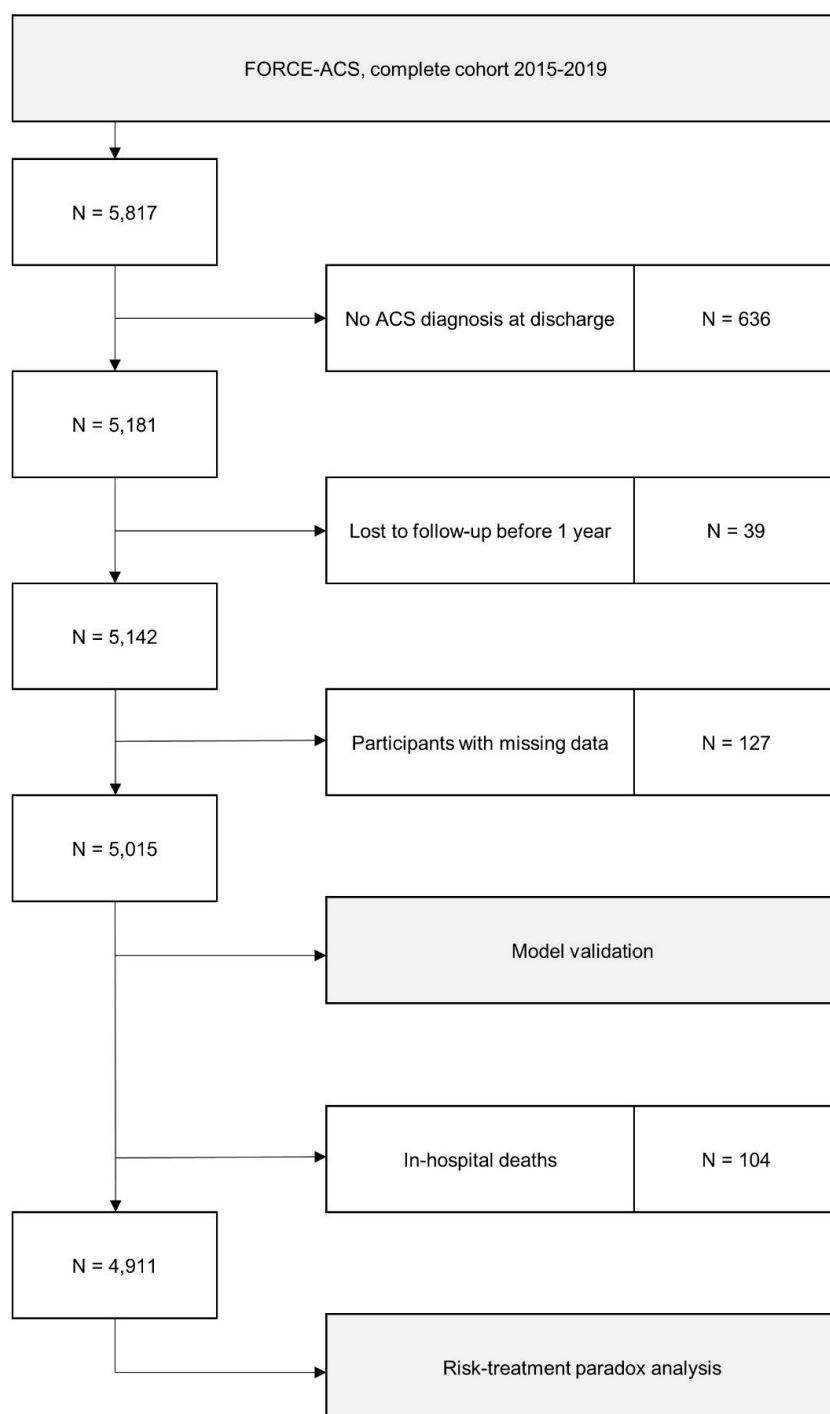


Supplementary Appendix**External validation of the GRACE risk score and the risk-treatment paradox in acute coronary syndrome patients**

Supplementary Figure 1.	Study flowchart
Supplementary Table 1.	Cause of death specification
Supplementary Figure 2.	ROC curve per sex
Supplementary Figure 3.	ROC curve per age category
Supplementary Figure 4.	ROC curve per type of ACS
Supplementary Figure 5.	ROC curve per PRECISE-DAPT score strata
Supplementary Figure 6.	Calibration plot per sex
Supplementary Figure 7.	Calibration plot per age category
Supplementary Figure 8.	Calibration plot per type of ACS
Supplementary Figure 9.	Calibration plot per PRECISE-DAPT score strata
Supplementary Figure 10.	All-cause mortality according to treatment status per GRACE risk score strata including in-hospital deaths
Supplementary Table 2.	Predictors for receiving optimal guideline-recommended care per GRACE risk score strata

**Supplementary Figure 1.** Flowchart of the FORCE-ACS validation cohort

ACS denotes acute coronary syndrome.

**Supplementary Table 1.** Observed rates of in-hospital and one-year mortality specified for cause of death in the FORCE-ACS validation cohort

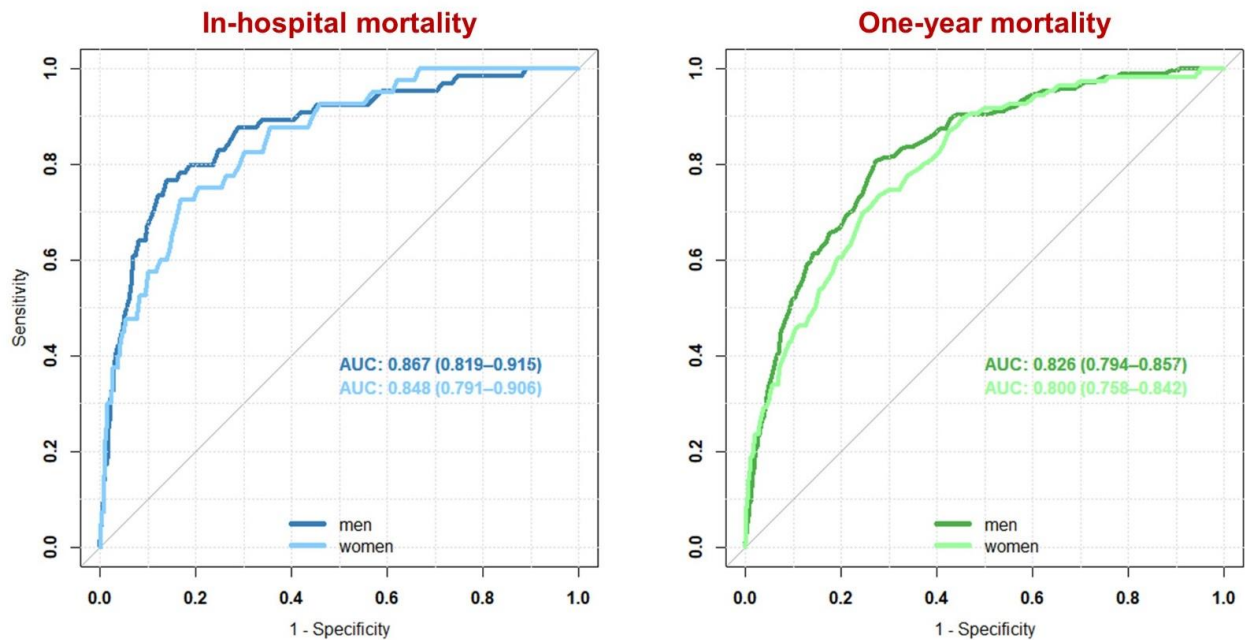
	N	No. of events†		
		All-cause mortality (%)	Cardiovascular mortality (%)	Non-cardiovascular mortality (%)
<b>In-hospital mortality</b>	5,015	104 (2.1%)	93 (1.9%)	11 (0.2%)
Men	3,574	64 (1.8%)	55 (1.5%)	9 (0.3%)
Women	1,441	40 (2.8%)	38 (2.6%)	2 (0.1%)
<75 years	3,586	38 (1.1%)	35 (1.0%)	3 (0.1%)
≥75 years	1,429	66 (4.6%)	58 (4.1%)	8 (0.6%)
NSTE-ACS	2,965	39 (1.3%)	35 (1.2%)	4 (0.1%)
STE-ACS	2,050	65 (3.2%)	58 (2.8%)	7 (0.3%)
PRECISE-DAPT score <25	3,408*	26 (0.8%)	24 (0.7%)	2 (0.1%)
PRECISE-DAPT score ≥25	1,510*	75 (5.0%)	66 (4.4%)	9 (0.6%)
<b>One-year mortality</b>	5,015	271 (5.4%)	204 (4.1%)	67 (1.3%)
Men	3,574	165 (4.6%)	119 (3.3%)	46 (1.3%)
Women	1,441	106 (7.4%)	85 (5.9%)	21 (1.5%)
<75 years	3,586	90 (2.5%)	68 (1.9%)	22 (0.6%)
≥75 years	1,429	181 (12.7%)	136 (9.5%)	45 (3.1%)
NSTE-ACS	2,965	157 (5.3%)	116 (3.9%)	41 (1.4%)
STE-ACS	2,050	114 (5.6%)	88 (4.3%)	26 (1.3%)
PRECISE-DAPT score <25	3,408*	63 (1.8%)	47 (1.4%)	16 (0.5%)
PRECISE-DAPT score ≥25	1,510*	200 (13.2%)	150 (9.9%)	50 (3.3%)

\* The PRECISE-DAPT score could not be calculated in 97 cases (1.9%).

† Cause of death was assumed to be cardiovascular unless a non-cardiovascular cause could be identified.

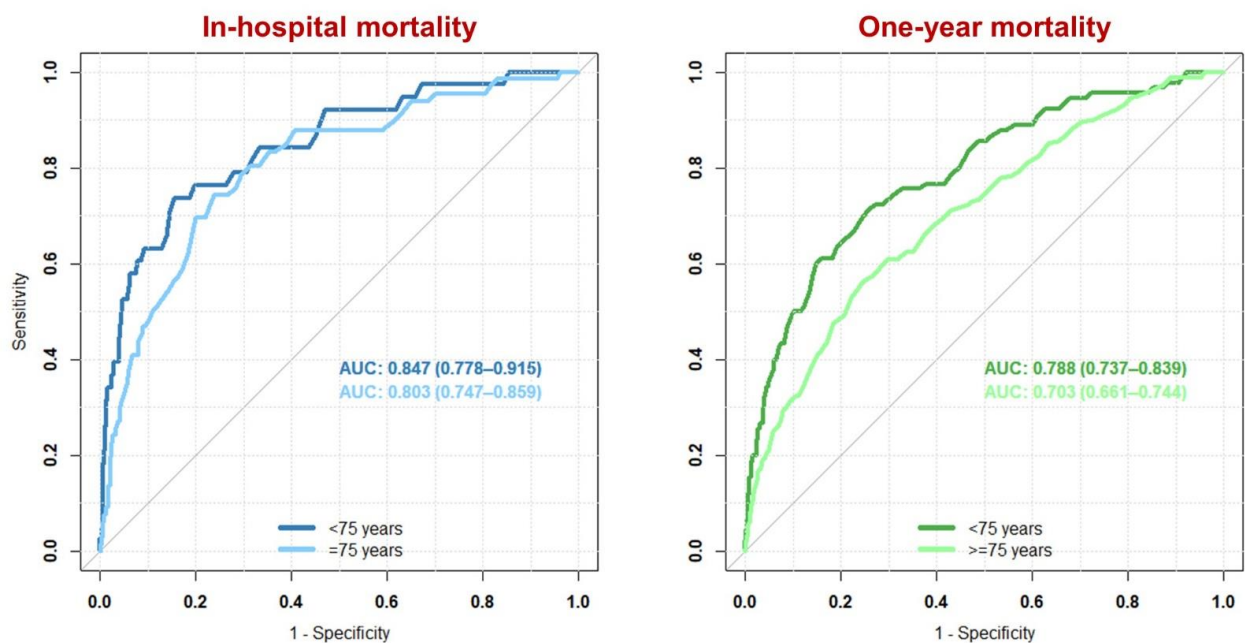
NSTE-ACS denotes non-ST-segment elevation acute coronary syndrome and STE-ACS ST-segment elevation acute coronary syndrome.

**Supplementary Figure 2.** Receiver operating characteristic curve of the GRACE risk score for in-hospital and one-year mortality for men and women separately



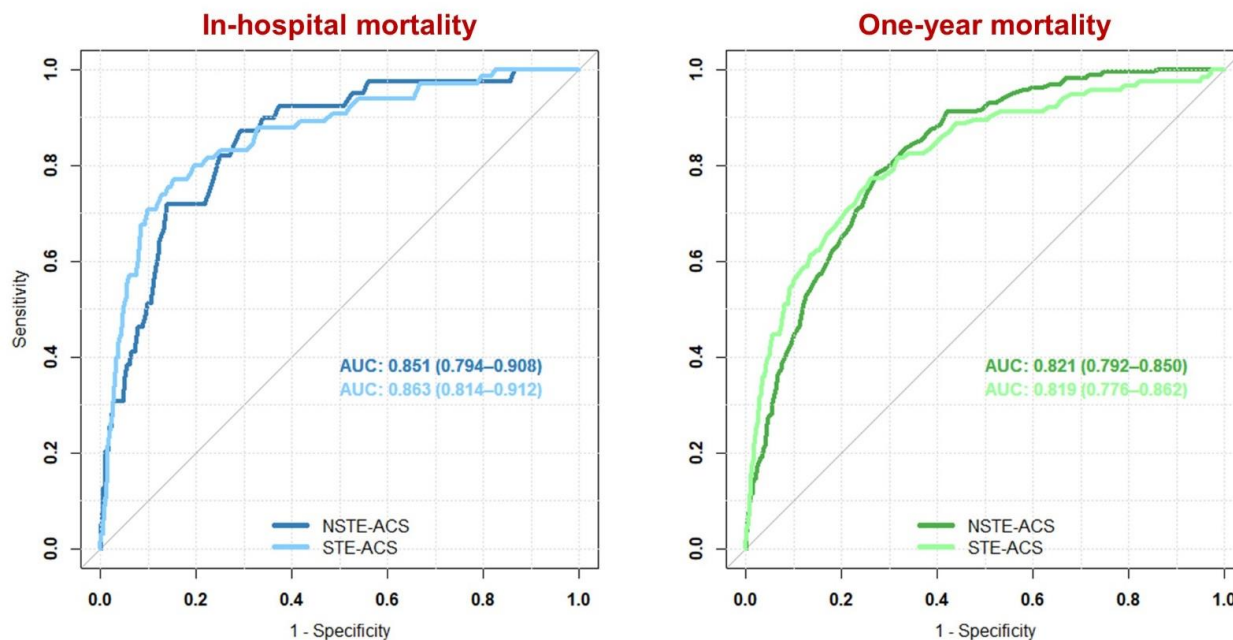
AUC denotes area under the curve.

**Supplementary Figure 3.** Receiver operating characteristic curve of the GRACE risk score for in-hospital and one-year mortality for patients <75 years and ≥75 years separately



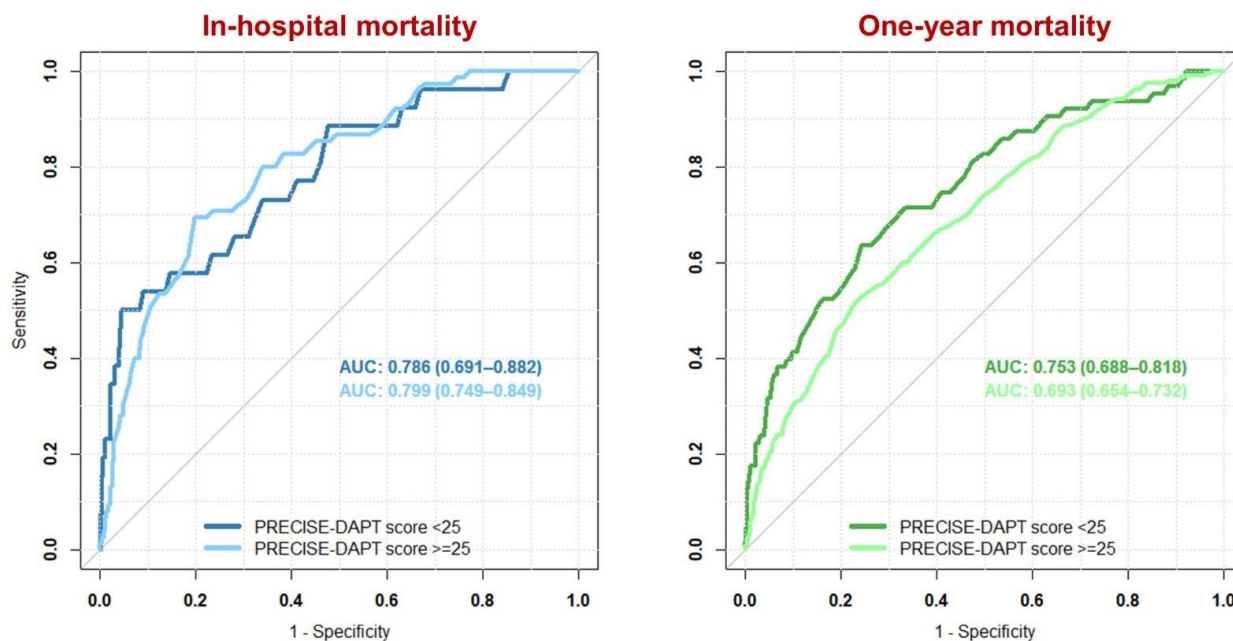
AUC denotes area under the curve.

**Supplementary Figure 4.** Receiver operating characteristic curve of the GRACE risk score for in-hospital and one-year mortality for NSTEMI-ACS and STEMI-ACS patients separately



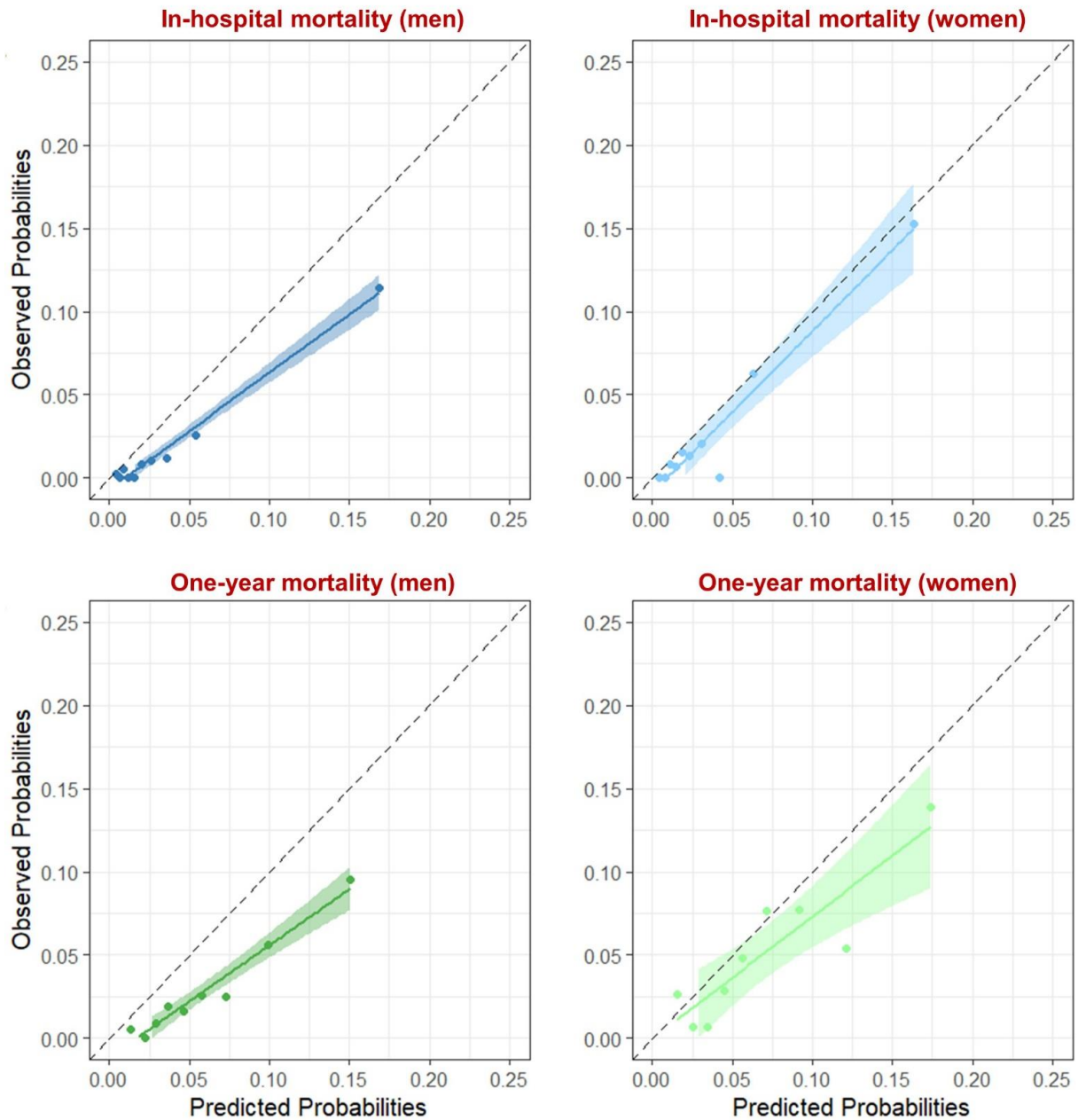
AUC denotes area under the curve, NSTEMI-ACS non-ST-segment elevation acute coronary syndrome and STEMI-ACS ST-segment elevation acute coronary syndrome.

**Supplementary Figure 5.** Receiver operating characteristic curve of the GRACE risk score for in-hospital and one-year mortality for patients without and with a high PRECISE-DAPT score separately



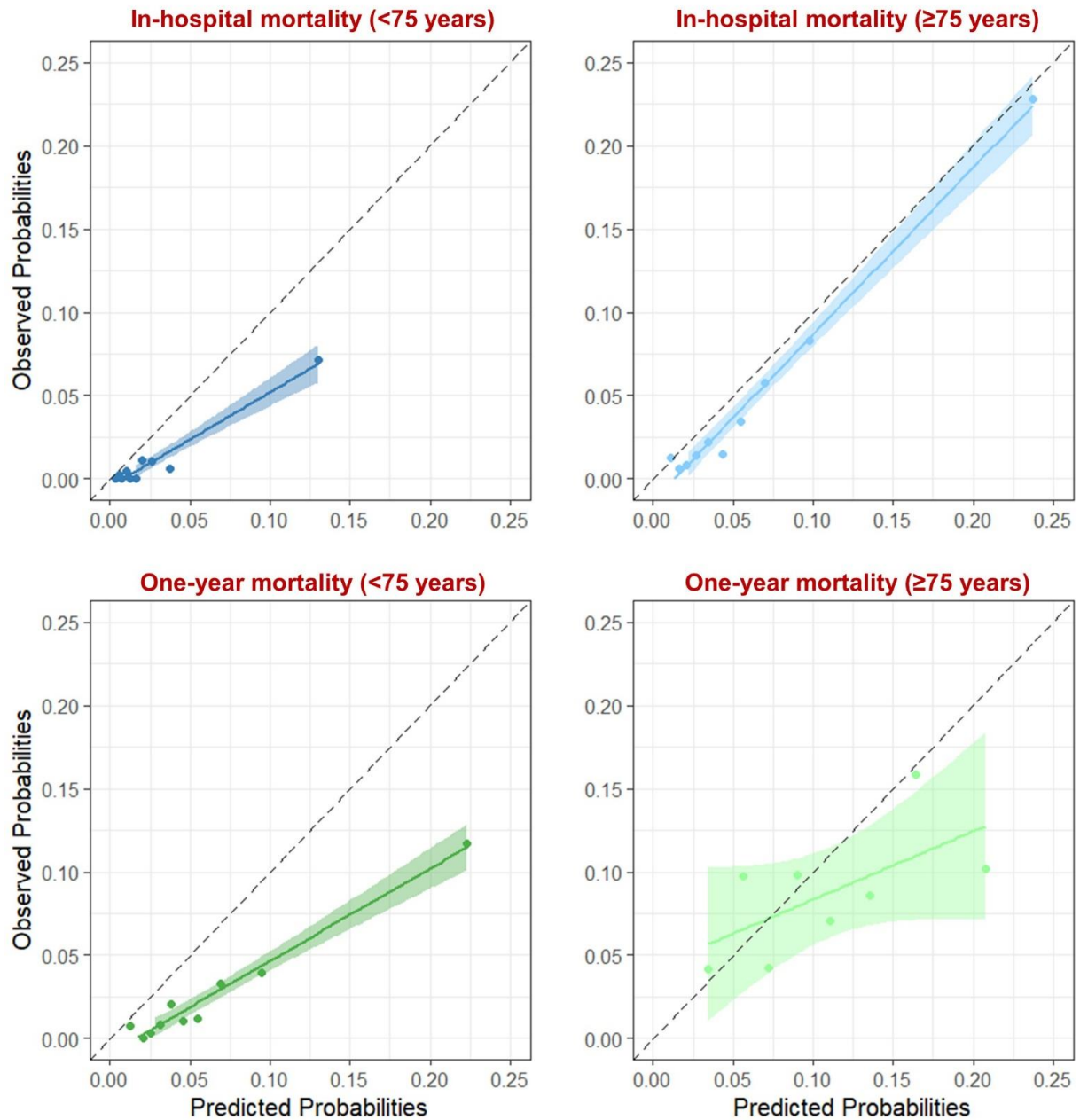
AUC denotes area under the curve.

**Supplementary Figure 6.** Calibration plot of the GRACE risk score for in-hospital and one-year mortality for men and women separately



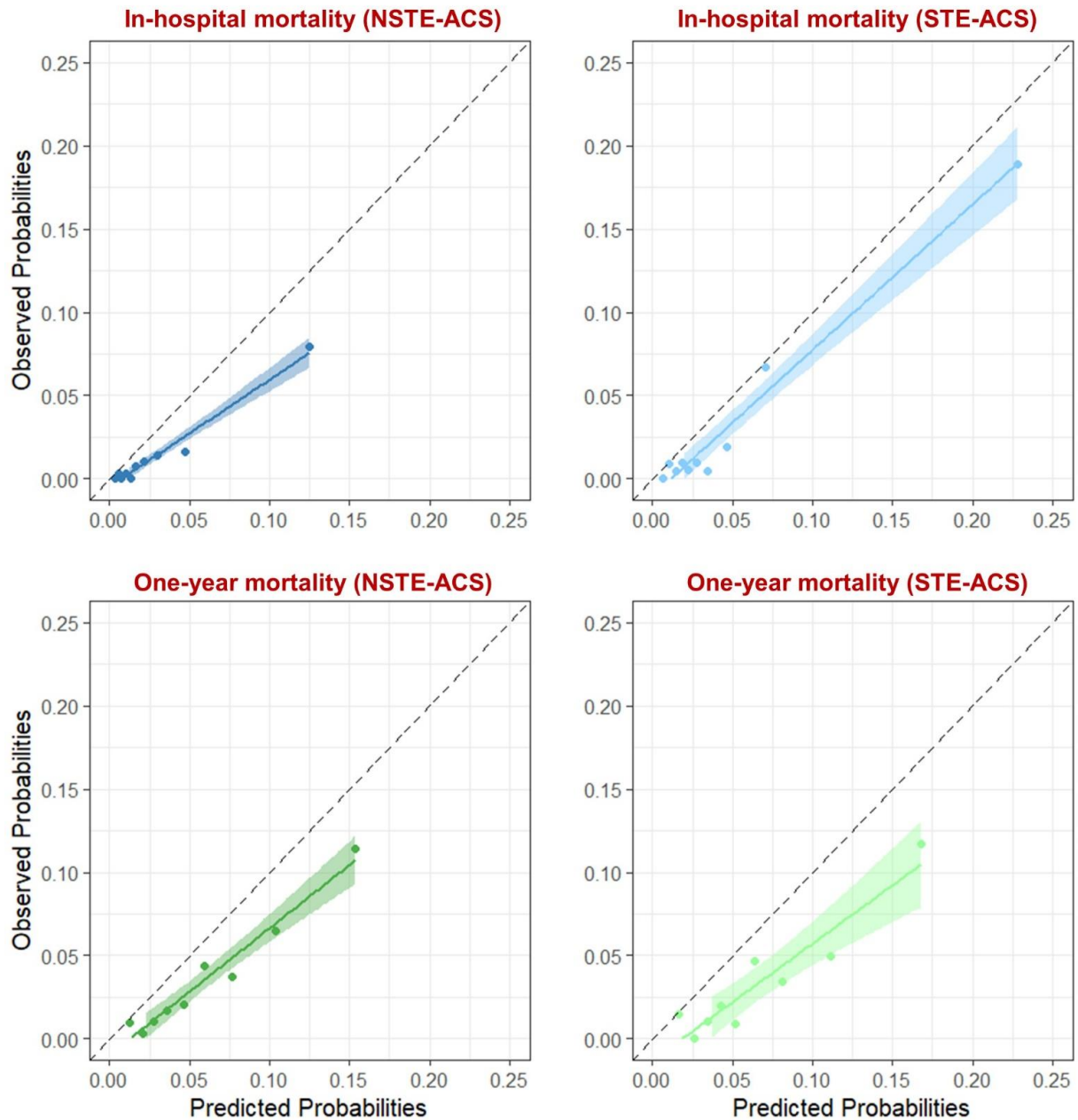
Patients were divided into deciles based on the predicted risk of mortality, each data point represents one decile. The dashed line shows absolute agreement between the observed and predicted rates.

**Supplementary Figure 7.** Calibration plot of the GRACE risk score for in-hospital and one-year mortality for patients <75 years and  $\geq 75$  years separately



Patients were divided into deciles based on the predicted risk of mortality, each data point represents one decile. The dashed line shows absolute agreement between the observed and predicted rates.

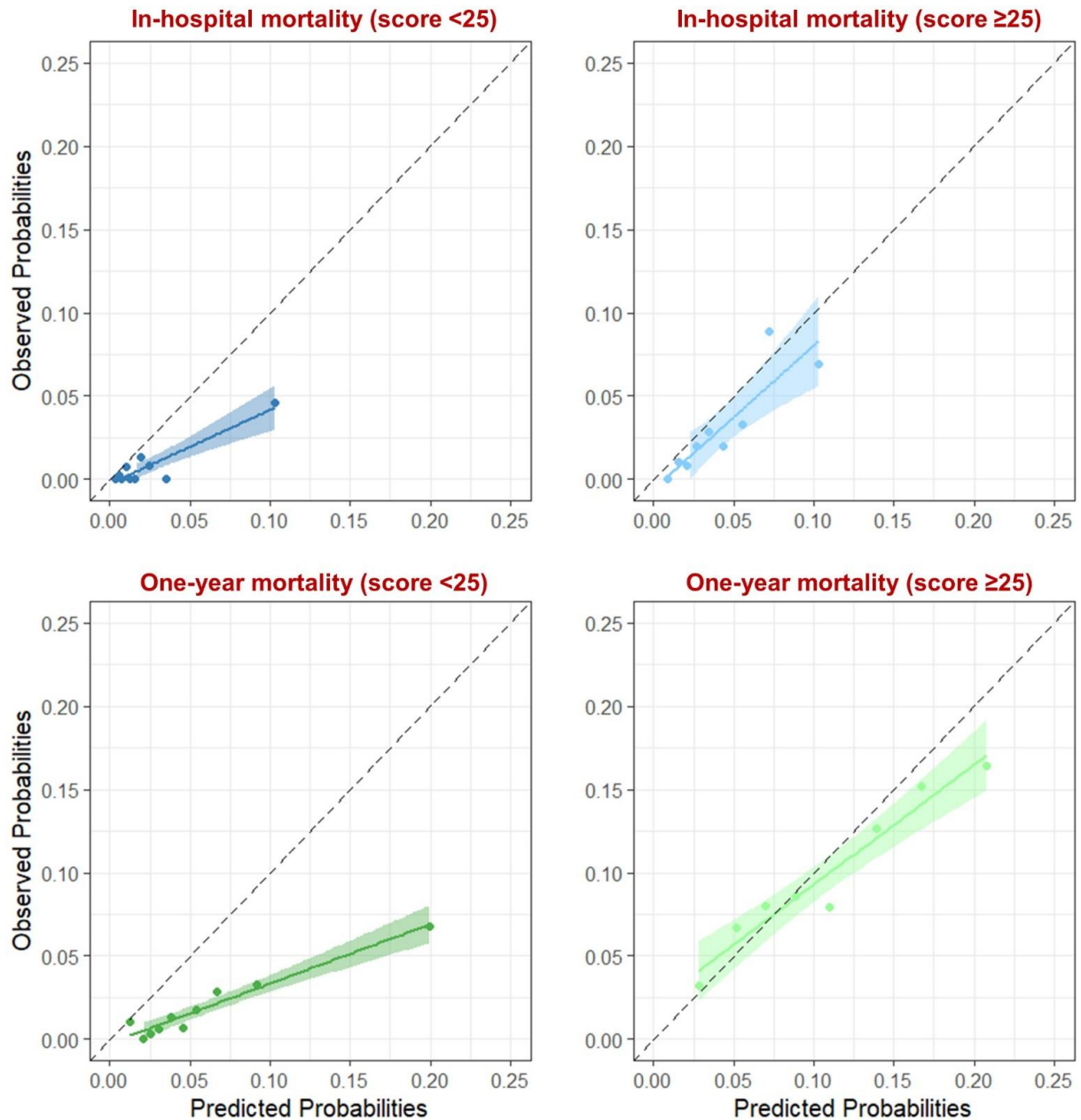
**Supplementary Figure 8.** Calibration plot of the GRACE risk score for in-hospital and one-year mortality for NSTEMI-ACS and STEMI-ACS patients separately



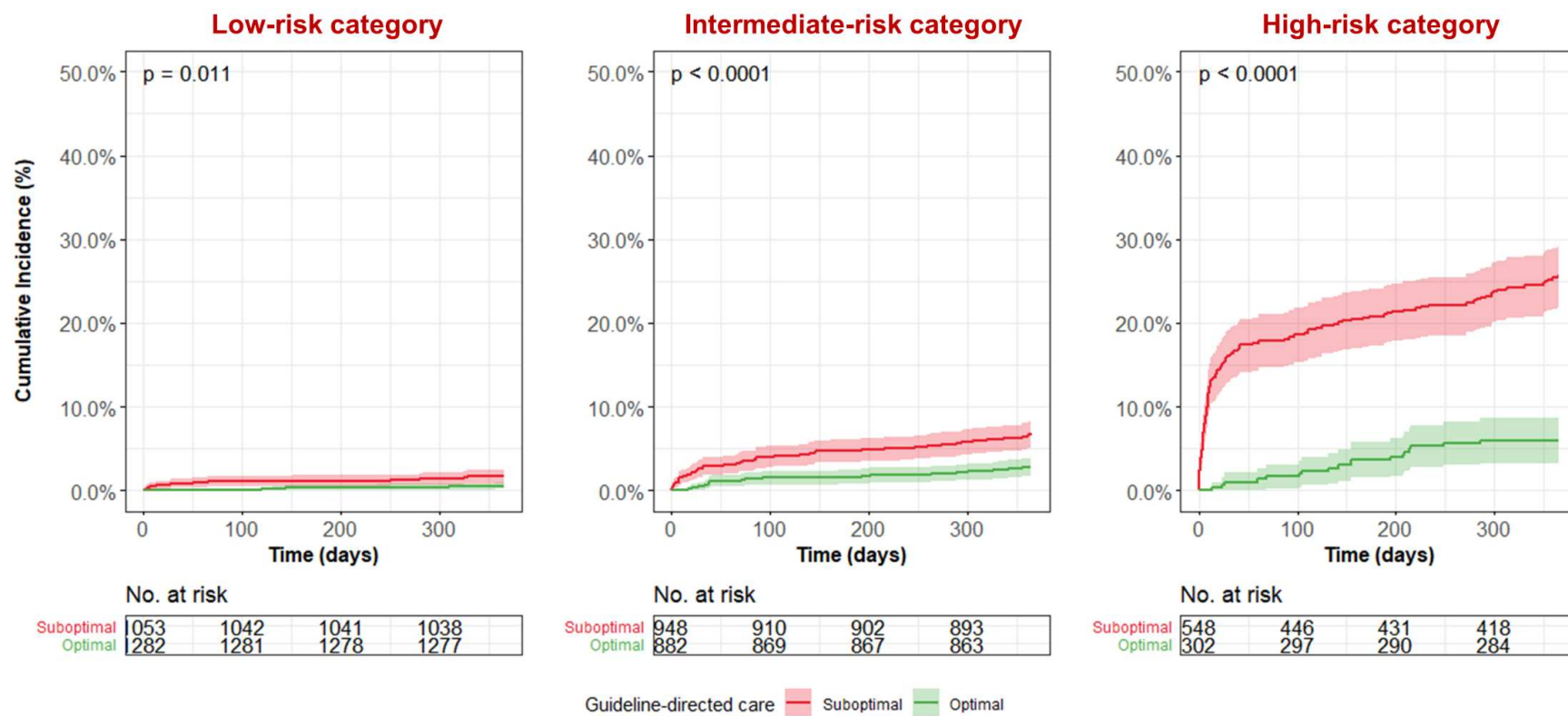
Patients were divided into deciles based on the predicted risk of mortality, each data point represents one decile. The dashed line shows absolute agreement between the observed and predicted rates. NSTEMI-ACS denotes non-ST-segment elevation acute coronary syndrome and STEMI-ACS ST-segment elevation acute coronary syndrome.



**Supplementary Figure 9.** Calibration plot of the GRACE risk score for in-hospital and one-year mortality for patients without and with a high PRECISE-DAPT score separately



Patients were divided into deciles based on the predicted risk of mortality, each data point represents one decile. The dashed line shows absolute agreement between the observed and predicted rates.

**Supplementary Figure 10.** All-cause mortality according to treatment status for the low-, intermediate- and high-risk categories (sensitivity analysis)

**Supplementary Table 2.** Predictors for receiving optimal guideline-recommended care in the low-, intermediate- and high-risk categories

	Low-risk category		Intermediate-risk category		High-risk category	
	Unadjusted OR (95%-CI)	Adjusted OR (95%-CI)	Unadjusted OR (95%-CI)	Adjusted OR (95%-CI)	Unadjusted OR (95%-CI)	Adjusted OR (95%-CI)
Age (for each increase of 10 yrs.)	0.84 (0.77-0.92)	0.90 (0.81-0.99)	0.78 (0.69-0.88)	-	0.69 (0.59-0.83)	0.77 (0.64-0.92)
Female sex	0.79 (0.66-0.96)	0.77 (0.63-0.93)	1.07 (0.88-1.31)	-	0.66 (0.48-0.90)	0.68 (0.49-0.96)
Current smoker	1.08 (0.92-1.28)	-	1.06 (0.85-1.32)	-	1.38 (0.90-2.12)	-
Hypertension	1.17 (0.99-1.38)	-	1.21 (1.00-1.46)	-	1.15 (0.84-1.56)	-
Hyperlipidemia	1.04 (0.89-1.23)	-	1.11 (0.92-1.34)	-	0.80 (0.60-1.07)	-
Diabetes mellitus	0.88 (0.71-1.08)	-	0.90 (0.72-1.12)	-	0.94 (0.67-1.33)	-
Prior stroke or TIA	0.79 (0.55-1.14)	-	0.79 (0.59-1.06)	-	0.65 (0.42-1.00)	-
Prior MI	0.85 (0.69-1.04)	-	0.85 (0.68-1.06)	-	0.85 (0.61-1.17)	-
Prior PCI	0.76 (0.62-0.93)	-	0.88 (0.71-1.09)	-	0.67 (0.47-0.96)	-
Prior CABG	0.78 (0.54-1.12)	-	0.65 (0.48-0.87)	-	0.73 (0.48-1.11)	-
Heart rate (for each increase of 10 bpm)	1.13 (1.06-1.18)	1.10 (1.05-1.17)	1.04 (1.00-1.09)	-	1.04 (0.99-1.09)	-
SBP (for each increase of 10 mmHg)	1.04 (1.01-1.08)	1.09 (1.05-1.17)	1.02 (0.98-1.05)	-	1.01 (0.99-1.06)	-
Serum creatinine (for each increase of 10 $\mu$ mol/L)	0.97 (0.93-1.00)	-	0.96 (0.93-0.99)	-	0.98 (0.96-1.00)	-
STE-ACS diagnosis	1.77 (1.49-2.11)	1.88 (1.55-2.27)	2.16 (1.79-2.61)	2.16 (1.79-2.61)	2.29 (1.70-3.07)	2.18 (1.60-2.97)
Cardiac arrest at admission	N/A	-	1.63 (0.91-2.93)	-	1.81 (1.21-2.70)	-
Cardiogenic shock	N/A	-	N/A	-	2.10 (1.09-4.02)	-
PRECISE-DAPT score $\geq 25^*$	0.83 (0.61-1.13)	-	0.80 (0.66-0.96)	-	0.65 (0.46-0.91)	-

Predictors in the adjusted model were selected using forward stepwise selection at an  $\alpha$  of 0.05.

\* PRECISE-DAPT score could not be calculated in 46, 29 and 19 cases in the low-risk, intermediate-risk and high-risk category, respectively.

CABG denotes coronary artery bypass grafting, CI confidence interval, MI myocardial infarction, PCI percutaneous coronary intervention, OR odds ratio, SBP systolic blood pressure, STE-ACS ST-segment elevation acute coronary syndrome and TIA transient ischemic attack.