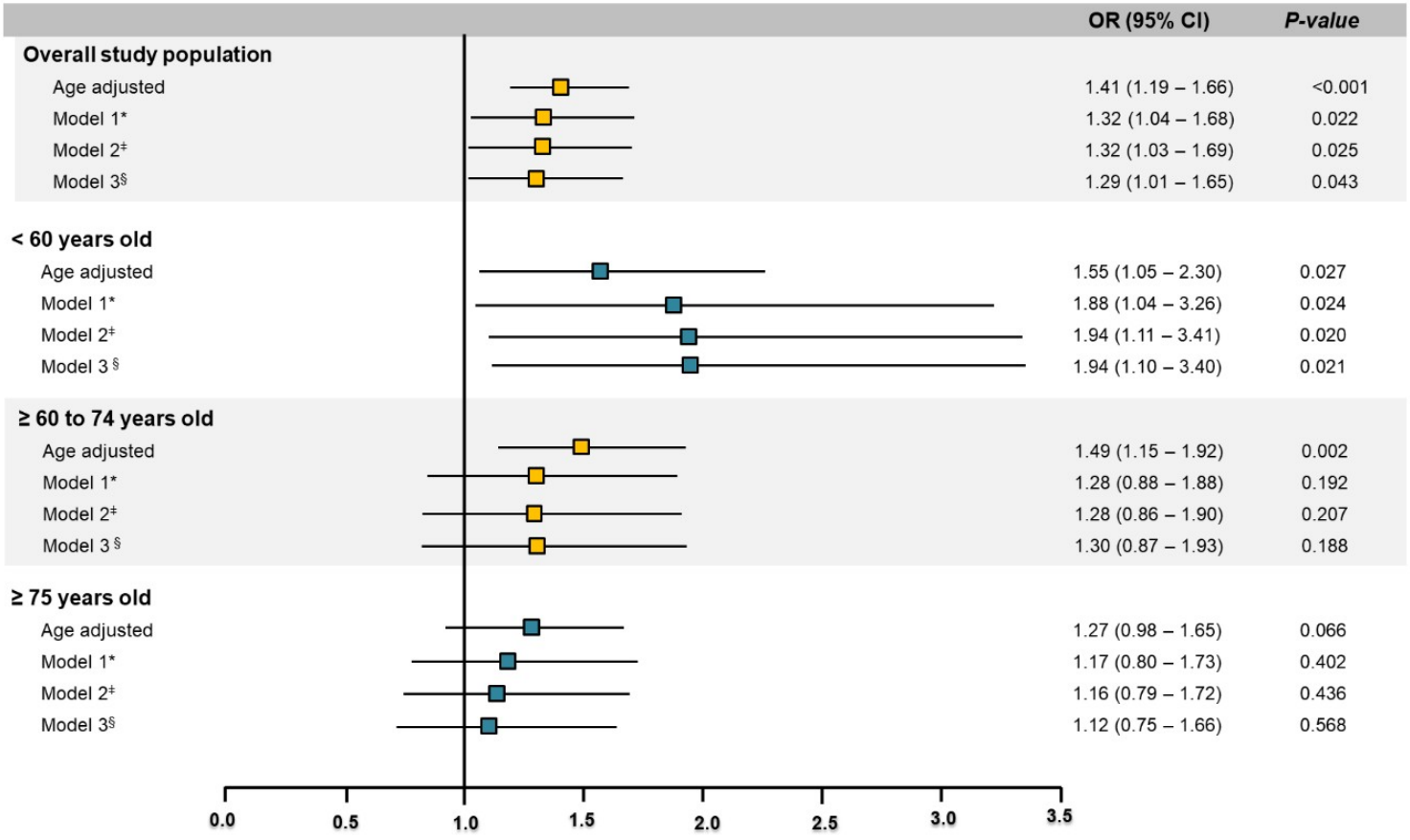
Supplemental Table 2. Multivariate analysis of factors associated with 30-day all-cause mortality including angiographic disease severity: women versus men

	Odds Ratio	95% CI	*P* value
Women	1.58	1.13 – 2.21	0.007
Age	1.05	1.03 – 1.07	<0.001
Diabetes mellitus	1.44	1.02 – 2.03	0.037
Hypertension	0.88	0.61 – 1.26	0.497
Current smoking	0.83	0.57 – 1.21	0.338
Prior angina pectoris	0.62	0.39 – 0.99	0.046
Prior MI	1.12	0.63 – 1.99	0.682
Prior PCI/prior CABG	1.15	0.55 – 2.37	0.701
Prior stroke	2.36	1.24 – 4.46	0.008
Prior HF	0.76	0.37 – 1.53	0.449
Killip Class ≥2	2.43	1.60 – 3.70	<0.001
HR at admission (SD increment) *	1.23	1.80 – 1.41	0.001
SBP at admission (SD increment) *	0.69	0.61 – 0.79	<0.001
Time to admission ≤ 2 hrs	0.96	0.64 – 1.44	0.874
Multi-vessel disease	1.63	1.17 – 2.27	0.004

*SDs for heart rate and systolic blood pressure in the overall population are 16.6 bpm and 23.8 mmHg

Abbreviations: **CABG** = coronary artery by-pass graft; **HF** = heart failure; **HR** = heart rate; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SBP** = systolic blood pressure

Supplemental Figure 5. Sequential logistic regression for the effect of medications within 24 hours and primary PCI on the odds of mortality for women versus men



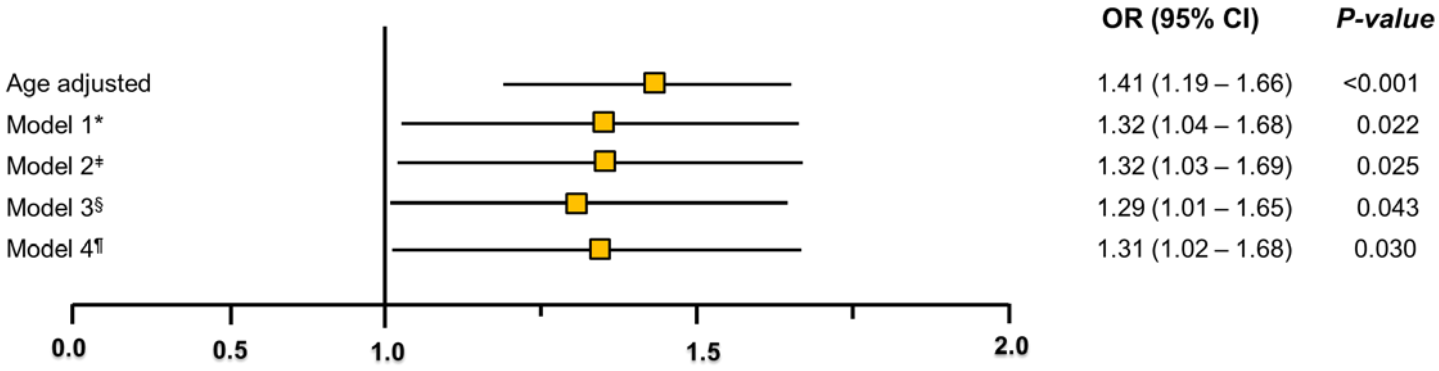
The following covariates are sequentially included in the adjusted models:

*Adjusted model 1: sex, age, diabetes mellitus, hypertension, current smoking, prior myocardial infarction, prior PCI, prior CABG, prior stroke, prior heart failure, prior angina pectoris, heart rate at admission, systolic blood pressure at admission, Killip Class ≥2 and time from symptoms onset to admission ≤ 2 hours

‡Adjusted Model 2: Model 1 including, aspirin, clopidrogrel and Unfractionated heparin

§Adjusted Model 3: Model 2 including use of primary PCI

Supplemental Figure 6. Sequential logistic regression for the effect of medications within 24 hours, primary PCI and PHE country variability on the odds of mortality for women versus men



The following covariates are sequentially included in the adjusted models:

*Adjusted model 1: sex, age, diabetes mellitus, hypertension, current smoking, prior myocardial infarction, prior PCI, prior CABG, prior stroke, prior heart failure, prior angina pectoris, heart rate at admission, systolic blood pressure at admission, Killip Class ≥2 and time from symptoms onset to admission ≤ 2 hours

ǂ Adjusted Model 2: Model 1 including, aspirin, clopidrogrel and Unfractionated heparin

§Adjusted Model 3: Model 2 including use of primary PCI

¶Adjusted Model 4: Model 3 including low versus high PHE countries

Abbreviations: PHE: Public Healthcare Expenditure

Sex-age interactions

Interaction tests

We tested (**Supplemental Table 3**) whether there is a significant interaction between sex (women versus men) and age (≤ 60 years versus ≥75 years) in function of the outcome (30-day mortality). We obtained the logs of the odds ratios 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= 0.0459 and its standard error 0.2408 (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= 0.1906, which gives P=0.4244 when we referred it to a table of the normal distribution (row 10). The estimated interaction effect was exp =1.0470 (row 11). The confidence interval for this effect was -0.4261 to 0.5179 on the log scale (row 9). Transforming back to the relative risk scale, we got 0.6530 to 1.6786 (row 12). There was thus no evidence to support a different outcome effect in younger and older women. We repeated the interaction test for age ≤ 60 years versus ≥60 to 74 years **(Supplemental Table 4)** and for age ≥60 to 74 years versus ≥75 years **(Supplemental Table 5)**. Still, there was no significant interactions between outcome and age categories.

Supplemental Table 3. Interaction test: calculations for comparing the estimated odd ratios of mortality of women versus men (<60 years versus ≥75 years)

		Group 1 [Age < 60] (n = 3806)	Group 2 [Age ≤75] (n = 1472)
1	**OR**	1.64	1.28
2	**log OR**	0.4947 (EE_1)	0.2469 (EE_2)
3	**95% CI for OR**	1.09 ~ 2.46	0.97 ~ 1.69
4	**95% CI for log OR**	0.0862 ~ 0.9002	-0.0305 ~ 0.5247
5	**Width of CI**	0.8140	0.5552
6	**SE (=width / (2*1.96))**	0.2076	0.1416
	Difference between log odd ratios		
7	**d** ($=EE_{11} - EE_{22}$)	**0.2478**	
8	**SE (d)**	**0.2514**	
9	**CI (d)**	**-0.2448 ~ 0.7405**	
10	**Test of Interaction**	**0.9860 (p-value: 0.1621)**	
	Ratio of odd ratios		
11	**ROR (=exp(d))**	1.2813	
12	**CI (ROR)**	0.7829 ~ 2.0969	

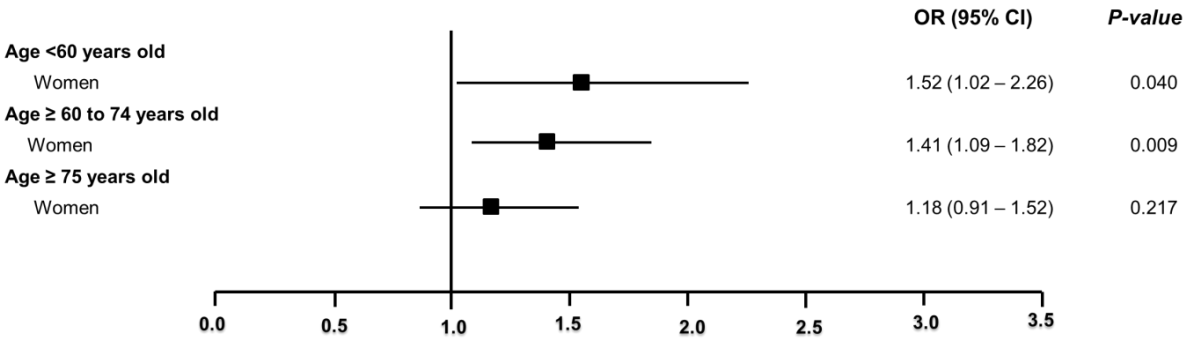
Supplemental Table 4. Interaction test: calculations for comparing the estimated odd ratios of mortality of women versus men (<60 years versus ≥60 to 74 years)

		Group 1 [Age <60] (n = 3806)	Group 2 [Age ≥60 to 74] (n = 3556)
1	**OR**	1.64	1.52
2	**log OR**	0.4947 (EE_1)	0.4187 (EE_2)
3	**95% CI for OR**	1.09 ~ 2.46	1.16 ~ 2.00
4	**95% CI for log OR**	0.0862 ~ 0.9002	0.1484 ~ 0.6931
5	**Width of CI**	0.8140	0.5447
6	**SE (=width / (2*1.96))**	0.2076	0.1390
	Difference between log odd ratios		
7	**d** ($=EE_{11} - EE_{22}$)	**0.0760**	
8	**SE (d)**	**0.2499**	
9	**CI (d)**	**-0.4137 ~ 0.5657**	
10	**Test of Interaction**	**0.3041 (p-value: 0.3805)**	
	Ratio of odd ratios		
11	**ROR (=exp(d))**	1.0789	
12	**CI (ROR)**	0.6612 ~ 1.7607	

Supplemental Table 5. Interaction test: calculations for comparing the estimated odd ratios of mortality of women versus men (≥60 to 74 years versus ≥75 years)

		Group 1 [Age ≥60 to 74] (n = 3556)	Group 2 [Age ≥75] (n = 1472)
1	**OR**	1.52	1.28
2	**log OR**	0.4187 (EE_2)	0.2469 (EE_2)
3	**95% CI for OR**	1.16 ~ 2.00	0.97 ~ 1.69
4	**95% CI for log OR**	0.1484 ~ 0.6931	-0.0305 ~ 0.5247
5	**Width of CI**	0.5447	0.5552
6	**SE (=width / (2*1.96))**	0.1390	0.1416
	Difference between log odd ratios		
7	**d (=$EE_{11} - EE_{22}$)**	**0.1719**	
8	**SE (d)**	**0.1984**	
9	**CI (d)**	**-0.2170 ~ 0.5607**	
10	**Test of Interaction**	**0.8661 (p-value: 0.1932)**	
	Ratio of odd ratios		
11	**ROR (=exp(d))**	1.1875	
12	**CI (ROR)**	0.8049 ~ 1.7520	

Supplemental Figure 7. Multivariate analysis of 30-day mortality in the three age subgroups using kNN imputation



Adjusted for: sex, age, diabetes mellitus, hypertension, current smoking, prior myocardial infarction, prior PCI, prior CABG, prior stroke, prior heart failure, prior angina pectoris, heart rate at admission, systolic blood pressure at admission, Killip Class ≥2 and time from symptoms onset to admission ≤ 2 hours.

Inverse probability of treatment weighting

Supplemental Table 6. Inverse probability of treatment weighting: 30-day mortality among women compared with men in patients <60 years old.

	Women (n=757)	Men (n=3049)	*P* value
Age	50.7 ± 6.6	50.7 ± 6.8	0.88
Risk factors			
Diabetes	17.1%	16.9%	0.90
Hypertension	54.6%	54.9%	0.88
Current smoking	57.0%	57.0%	0.99
History of ischemic heart disease			
Prior angina pectoris	11.4%	11.2%	0.89
Prior MI	10.6%	11.1%	0.75
Prior PCI	12.2%	12.6%	0.76
Prior CABG	0.6%	0.7%	0.91
History of cardiovascular disease			
Prior stroke	2.0%	2.0%	0.98
Prior HF	2.5%	2.4%	0.85
Clinical presentation at admission			
HR at admission	80.0 ± 15.0	80.2 ± 15.6	0.78
SBP at admission	139.3 ± 23.9	139.5 ± 22.7	0.79
Time to admission ≤ 2 hrs	28.7%	29.2%	0.81
Outcomes			
30-day mortality	4.7%	3.0%	0.0270
OR (95% CI)	1.56 (1.05 – 2.32)		0.0282

Values are percentages, mean ± standard deviation and odd ratios (OR) and 95% confidence intervals (CI)

Abbreviations**: CABG** = coronary artery by-pass graft; **HF** = heart failure; **HR** = heart rate; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SBP** = systolic blood pressure

Supplemental Table 7. Inverse probability of treatment weighting: 30-day mortality among women compared with men in patients ≥60 to 74 years old.

	Women (n=1194)	Men (n=2362)	*P* value
Age	66.2 ± 4.5	66.2 ± 4.4	0.97
Risk factors			
Diabetes	27.9%	28.1%	0.93
Hypertension	71.1%	70.7%	0.81
Current smoking	33.6%	33.5%	0.98
History of ischemic heart disease			
Prior angina pectoris	16.0%	15.9%	0.92
Prior MI	12.9%	13.2%	0.79
Prior PCI	10.9%	11.4%	0.64
Prior CABG	1.6%	1.8%	0.65
History of cardiovascular disease			
Prior stroke	5.5%	5.3%	0.88
Prior heart failure	4.0%	4.1%	0.95
Clinical presentation at admission			
HR at admission	80.1 ± 17.2	80.1 ± 16.5	0.96
SBP at admission	139.8 ± 25.0	139.9 ± 23.4	0.91
Time to admission ≤ 2 hrs	22.3%	22.4%	0.95
Outcomes			
30-day mortality	9.2%	6.4%	0.0024
OR (95% CI)	1.49 (1.15 – 1.92)		0.0025

Values are percentages, mean ± standard deviation and odd ratios (OR) and 95% confidence intervals (CI)

Abbreviations**: CABG** = coronary artery by-pass graft; **HF** = heart failure; **HR** = heart rate; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SBP** = systolic blood pressure

Supplemental Table 8. Inverse probability of treatment weighting: 30-day mortality among women compared with men in patients ≥ 75 years old.

	Women (n=706)	**Men (n=766)**	***P* value**
Age	79.7 ± 4.1	79.7 ± 4.1	0.97
Risk factors			
Diabetes	29.0%	29.1%	0.99
Hypertension	71.6%	71.8%	0.93
Current smoking	12.5%	12.0%	0.78
History of ischemic heart disease			
Prior angina pectoris	19.5%	19.6%	0.98
Prior MI	14.5%	14.6%	0.96
Prior PCI	9.1%	9.5%	0.81
Prior CABG	1.9%	1.8%	0.83
History of cardiovascular disease			
Prior stroke	7.7%	7.8%	0.92
Prior heart failure	7.8%	7.6%	0.88
Clinical presentation at admission			
HR at admission	81.5 ± 18.2	81.6 ± 19.4	0.90
SBP at admission	137.1 ± 25.4	137.3 ± 26.0	0.87
Time to admission ≤ 2 hrs	17.9%	17.7%	0.94
Outcomes			
30-day mortality	20.9%	17.9%	0.1487
OR (95% CI)	1.21 (0.93 – 1.57)		0.1490

Values are percentages, mean ± standard deviation and odd ratios (OR) and 95% confidence intervals (CI)

Abbreviations**: CABG** = coronary artery by-pass graft; **HF** = heart failure; **HR** = heart rate; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SBP** = systolic blood pressure

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