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Supplementary appendix

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Supplementary Material Accompanying:
Extension of the GRACE score for non-ST-elevation acute coronary syndrome: a development and validation study in ten countries

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Description of the statistical analyses (detailed)

Datasets

In the UK, data of patients were retrieved from the Myocardial Ischaemia National Audit Project (MINAP), a prospective nation-wide registry of patients with ACS admitted to all acute care hospitals within the National Health System (NHS). Collectively, the MINAP represents one of the largest single health-care system ACS registries globally, and depicts the complete patient pathway from onset of symptom to hospital discharge.[1,2] MINAP documents patient demographics, clinical characteristics and investigations, medical history, medication before admission, information on type of the primary reperfusion, in-hospital medication, and clinical complications.[1] Among 1 067 439 patients presenting with ACS to any of the hospitals participating in England, Wales, and Northern Ireland between Jan 1, 2005, and Mar 31, 2017, 400 054 patients with a discharge diagnosis of NSTE-ACS were included.[1,2]

In Sweden, we used data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART), a prospective nation-wide registry of patients with ACS. Over 100 variables are prospectively collected from patients, including patient characteristics, admission information, risk factors, medical history, medication prior to admission, electrocardiographic changes, laboratory parameters, additional clinical features and investigations, in-hospital medication, interventions, hospital outcome, discharge diagnosis, and medication at discharge.[3] Among 251 262 patients presenting with ACS to any of the participating hospitals in Sweden between Jan 1, 2005, and Jan 16, 2022, 172 634 patients had a diagnosis of NSTE-ACS.

In Switzerland, we used data from the nation-wide Acute Myocardial Infarction in Switzerland (AMIS) Plus registry (NCT01305785) as well as the Special Programme University Medicine Acute Coronary Syndrome (SPUM-ACS) cohort (NCT01000701). AMIS Plus is a prospective national registry of patients admitted to Swiss hospitals with ACS. Patient demographics, symptoms, risk factors, laboratory parameters, invasive therapy, complications and medication are collected. Between Jan 1, 2005, and Sep 30, 2023, 53 832 patients were admitted with ACS, of which 22 706 patients with NSTE-ACS were included. The prospective multicentre SPUM-ACS cohort study includes 4787 consecutive patients with ACS admitted to four major university hospitals in Switzerland between Dec 8, 2009, and Dec 31, 2017. Of these, 2239 had a diagnosis of NSTE-ACS. All diagnoses in SPUM-ACS were independently confirmed by blinded study personnel.[4] Patients enrolled in both AMIS Plus and SPUM-ACS were considered only once, as appropriate. In Switzerland, overlapping records (n=1167) were removed from AMIS Plus. In case of conflicting variable values, values from SPUM-ACS were used, given its external event adjudication.

In Germany, patient data were retrieved from the prospective Heidelberg-ACS cohort study.[5-7] Heidelberg-ACS enrolled 2517 consecutive patients with ACS presenting to Heidelberg University Hospital between Jun 9, 2009, and May 10, 2014, of which 2034 patients had a final diagnosis of NSTE-ACS.[8] All diagnoses in Heidelberg-ACS were independently adjudicated by two cardiologists using all clinical information available, including biomarker findings, imaging data, and results from invasive coronary angiography. In case of disagreement, a consensus was reached with the help of a third cardiologist.

In Denmark, we used data from the Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography (VERDICT) trial (NCT02061891).[9-11] VERDICT is the largest trial on the timing of invasive management in contemporary patients with NSTE-ACS. It included patients ≥ 18 years of age, with clinical suspicion of ACS, and ≥ 1 of the following high-risk criteria: (1) ECG changes indicative of new ischemia (ie, novel ST-segment depression, horizontal or down-sloping ≥ 0.05 mV in 2 consecutive leads, inversion of T-wave < 0.01 mV in two leads with prominent R wave or R/S ratio >1) and (2) increased troponin markers.[9] Inability to understand trial information, active pregnancy, clinical necessity for acute invasive coronary angiography, survival expectancy < 1 year, and known intolerance to heparin, platelet inhibitors, or x-ray contrast medium, comprised exclusion criteria.[9] VERDICT comprises 2147 patients with NSTE-ACS presenting to one of nine hospitals in the Capital Region of Copenhagen, Denmark, between Nov 26, 2010, and Apr 29, 2016.

In Spain, patient data were retrieved from the Incidence and Predictors of Heart Failure after Acute Coronary Syndromes (CORALYS-ACS) registry (NCT04895176).[12] Inclusion criteria were patient age > 18 years, confirmed diagnosis of ACS (including NSTE-ACS and STEMI), and treatment of ACS with PCI. Patients with previous hospitalisations for heart failure, known history of congestive heart failure, or left ventricular ejection fraction < 50% were excluded.[12] CORALYS enrolled 1928 patients with ACS in Spain between Jan 1, 2014, and Sep 27, 2020. Diagnosis of NSTE-ACS and STEMI was based on the 2016[13] and 2020[14] guideline by the European Society of Cardiology (ESC). Overall, 1061 patients with NSTE-ACS were included.

In the Netherlands, we used data from the prospective multicentre Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) registry (NCT03823547).[15,16] In FORCE-ACS, 6747 consecutive patients aged 18 years and above with suspected ACS (ie, NSTE-ACS and STEMI) were enrolled between Jan 1, 2015, and Mar 18, 2023 in one of nine study centres across the Netherlands.[15] A total of 3949 patients had a final diagnosis of NSTE-ACS, based on current guidelines.[15,16] All diagnoses in FORCE-ACS were independently adjudicated by blinded investigators. Patients were followed-up at one, twelve, 24, and 36 months after hospital admission.[15]

In Czechia, we used pooled data from two prospective cohorts recruited at the University Hospital Brno (Brno-ACS).[17,18] The first prospective cohort enrolled patients admitted for ACS to the University Hospital Brno between Jul 24, 2009, and Nov 7, 2012.[17,18] Age > 85 years, known inflammatory disease or malignancy, and absence of culprit lesion on coronary angiography served as exclusion critera.[17,18] The second prospective cohort consists of patients with ACS enrolled in the catheter laboratory database of the University Hospital Brno between Aug 26, 2011 and, Jun 24, 2024. For patients with incomplete outcome data, documented fatal events within three days after admission were considered in-hospital events. Patients enrolled in more than one cohort from Czechia were considered only once, as appropriate. Overall, a total of 4377 patients with ACS were enrolled between Jul 24, 2009, and Jun 24, 2024. Ultimately, 2239 patients with a diagnosis of NSTE-ACS were included.

The profiles of the cohorts used, detailed inclusion and exclusion criteria, and study protocols have been reported previously.[3-7,9-12,15-26] This study was conducted according to the declaration of Helsinki and was approved by the local ethics committees.

Machine learning algorithm

In accordance with the GRACE 3.0 in-hospital mortality model, we used extreme gradient boosting (XGBoost),[5] a widely established ensemble learning algorithm.[2,27-33] XGBoost constructs ensembles of decision tree models, with each new model aimed at correcting the errors of the previous ensemble. XGBoost uses advanced regularisation techniques to reduce overfitting and enhance generalizability.[34] The final model uses a weighted sum of all individual tree models, each contributing based on their ability to correct residual errors. XGBoost effectively captures complex data patterns and non-linear relationships, offering high predictive performance and robustness.

Preprocessing of GRACE score variables

Given their high clinical availability, worldwide implementation in acute cardiac care algorithms,[35,36] high predictive utility,[2] and incorporation in clinical trials[9,37-46], the GRACE variables sex (categorical), age (continuous), heart rate (continuous), systolic blood pressure (continuous), Killip class (categorical), creatinine concentration (continuous), cardiac arrest (categorical), presence of ST-segment deviation (categorical), and troponin elevation (categorical) were used to inform the models. The use of standardised, broadly available predictor variables supports further external validation and clinical implementation. For the individualised treatment effect model, Killip class IV was combined with class III and cardiac arrest was not used a model feature, as no patients with the respective characteristics participated in the VERDICT trial. Categorical variables were one-hot encoded.[8] Continuous variables were left unscaled.[27]

Development of the one-year mortality model

The one-year mortality model was developed in 400 054 patients from England, Wales, and Northern Ireland (Suppl. table 1). We tuned for the number of trees, learning rate, maximum tree depth (ie, maximum number of levels that a decision tree), learn rate, minimum child weight (ie, minimum sum of instance weight needed in a child), and gamma (ie, minimum loss reduction required to make a further partition on a leaf node of the tree), subsample proportion (proportion of the data set used for modelling within an iteration), early stopping (no. of iterations without improvement in the objective function before training is halted), and the no. of features that are randomly sampled at each split. Hyperparameters were tuned using Latin hypercube sampling (50 iterations) followed by Bayesian optimisation (additional 50 iterations) with tenfold cross-validation using an 80:20 split of the development cohort into a training cohort (n = 320 043) and an internal validation cohort (n = 80 011). Hyperparameter ranges explored, and final configurations are summarised in Suppl. table 8.

Development of the individualised treatment effect model

The individualised treatment effect model was developed using participant-level data from the prospective, multicentre, open label, parallel group, randomised controlled VERDICT trial evaluating the ideal timing of coronary invasive management in terms of long-term outcome in patients with NSTE-ACS (Suppl. table 6).[9-11] In VERDICT, patients were randomised 1:1 to receive either early invasive management within 12 hours from time of diagnosis, or delayed invasive management within 48 to 72 hours. Among all RCTs on the optimal timing of

invasive management to date,[9,37-56] VERDICT has the longest follow-up duration (median 4·3 years) and the highest event count (612 events), offering the highest statistical power to detect heterogeneity in the treatment effect of early invasive management. Given that there were no patients lost to follow-up in either arm of the VERDICT trial, the primary composite endpoint can be treated as a binary response variable in machine learning analyses. In addition, VERDICT is the only large-scale trial on the optimal timing of invasive management in contemporary patients with NSTE-ACS. The prediction model was developed in patients recruited in hospitals located in the geographical West of the VERDICT trial (n = 1111) and externally validated in patients recruited in hospitals located in the geographical East of the VERDICT trial (n = 1036), with remote study centres counted as West if they were located in the geographical South, and as East if they were located in the geographical North.

The individualised treatment effect of early *vs* delayed invasive management was assessed using the Rboost algorithm.[57] Rboost is an implementation of XGBoost into a flexible R learner framework, which applies Robinson transformation to estimate the individualised treatment effect of an intervention as a function of baseline characteristics.[57-59] Rboost has proven efficient in the accurate prediction of individualised treatment effect in other clinical settings.[57] In brief, Rboost incorporates three different XGBoost models: 1) a marginal outcome model to estimate the expected outcome given baseline covariates, 2) a model to estimate the probability of receiving treatment given the baseline covariates (ie, a treatment propensity score), which provides the option to also use the function for non-randomised data, and 3) a treatment effect model, that estimates the individualised treatment effect by integrating predictions from the former two models to obtain the ratio of the difference between observed and expected outcome over the difference between observed and expected intervention state. In the present study randomized data (1:1) were analysed resulting in a uniform propensity score approximating the randomization probability of 0.5 across all patients so that predicted individualised treatment effects are primarily estimated based on the expected treatment-unrelated outcome given the baseline covariates (ie, the numerator of the ratio). Upon development, only this last model is needed to obtain predictions. To improve stability, we used differential seed initialisation in sequential runs and trained five different base models.[57,60] We used the rboost() function of the R package xnie/rlearner:'R-learner for Heterogeneous Treatment Effect Estimation' to train the Rboost base models using fivefold cross-validation, 100 search rounds, a maximum number of trees of 1000 and early stopping at 10 rounds.[57] The tuned hyperparameter configurations of the five base models for treatment effect are available from Suppl. table 9. Final predictions are means of these five different base model estimates and represent the expected absolute risk reduction in the primary endpoint from early invasive management compared to delayed invasive managment.[57,60]

Feature importance

We used the Shapley additive explanations (SHAP) approach to evaluate the importance of features of the risk model (GRACE 3.0 one-year mortality model).[61,62] SHAP values are model-agnostic representations of feature importance based on cooperative game theory.[61-64] A SHAP value indicates how much a single feature, considering its interaction with other features, contributes to the variance between the actual prediction and the mean prediction, given the current set of feature values.[61] The sum of the SHAP values for all features in a given patient plus the mean prediction equals the actual prediction in that patient.[62-64] We visualised the SHAP values of each model feature using a 1:20 dilution. The mean absolute SHAP value for a feature is the average of the absolute values of its SHAP values across all patients in the dataset and reflects the magnitude of a feature's impact on predictions, without regard to whether it increases or decreases the prediction. Mean absolute SHAP values were scaled to the feature with the highest value.

Variable importance in the GRACE 3.0 individualised treatment effect model was evaluated using an effect modelling-based adaptation of the SHAP approach. Variable importance was determined by calculating the mean absolute change in predicted treatment effect caused by replacing the value of a given variable with the median value from derivation cohort for each patient in the derivation cohort, as reported previously.[57,65] This procedure was repeated for all model features and the final means were scaled to the feature with the highest value.[57,65]

Evaluation of performance of mortality models

External validation of model performance was examined in study centres different from those involved in the development process to evaluate model transportability. Performance of GRACE 3.0 in-hospital mortality and GRACE 3.0 one-year mortality models was assessed by calculating the area under the receiver operating characteristic curve (AUC) and the time-dependent AUC (tAUC) at 365 days of follow-up, respectively. The tAUC[66-69] represents the area under the time-dependent ROC curve and was calculated using inverse probability of censoring weighting, as reported previously.[70,71] We derived 95% CIs for the AUC estimates using the DeLong method. For tAUC estimates, 95% CIs were calculated using inverse probability of censoring weighting estimates of time-dependent ROC curves based on the Kaplan-Meier estimator of the censoring distribution. In UK and Sweden, we modelled the censoring by using a Cox model and constructed 95% CIs using bootstrap resampling,[2] because the approach outlined above would have been computationally intractable. Calibration was evaluated by

constructing smoothed calibration curves, the calibration slope, and the calibration-in-the-large. Calibration plots were visualised using pooled predictions and outcome indicators from all external validation cohorts (manuscript figure 2B and figure 3D).[72] The calibration slope quantifies the spread of predicted risks, and the ideal value is 1. Calibration-in-the-large measures whether a model over- or underpredicts a risk systematically and is quantified as the intercept of the calibration plot with an optimal value is 0. We used decision curve analyses to evaluate the clinical utility of the mortality prediction models by quantifying the trade-off between correctly identifying true positives and incorrectly identifying false positives, weighted according to the threshold probability.[73] We evaluated potential performance heterogeneity in sex-specific subgroup analyses. One observation in Sweden could not be considered in-hospital mortality analyses owing to obstacles in data linkage. Due to the small sample size and the low count of in-hospital deaths in both sex-stratified subgroups in Denmark and in the subgroup of female patients in Spain, these groups could not be considered in subgroups analyses on in-hospital mortality. We further compared the GRACE 3.0 in-hospital mortality and one-year mortality models to respective models for in-hospital mortality and for one-year mortality of the previous score version (v.2.0)[74] by 1) assessing the difference in AUC and tAUC[75], respectively, 2) evaluating the continuous net reclassification improvement (NRI),[76,77] and 3) calculating the integrated discrimination improvement (IDI) index[78]. The NRI constitutes an index to quantify how accurately a respective model has reclassified subjects in comparison to another model.[79] The IDI can be described as the difference in discrimination slopes between two alternative models.[78] Performance metrics were pooled across countries using a random effects meta-analysis to derive overall point estimates, and 95% CIs, as described previously.[27,28] Given the low number of observed in-hospital deaths in Denmark, we conducted a sensitivity analysis on the performance of the in-hospital mortality model excluding patients from this cohort (Supplementary figure 4).

Evaluation of performance of individualised treatment effect model

Performance evaluation of effect prediction models involves novel statistical metrics that were introduced to the medical literature within the past decade. The performance of the GRACE 3.0 individualised treatment effect model was evaluated in the Eastern study centres of the VERDICT trial (validation cohort).

The C-for-benefit describes the concordance between predicted and observed benefit and is characterised as the probability that from two randomly chosen patient pairs, matched on predicted benefit but discordant for treatment assignment, the pair with greater observed benefit also has a higher predicted benefit.[57,80] The C-for-benefit commonly ranges from 0·5 (chance) to 0·6 in clinical trial data with higher values indicating better discrimination and values > 0·6 being considered unusual. A bootstrapped 95% confidence interval where the lower bound exceeds 0.5 was suggested as robust indicator of concordance, while a value above 0.5 with a confidence interval overlapping 0.5 offers moderate statistical evidence.[57]

In addition, we calculated the adjusted qini value, which can be constructed based on the qini curve (Suppl. figure 9). The qini curve addresses the fundamental problem that two different potential (counterfactual) outcomes under alternative therapy are inherently unobservable for one individual patient by illustrating the difference in the observed outcome frequency across a proportion of the treated population. The x-axis in the qini plot displays the proportion of the population, ranked from highest to lowest predicted treatment effect, receiving early invasive management. The y-axis in the qini plot displays the total effect on the whole population (or "incremental uplift") from treating the top x-proportion with early, and the remaining patients with delayed invasive management. The qini value is calculated as the area between the qini curve (derived from model-based intervention assignment) and a reference line generated by randomly ordering patients for intervention assignment on the x-axis. A qini curve value greater than zero indicates discrimination between patients likely to benefit and those unlikely to benefit, with larger values signifying stronger discrimination. The adjusted qini value is the qini value scaled by Kendall's rank correlation. While the adjusted qini is more sensitive than the C-for-benefit, allowing detection of subtle differences in model performance, it is less interpretable and depends on the number of groups used to construct the qini curve.

We also calculated the concentration of benefit (Cb) of the predicted individualised treatment effect values, which ranges from 0 to 1 with increasing values indicating higher value for informing treatment selection.[81] The Cb represents the relative loss in the total effect when using a treatment rule agnostic of the predicted individualised treatment effect, compared with a treatment rule that is informed by the predicted individualised treatment effect, and can be expressed as percentage.

The calibration of the GRACE 3.0 individualised treatment effect model was evaluated in the validation cohort by assessing the agreement of the absolute observed benefit with the predicted benefit across tertiles of predicted effect, as described previously (Suppl. figure 10).[57,80] Based on the PATH statement,[82,83] we defined a threshold of predicted effect of early invasive management at the second tertile cut-point (ie, 9·5% absolute risk reduction)

of predicted individualised treatment effect in the development cohort and applied this threshold to the external validation cohort. Sensitivity analyses were conducted using a zero-threshold for the predicted treatment effect to derive a moderate-to-high-benefit group and a no-benefit group (Suppl. table 16).

Multiple imputation
Completeness, representation, and plausibility of the data have been checked for each patient cohort, as appropriate.[84] Subsequently, the analyses were conducted using multiply imputed data (10 imputations and 10 iterations), and results were pooled using Rubin's rules.[85,86] Geographically distinct regions were imputed separately to account for potential geographical variability, as reported previously.[2] We used predictive mean matching for continuous variables, proportional odds models for ordinal variables, and logistic regression models for binary variables to impute missing data for age, sex, heart rate, systolic blood pressure, Killip class, creatinine concentration, cardiac arrest, presence of ST-segment deviation, and troponin elevation under the missing at random assumption. The imputation models contained all predictors, the endpoint indicators, corresponding Nelson-Aalen cumulative hazard estimates, and the date of cohort entry. The imputation models applied to the VERDICT trial additionally contained randomisation status, as appropriate.[57] Training and cross-validation of newly developed prediction models and effect-based analyses were performed on a single imputed dataset generated, as described above.[2,27,29,57] Convergence was assessed visually. Imputed data were visualised and compared to observed data using strip plots.

Deployment of GRACE 3.0 scoring system
All GRACE 3.0 models will be available at www.grace-3.com.[2,87] GRACE 3.0 requires a single set of nine variables that are routinely available in clinical care settings.

Software packages
Analyses were performed in R (version 4.3 or later), Stata (version 14.0), and IBM SPSS (version 28.0.1.1). The software environment in R for the performed analyses was created by the R packages *caret, data.table, DataExplorer, dplyr, eventglm, faux, fmsb, ggalluvial, ggpattern, ggplot2, ggsurvfit, Hmisc, Matrix, MatrixModels, meta, mice, miceadds, nricens, openxlsx, pec, PredictABEL, psfmi, pROC, Rcpp, readxl, recipes, rmda, rms, rlearner, shap, SHAPforxgboost, survival, survminer, tableone, tabnet, themis, tictoc, tidyverse, tidymodels, tidyr, timeROC, tools4uplift, txBenefit, vtable, VIM, xgboost.*

Public involvement
Since the publication of the GRACE 3.0 in-hospital mortality derivation study[2], the public dialogue on the societal implications of AI-enhanced treatment for patients with NSTE-ACS using the GRACE 3.0 was supported by a team of public relations experts from the Royal Brompton and Harefield Hospitals, UK and the University of Zurich, Switzerland. To make the topic more accessible to individuals with impaired vision, discussions were broadcast in layman's terms on radio (e.g., BBC Radio 4). Additionally, to ensure accessibility to people with hearing difficulties, lay summary videos were produced. Our team also facilitated worldwide print media coverage to encourage public involvement and broaden accessibility to a general audience. The feedback received from lay persons and health care professionals from other fields was taken into account in the present study.

Ethics
Data from the MINAP were fully anonymised, and as such, did not require ethical approval according to NHS research governance arrangements. The National Institute of Cardiovascular Outcomes Research (NICOR), which includes the MINAP database (reference number: NIGB: ECC 1-06 (d)/2011), has support under section 251 of the NHS Act 2006 to use patient information for medical research without consent.[88,89] The analyses involving data from the SWEDEHEART Registry were approved by the Swedish Ethical Review Authority (registration number: 2011/60-31/2, 2012/60-31/2). Ethical approval for AMIS Plus was granted by the Swiss Over-Regional Ethics Committee for Clinical Studies, the Swiss Board for Data Security, and all Cantonal Ethics Committees (reference number: 1.05.01.10–40) and for SPUM-ACS by the Cantonal Ethics Committee Zurich (reference number: EK-1688/2019-01809). Ethical approval for Heidelberg-ACS was granted by the local institutional ethics committee.[5,6] Ethical approval for the VERDICT trial was granted by the Danish National Committee on Health Research Ethics (no. H-4-2010-039) and the Danish Data Protection Agency.[9,90,91] In the CORALYS registry, study investigators received approval from their local institutional boards or ethic committees.[12] In FORCE-ACS, ethical approval was granted by Medical Research Ethics Committees United (MEC-U Reference number: V.32279/W14.073/hs/cl).[16] In the Czech cohorts, ethical approval was granted by the ethics committee of the University Hospital Brno, as described previously.[17,18] The study was conducted in compliance with the declaration of Helsinki.

Supplementary table 1: Summary of participating hospitals in the United Kingdom with geographic location

United Kingdom (England, Wales, Northern Ireland) (MINAP; *n* = 400 054)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Addenbrooke's Hospital	East of England	Papworth Hospital	East of England
Airedale General Hospital	Yorkshire and the Humber	Pennine Acute Trust	North West
Altnagelvin Hospital	Northern Ireland	Perth Royal Infirmary	N/A
Antrim Area Hospital	Northern Ireland	Peterborough District Hospital	East of England
Arrowe Park Hospital	North West	Pilgrim Hospital	East Midlands
Barnet General Hospital	London	Pinderfields General Hospital	Yorkshire and the Humber
Barnsley Hospital	Yorkshire and the Humber	Pontefract General Infirmary	Yorkshire and the Humber
Barts and The London	London	Poole Hospital	South West
Basildon Hospital	East of England	Prince Charles Hospital	Wales
Bassetlaw District General Hospital	East Midlands	Prince Philip Hospital	Wales
Bedford Hospital	East of England	Princess Alexandra Hospital	East of England
Belfast City Hospital	Northern Ireland	Princess Elizabeth Hospital	Guernsey
Birmingham Heartlands Hospital	West Midlands	Princess Of Wales Hospital	Wales
Blackpool Victoria Hospital	North West	Princess Royal Hospital Haywards Heath	South East
Bradford Royal Infirmary	Yorkshire and the Humber	Princess Royal Hospital Telford	West Midlands
Bristol Royal Infirmary	South West	Princess Royal University Hospital	London
Bronglais General Hospital	Wales	Queen Alexandra Hospital	South East
Broomfield Hospital	East of England	Queen Elizabeth Hospital Edgbaston	West Midlands
Calderdale Royal Hospital	Yorkshire	Queen Elizabeth Hospital Gateshead	North East
Castle Hill Hospital	Yorkshire	Queen Elizabeth Hospital Kings Lynn	East of England
Causeway Hospital	Northern Ireland	Queen Elizabeth II Hospital	East of England
Central Middlesex Hospital	London	Queen Elizabeth the Queen Mother	South East
Charing Cross Hospital	London	Queen Mary's Hospital Sidcup	London
Chase Farm Hospital	London	Queen's Hospital Burton	West Midlands
Chelsea & Westminster Hospital	London	Queen's Hospital Romford	London
Cheltenham General Hospital	South West	Rochdale Infirmary	North West
Chesterfield Royal	East Midlands	Rotherham General Hospital	Yorkshire and the Humber
Chorley and South Ribble Hospital	North West	Royal Albert Edward Infirmary	North West
City Hospital Birmingham	West Midlands	Royal Alexandra Hospital	South East
Colchester General Hospital	East of England	Royal Berkshire Hospital	South East
Conquest Hospital	South East	Royal Blackburn Hospital	North West
Countess of Chester Hospital	North West	Royal Bolton Hospital	North West
County Hospital Hereford	West Midlands	Royal Bournemouth General Hospital	South West
County Hospital Louth	East Midlands	Royal Brompton Hospital	London
Craigavon Area Hospital	Northern Ireland	Royal Cornwall Hospital	South West
Croydon University Hospital	South East	Royal Derby Hospital	East Midlands
Cumberland Infirmary	North West	Royal Devon & Exeter Hospital	South West
Daisy Hill Hospital	Northern Ireland	Royal Free Hospital	London
Darent Valley Hospital	South East	Royal Glamorgan Hospital	Wales
Darlington Memorial Hospital	North East	Royal Gwent Hospital	Wales
Derriford Hospital	South West	Royal Hallamshire Hospital	Yorkshire and the Humber
Dewsbury District Hospital	Yorkshire and the Humber	Royal Hampshire County Hospital	South East
Diana Princess of Wales Hospital Grimsby	East Midlands	Royal Lancaster Infirmary	North West

Doncaster Royal Infirmary	Yorkshire and the Humber
Dorset County Hospital	South West
Downe General Hospital	Northern Ireland
Ealing Hospital	South East
East Surrey Hospital	South East
Eastbourne DGH	South East
Epsom Hospital	South East
Fairfield General Hospital	North West
Freeman Hospital	North East
Frenchay Hospital	South West
Friarage Hospital	Yorkshire and the Humber
Frimley Park Hospital	South East
Furness General Hospital	North West
George Elliot Hospital	West Midlands
Glan Clwyd DGH Trust	Wales
Glenfield Hospital	East Midlands
Gloucestershire Royal Hospital	South West
Good Hope General Hospital	West Midlands
Grantham And District General	East Midlands
Hammersmith Hospital	London
Harefield Hospital	London
Harrogate District Hospital	Yorkshire and the Humber
Hexham General Hospital	North East
Hillingdon Hospital	London
Hinchingbrooke Hospital	East of England
Homerton Hospital	London
Good Hope Hospital	West Midlands
Horton General Hospital	South East
Huddersfield Royal Infirmary	Yorkshire and the Humber
Hull Royal Infirmary	Yorkshire and the Humber
James Cook University Hospital	Yorkshire and the Humber
James Paget Hospital	East of England
Jersey General Hospital	Jersey
John Radcliffe Hospital	South East
Kent & Sussex Hospital	South East
Kent and Canterbury Hospital	South East
Kettering General Hospital	East Midlands
King George Hospital	London
King's College Hospital	London
Kings Mill Hospital	East Midlands
Kingston Hospital	South East
Lagan Valley Hospital	Northern Ireland
Lancashire Cardiac Centre Blackpool	North West
Leeds General Infirmary	Yorkshire and the Humber
Leicester Royal Infirmary	East Midlands
Leighton Hospital	North West
Lincoln County Hospital	East Midlands
Lister Hospital	London
Liverpool Heart and Chest Hospital	North West
Royal Liverpool University Hospital	North West
Royal London Hospital	London
Royal Oldham Hospital	North West
Royal Preston Hospital	North West
Royal Shrewsbury Hospital	West Midlands
Royal Surrey County Hospital	South East
Royal Sussex County Hospital	South East
Royal United Hospital Bath	South West
Royal Victoria Hospital	Northern Ireland
Royal Victoria Infirmary	North East
Russells Hall Hospital	West Midlands
Salisbury District Hospital	South West
Sandwell District Hospital	West Midlands
Scarborough General Hospital	Yorkshire and the Humber
Scunthorpe General Hospital	Yorkshire and the Humber
Selly Oak Hospital	West Midlands
Singleton Hospital	Wales
Solihull General Hospital	West Midlands
South Tyneside District Hospital	North East
South West Acute Hospital	Northern Ireland
Southampton General Hospital	South Central
Southend Hospital	East of England
Southmead Hospital	South West
Southport and Formby District General	North West
St Bartholomew's Hospital	London
St George's Hospital	London
St Helier Hospital	London
St Mary's Hospital Newport	Isle of Wight
St Mary's Hospital Paddington	London
St Peter's Hospital	South East
St Richards Hospital	South East
St Thomas' Hospital	London
Staffordshire General Hospital	West Midlands
Stepping Hill Hospital	North West
Stoke Mandeville Hospital	South East
Sunderland Royal Hospital	North East
Tameside General Hospital	North West
Taunton & Somerset Hospital	South West
The Alexandra Hospital	North West
The Great Western Hospital	South West
The Ipswich Hospital	East of England
Torbay Hospital	South West
Trafford General Hospital	North West
Ulster Hospital	Northern Ireland
University College Hospital	London
University College Hospital Gower Street	London
University Hospital Aintree	North West
University Hospital Coventry	West Midlands
University Hospital Lewisham	London

Llandough Hospital	Wales	University Hospital of Hartlepool	North East
Llandudno General Hospital	Wales	University Hospital of North Durham	North East
London Chest Hospital	London	University Hospital of North Staffordshire	West Midlands
Luton & Dunstable Hospital	East of England	University Hospital of North Tees	North East
Macclesfield District General	North West	University Hospital of Wales	Wales
Maelor Hospital	Wales	University Hospital Queen's Medical	East Midlands
Maidstone General Hospital	South East	Wansbeck General Hospital	North East
Manchester Royal Infirmary	North West	Warrington District General Hospital	North West
Manor Hospital	West Midlands	Warwick Hospital	West Midlands
Mater Infirmorum Hospital	Northern Ireland	Watford General Hospital	East of England
Mayday University Hospital	London	West Cornwall Hospital	South West
Medway Maritime Hospital	South East	West Cumberland Hospital	North West
Milton Keynes General Hospital	South East	West Middlesex University Hospital	London
Montagu Hospital	Yorkshire and the Humber	West Suffolk Hospital	East of England
Morriston Hospital	Wales	West Wales General	Wales
Neath Port Talbot Hospital	Wales	Weston General Hospital	South West
Nevill Hall Hospital	Wales	Wexham Park Hospital	South East
Newham General Hospital	London	Whipps Cross Hospital	London
Noble's Hospital	Isle of Man	Whiston Hospital	North West
Norfolk and Norwich Hospital	East of England	Whittington Hospital	London
North Devon District Hospital	South West	William Harvey Hospital	South East
North Hampshire Hospital	South East	Withybush General Hospital	Wales
North Manchester General Hospital	North West	Wolverhampton Heart Centre	West Midlands
North Middlesex Hospital	London	Worcestershire Royal Hospital	West Midlands
North Tyneside General Hospital	North East	Worthing Hospital	South East
Northampton General Hospital	East Midlands	Wycombe General Hospital	South East
Northern General Hospital	Yorkshire and the Humber	Wythenshawe Hospital	North West
Northumbria Emergency Hospital Cramlington	North East	Yeovil District Hospital	South West
Northwick Park Hospital	London	York District Hospital	Yorkshire and the Humber
Nottingham City Hospital	East Midlands	Ysbyty Gwynedd	Wales

Data retrieved from the British Cardiovascular Intervention Society (https://www.bcis.org.uk/) and the University Hospital Association (https://www.universityhospitals.org.uk/).[2]

Supplementary table 2: Summary of participating hospitals in Sweden with geographic location

Sweden (SWEDEHEART; *n* = 172 634)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Alingsås Hospital	Västra Götaland County	Mora Hospital	Dalarna County
Arvika Hospital	Värmland County	Motala Hospital	Östergötland
Avesta Hospital	Dalarna County	Norrköping Vrinnevi Hospital	Östergötland
Bollnäs Hospital	Gävleborg County	Norrtälje Hospital	Stockholm County
Borås Hospital	Västra Götaland County	Nyköping Hospital	Södermanlands
Eksjö Hospital	Jönköping County	Örebro Hospital	Örebro County
Enköping Hospital	Uppsala County	Örnsköldsvik Hospital	Västernorrland
Eskilstuna Hospital	Södermanland County	Oskarshamn Hospital	Kalmar County
Falun Hospital	Dalarna County	Östersund Hospital	Jämtland County
Gällivare Hospital	Norrbotten County	Piteå Hospital	Norrbotten County
Gävle Hospital	Gävleborg County	Sahlgrenska University Hospital, Mölndal	Västra Götaland County
Halmstad Hospital	Halland County	Sahlgrenska University Hospital, Östra	Västra Götaland County
Hässleholm Hospital	Skåne County	Sahlgrenska University Hospital, Sahlgrenska	Västra Götaland County
Helsingborg Hospital	Skåne County	Skellefteå Hospital	Västerbotten County
Hudiksvall Hospital	Gävleborg County	Skene Hospital	Västra Götaland Countyl
Jönköping Hospital	Jönköping County	Skövde Hospital	Västra Götaland County
Kalix Hospital	Norrbotten County	Södersjukhuset	Stockholm County
Karlshamn Hospital	Blekinge County	Södertälje Hospital	Stockholm County
Karlskoga Hospital	Örebro County	Sollefteå Hospital	Västernorrland County
Karlskrona Hospital	Blekinge County	Stockholm Danderyd Hospital	Stockholm County
Karlstad Hospital	Värmland County	Stockholm St Göran Hospital	Stockholm County
Karolinska University Hospital, Huddinge	Stockholm County	Sunderbyn Hospital	Norrbotten County
Karolinska University Hospital, Solna	Stockholm County	Sundsvall Hospital	Västernorrland County,
Katrineholm Hospital	Södermanland County	Torsby Hospital	Värmland County
Kiruna Hospital	Norrbotten County	Trelleborg Hospital	Skåne County
Köping Hospital	Västmanland County	Trollhättan NU-sjukvården Hospital	Västra Götaland County
Kristianstad Hospital	Skåne County	Uddevalla Hospital	Västra Götaland County
Kungälv Hospital	Västra Götaland County	Umeå University Hospital	Västerbotten County
Landskrona Hospital	Skåne County	Uppsala University Hospital	Uppsala County
Lidköping Hospital	Västra Götaland County	Värnamo Hospital	Jönköping County
Lindesberg Hospital	Örebro County	Västerås Hospital	Västmanland County
Linköping Hospital	Östergötland County	Västervik Hospital	Kalmar County
Ljungby Hospital	Kronoberg County	Växjö Hospital	Kronoberg County
Ludvika Hospital	Dalarna County	Visby Hospital	Gotland County
Lycksele Hospital	Västerbotten County	Ystad Hospital	Skåne County

Supplementary table 3: Summary of participating hospitals in Switzerland with geographic location

Switzerland (AMIS Plus & SPUM-ACS; *n* = 24 945)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Altdorf, Cantonal Hospital	Uri	Monthey, Hôpital du Chablais	Valais
Altstätten, Cantonal Hospital	St· Gallen	Montreux, Hôpital Riviera	Vaud
Aarau, Cantonal Hospital Aarau	Argau	Montreux, Hôpital Riviera	Vaud
Baden, Cantonal Hospital	Baden	Muri, Kreisspital für das Freiamt	Aargau
Basel, University Hospital	Basel-Stadt	Münsingen, Regionales Spitalzentrum	Bern
St· Claraspital Basel	Basel-Stadt	Münsterlingen, Kantonsspital	Thurgau
Hirslanden Klink Beau-Site	Bern	Nyon, Group· Hospitalier Ouest lémanique	Vaud
Hirslanden Salem Hospital	Bern	Olten, Kantonsspital	Solothurn
Spital Tiefenau	Bern	Rheinfelden, Regionalspital	Aargau
Hospital Biel	Bern	Rorschach, Kantonales Spital	St· Gallen
Brig-Glis, Oberwalliser Kreisspital	Valais	Samedan, Spital Oberengadin	Grisons
Hospital Bülach	Zurich	Schaffhausen, Kantonsspital	Schaffhausen
Burgdorf, Regionalspital Emmental	Bern	Schlieren, Spital Limmattal	Zurich
Chur, Kreuzspital	Grisons	Schwyz, Spital	Schwyz
Chur, Rätisches Kantons- und Regionalspital	Grisons	Scuol, Ospidal d'Engiadina Bassa	Grisons
Davos, Spital	Grison	Sion, Hôpital du Valais (RSV)	Valais
Dornach, Spital	Solothurn	Solothurn, Bürgerspital	Solothurn
Einsiedeln, Regionalspital	Schwyz	Spital Affoltern	Zurich
Flawil, Spital	St· Gallen	Stans, Kantonsspital Nidwalden	Nidwalden
Frauenfeld, Kantonsspital	Thurgau	St· Gallen, Kantonsspital	St· Gallen
Fribourg, Kantonsspital	Fribourg	Sursee, Luzerner Kantonsspital	Lucerne
Frutigen, Spital	Bern	Thun, Spital	Bern
Glarus, Kantonsspital	Glarus	Thusis, Krankenhaus	Grisons
Grosshöchstetten, Bezirksspital	Bern	University Hospital Bern	Bern
Heiden, Kantonales Spital	Appenzell Ausserrhoden	University Hospital Geneva	Geneva
Herisau, Kantonales Spital	Appenzell Ausserrhoden	University Hospital Lausanne	Vaud
Horgen, See-Spital	Zurich	University Hospital Zurich	Zurich
Interlaken, Spital	Bern	Uznach, Kantonales Spital	St· Gallen
Jegenstorf, Bezirksspital	Bern	Walenstadt, Kantonales Spital	St· Gallen
Kreuzlingen, Herz-Zentrum Bodensee	Thurgau	Wetzikon, Gesundheitsversorgung Zürcher Oberland	Zurich
La Chaux-de-Fonds, Hôpital	Neuchâtel	Winterthur, Kantonsspital	Zurich
Lachen, Spital	Schwyz	Wolhusen, Luzerner Kantonspital	Lucerne
Langnau im Emmental, Regionalspital	Bern	Zofingen, Spital	Aargau
Laufenburg, Regionalspital	Aargau	Zollikerberg, Spital	Zurich
Lugano, Cardiocentro Ticino	Lugano	Zug, Kantonsspital	Zug
Luzern, Luzerner Kantonsspital	Lucerne	Zürich, Klinik Hirslanden	Zurich
Luzern, Klinik St· Anna	Lucerne	Zürich, Klinik im Park	Zurich
Männedorf, Spital	Zurich	Zürich, Stadtspital Triemli	Zurich
Martigny, Hôpital régional	Valais	Zürich, Stadtspital Waid	Zurich
Meyrin, Hôpital de la Tour	Geneva		

Supplementary table 4: Summary of participating hospitals in Denmark, Germany, Spain, the Netherlands, and Czechia with geographic location

Germany (Heidelberg-ACS; *n* = 2034)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Heidelberg University Hospital	Baden-Wuerttemberg		
Denmark (VERDICT; *n* = 2147)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Amager Hospital	Copenhagen, Hovedstaden (East)	Herlev Hospital	Hovedstaden (West)
Bispebjerg Hospital	Copenhagen, Hovedstaden (East)	Hillerød Hospital	Hovedstaden (East)
Frederiksberg Hospital	Copenhagen, Hovedstaden (West)	Hvidovre Hospital	Hovedstaden (West)
Gentofte Hospital	Hovedstaden Hovedstaden (East)	Rigshospitalet	Copenhagen, Hovedstaden (East)
Glostrup Hospital	Hovedstaden (West)		
Spain (CORALYS; *n* = 1061)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Hospital Universitario Alvaro Cunqueiro, Vigo	Pontevedra		
Netherlands (FORCE-ACS; *n* = 3949)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
Amsterdam UMC, location AMC	Amsterdam	Rivierenland Hospital	Tiel
Amsterdam UMC, location VUmc	Amsterdam	St. Antonius Hospital	Nieuwegein
Gerle Hospitals	Apeldoorn	Tergooi Hospital	Hilversum
Hospital Gelderse Vallei	Ede	University Medical Center Utrecht	Utrecht
Rijnstate Hospital	Arnhem		
Czechia (Brno-ACS; *n* = 2239)			
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**
University Hospital Brno	Brno		

Supplementary table 5: Treatment characteristics and outcomes of patients with non-ST-elevation acute coronary syndrome

	England, Wales & Northern Ireland (MINAP; *n* = 400 054	Sweden (SWEDEHEART; *n* = 172 634)	Switzerland (AMIS Plus & SPUM-ACS; *n* = 24 945)	Germany (Heidelberg-ACS; *n* = 2034)	Denmark (VERDICT; *n* = 2147)	Spain (CORALYS; *n* = 1061)	Netherlands (FORCE-ACS; *n* = 3949)	Czechia (Brno-ACS; *n* = 2239)
Management delay								
Onset-to-door, min	221 (108– 676)	193 (99–495)	330 (128–929)	300 (120–540)	350 (147–997)	..	..	180 (125–475)
Door-to-PCI, min†	..	153 (94– 248)	324 (110–1130)	464 (206–1304)	1550 (753–4204)	..	..	…
Onset-to-PCI, min	..	419 (240–870)	1047 (509–1913)	1039 (571–1905)	2750 (1205–5295)	..	..	…
Type of intervention								
Coronary angiography	228 020/400 054 (57·0%)	136 759/172 634 (79·2%)	19 290/24 919 (77·4%)	1682/1919 (87·7%)	2048/2147 (95·4%)	1061/1061 (100·0%)	3654/3937 (92·8%)	2239/2239 (100·0%)
PCI	107 350/253 551 (42·3%)	93 669 (54·3%)	18 238/24 712 (73·8%)	1043/1683 (62·0%)	940/2147 (43·8%)	1061/1061 (100·0%)	2193/3812 (57·5%)	1591/2239 (71·1%)
Coronary artery bypass grafting	10 547/253 551 (4·2%)	15 256 (8·8%)	1104/22 831 (4·8%)	..	..	0/1061 (0·0%)	581/3934 (14·8%)	9/368 (2·4%)
Thrombolysis	740/342 923 (0·2%)	231 (0·1%)	159/24 182 (0·7%)	..	..	0/1061 (0·0%)	..	…
Procedural characteristics								
Duration of PCI, min	..	..	28 (18–45)	31 (23 – 42)	..	..	..	…
ASS	10 784/39 130 (27·6%)	2602/172 634 (2·8%)	22 356/24 079 (92·8%)	..	..	..	..	…
P2Y12 receptor inhibitor	307 718/361 036 (85·2%)	13 881/172 634 (15·1%)	19 344/20 384 (94·9%)	..	..	..	..	…
Glycoprotein IIb/IIIa receptor inhibitor	10 723/336 097 (3·2%)	2107/172 634 (2·3%)	2579/23 743 (10·9%)	..	..	..	56/3563 (1·6%)	…
Unfractionated heparin	40 333/330 462 (12·2%)	1975/172 634 (2·1%)	16 482/23 875 (69·0%)	..	..	..	3535/3590 (98·5%)	…
Low-molecular-weight heparin	194 468/335 290 (58·0%)	284/172 634 (0·3%)	5889/23 791 (24·8%)	..	..	..	..	…
Fondaparinux	127 113/312 586 (40·7%)	275/172 634 (0·3%)	1040/20 116 (5·2%)	..	..	..	..	…
Duration of hospital stay, days	5 (3–9)	4 (3–6)	4 (2–7)	..	2 (1–4)	..	..	5 (4–7)
Discharge destination				..	..			
Rehabilitation or other hospital	86 996/351 847 (24·7%)	..	11 444/23 027 (49·7%)	..	..	..	..	59/368 (16·0%)
Home	264 851/351 847 (75·3%)	..	11 583/23 027 (50·3%)	..	..	..	..	309/368 (84·0%)
Discharge medication								
ASS ‡	268 684/296 745 (90·5%)	151 101/172 634 (88·8%)	22 859/24 003 (95·2%)	1165/1303 (89·4%)	1768/2083 (84·9%)	..	3308/3949 (83·8%)	338/368 (91·8%)

P2Y12 receptor inhibitor	190 099/258 497 (73·5%)	126 882/172 634 (74·5%)	19 495/21 468 (90·8%)	921/1303 (70·7%)	1490/2084 (71·5%)	..	3612/3949 (91·5%)	…
β-blocker	232 646/286 138 (81·3%)	140 662/172 634 (82·6%)	17 853/23 908 (74·7%)	1146/1303 (88·0%)	1511/2068 (73·1%)	736/1040 (70·8%)	2661/3949 (67·4%)	325/368 (88·3%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	228 871/355 242 (64·4%)	115 944/172 634 (68·4%)	18 135/23 863 (76·0%)	1141/1303 (87·6%)	827/2067 (40·0%)	..	2805/3949 (71·0%)	323/368 (87·8%)
Vitamin K antagonist or direct oral anticoagulant	..	21 210/172 634 (12·5%)	2175/7353 (29·6%)	130/1301 (10·0%)	148/2077 (7·1%)	..	747/3949 (18·9%)	47/368 (12·8%)
Statin	267 629/295 105 (90·7%)	145 911/170 253 (85·7%)	21 535/23 910 (90·1%)	1161/1303 (89·1%)	1790/2069 (86·5%)	954/1040 (91·7%)	3463/3949 (87·7%)	334/368 (90·8%)
Outcomes								
Death in hospital§	17 806/386 591 (4·6%)	5293/172 634 (3·1%)	841/24 945 (3·4%)	45/2034 (2·2%)	6/2147 (0·3%)	14/1061 (1·3%)	54/3949 (1·4%)	120/2239 (5·4%)
Death at 1 year¶	61 741/400 054 (15·4%)	21 073/172 634 (12·2%)	85/2239 (3·8%)	116/1975 (5·9%)	94/2147 (4·4%)	45/1061 (4·2%)	216/3949 (5·5%)	275/2239 (12·3%)

Data are median (IQR) or n/N (%). ASS = acetyl salicylic acid. PCI = percutaneous coronary intervention. †Truncated at 15 hours in Germany. ‡Defined as anti-aggregation at discharge in Czechia. §Based on MINAP data in UK. ¶Not documented in AMIS Plus.

Supplementary table 6: Baseline characteristics of patients with non-ST-elevation acute coronary syndrome in the GRACE 3.0 individualised treatment effect model development and validation cohorts

	Development (VERDICT; *n* = 1111)	Validation (VERDICT; *n* = 1036)
Age, years	64 (54–73)	64 (55–72)
Female	373/1111 (33·6%)	362/1036 (34·9%)
BMI, kg/m²	26·3 (23·9–29·8)	26·3 (23·9–29·4)
Current smoker	350/1111 (31·5%)	315/1036 (30·4%)
Heart rate, bpm	75 (65–88)	73 (65–86)
Systolic blood pressure, mm Hg	144 (130–162)	142 (128–160)
Cardiac arrest	0/1111 (0·0%)	0/1036 (0·0%)
ST-segment deviation	389/1091 (35·7%)	436/1022 (42·7%)
Left ventricular ejection fraction ≥50%	729/969 (75·2%)	642/865 (74·2%)
Killip class		
I	1049/1096 (95·7%)	989/1030 (96·0%)
II	41/1096 (3·7%)	29/1030 (2·8%)
III	6/1096 (0·5%)	12/1030 (1·2%)
IV	..	..
Medical history		
Diabetes	175/1111 (15·8%)	156/1036 (15·1%)
Hypertension	573/1111 (51·6%)	548/1036 (52·9%)
Previous PCI	143/1111 (12·9%)	171/1036 (16·5%)
Previous coronary artery bypass graft	59/1111 (5·3%)	55/1036 (5·3%)
Family history of coronary artery disease	..	..
Peripheral vascular disease	..	..
Cerebrovascular disease	88/1111 (7·9%)	88/1036 (8·5%)
Heart failure	94/1111 (8·5%)	120/1036 (11·6%)
Chronic kidney disease	105/1111 (9·5%)	93/1036 (9·0%)
Clinical chemistry and haematology		
White blood count, 10^9/L	10·1 (7·5–11·6)	9·5 (7·4–11·3)
Haemoglobin, g/L	137 (127–147)	138 (129–148)
C-reactive protein, mg/L	..	..
Total cholesterol, mmol/L	..	..
Low-density lipoprotein cholesterol, mmol/L	..	..
Haemoglobin A1c, %	..	..
Troponin elevation†	907/1109 (81·8%)	811/1034 (78·4%)
N-terminal-pro hormone BNP, ng/L	..	..
Creatinine, µmol/L	74 (63–87)	75 (64–88)
Estimated glomerular filtration rate, ml/min/1·73m^2‡	93·0 (79·1 –102·4)	92·8 (78·6–101·8)
Baseline medication		
ASS	913/1078 (84·7%)	855/1005 (85·1%)
$P2Y_{12}$ receptor inhibitor	791/1079 (73·3%)	699/1005 (70·0%)
β-blocker	801/1071 (74·8%)	710/997 (71·2%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	404/1070 (37·8%)	423/997 (42·4%)
Vitamin K antagonist or direct oral anticoagulant	77/1078 (7·1%)	71/999 (7·1%)
Statin	938/1072 (87·5%)	852/997 (85·5%)
Primary outcome	306/1111 (27·5%)	306/1036 (29·5%)

Data are median (IQR) or n/N (%). ASS = acetyl salicylic acid. BMI = body mass index. BNP=brain natriuretic peptide. bpm = beats per minute. PCI = percutaneous coronary intervention. †Refers to values > 99th percentile. ‡Estimated according to Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation.

Supplementary table 7: Baseline characteristics of patients with non-ST-elevation acute coronary syndrome in the external validation cohort stratified by predicted benefit from early invasive management

	No/moderate-benefit (VERDICT; *n* = 708)	High-benefit (VERDICT; *n* = 328)	p-value
Age, years	65 (57–73)	62 (52–69)	0·0012
Female	231/708 (32·6%)	131/328 (39·9%)	0·026
BMI, kg/m²	26·3 (23·9–29·4)	26·3 (24·2–29·4)	0·72
Current smoker	208/708 (29·4%)	107/328 (32·6%)	0·29
Heart rate, bpm	70 (69–81)	82 (72–100)	<0·0001
Systolic blood pressure, mm Hg	145 (133–164)	131 (119–152)	0·0004
Cardiac arrest	0/708 (0·0%)	0/328 (0·0%)	..
ST-segment deviation	272/700 (38·9%)	164/322(50·9%)	<0·001
Left ventricular ejection fraction ≥50%	450/588 (76·5%)	192/277 (69·3%)	0·024
Killip class			0.016
I	684/704 (97·2%)	305/326 93·6%)	
II	13/704 (1·8%)	16/326 (4·9%)	
III	7/704 (1·0%)	5/326 (1·5%)	
IV	..	..	
Medical history			
Diabetes	95/708 (13·4%)	61/328 (18·6%)	0·030
Hypertension	377/708 (53·3%)	171/328 (52·1%)	0·74
Previous PCI	121/708 (17·1%)	50/328 (15·2%)	0·46
Previous coronary artery bypass graft	42/708 (5·9%)	13/328 (4·0%)	0·19
Family history of coronary artery disease	..	..	..
Peripheral vascular disease	..	..	..
Cerebrovascular disease	59/708 (8·3%)	29/328 (8·8%)	0·79
Heart failure	72/708 (10·2%)	48/328 (14·6%)	0·037
Chronic kidney disease	74/708 (10·5%)	19/328 (5·8%)	0·015
Clinical chemistry and haematology			
White blood count, 10^9/L	9·0 (7·0–10·6)	10·4 (7·5–11·9)	0·0060
Haemoglobin, g/L	138 (129–148)	137 (126–147)	0·042
C-reactive protein, mg/L	..	..	..
Total cholesterol, mmol/L	..	..	..
Low-density lipoprotein cholesterol, mmol/L	..	..	..
Haemoglobin A1c, %	..	..	..
Troponin elevation†	544/706 (77·1%)	267/328 (81·4%)	0·13
N-terminal-pro hormone BNP, ng/L	..	..	..
Creatinine, µmol/L	77 (67–88)	69 (61–78)	<0·0001
Estimated glomerular filtration rate, ml/min/1·73m^2‡	92 (77–101)	96 (81–105)	0·0002
Baseline medication			
ASS	600/688 (87·2%)	255/317 (80·4%)	0·0051
$P2Y_{12}$ receptor inhibitor	501/688 (72·8%)	198/317 (62·5%)	0·0009
β-blocker	491/681 (72·1%)	219/316 (69·3%)	0·36
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	287/682 (42·1%)	136/315 (43·2%)	0·75
Vitamin K antagonist or direct oral anticoagulant	46/684 (6·7%)	25/315 (7·9%)	0·49
Statin	607/682 (89·0%)	245/315 (77·8%)	<0·0001
Primary outcome	199/708 (28·1%)	107/328 (32·6%)	0·16

Data are median (IQR) or n/N (%). ASS = acetyl salicylic acid. BMI = body mass index. BNP=brain natriuretic peptide. bpm = beats per minute. PCI = percutaneous coronary intervention. †Refers to values > 99th percentile. ‡Estimated according to Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation.

Supplementary table 8: Missing data table

	England, Wales & Northern Ireland (MINAP; *n* = 400 054)		Sweden (SWEDEHEART; *n* = 172 634)		Switzerland (AMIS Plus & SPUM-ACS; *n* = 24 945)		Germany (Heidelberg-ACS; *n* = 2034)		Denmark (VERDICT; *n* = 2147)		Spain (CORALYS; *n* = 1061)		Netherlands (FORCE-ACS; *n* = 3949)		Czechia (Brno-ACS; *n* = 2239)	
	Valid	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**	**Valid**	**Missing**
Model features																
Age	399 492	562 (0·1%)	172 634	0 (0·0%)	24 944	1 (0·0%)	2033	1 (0·0%)	2147	0 (0·0%)	1061	0 (0·0%)	3948	1 (0·0%)	2237	2 (0·1%)
Sex	400 054	0 (0·0%)	172 634	0 (0·0%)	24 944	1 (0·0%)	2034	0 (0·0%)	2147	0 (0·0%)	1061	0 (0·0%)	3947	2 (0·1%)	2239	0 (0·0%)
Heart rate	359 191	40 863 (10·2%)	170 071	2563 (1·5%)	24 134	811 (3·3%)	2029	5 (0·2%)	2102	45 (2·1%)	1059	2 (0·2%)	3919	30 (0·8%)	2150	89 (4·0%)
Systolic blood pressure	359 007	41 047 (10·3%)	169 824	2810 (1·6%)	24 127	818 (3·3%)	2029	5 (0·2%)	2136	11 (0·5%)	1060	1 (0·1%)	3907	42 (1·1%)	2230	9 (0·4%)
Cardiac arrest	389 378	10 676 (2·7%)	172 539	95 (0·1%)	24 888	57 (0·2%)	2030	4 (0·2%)	2147	0 (0·0%)	1061	0 (0·0%)	3941	8 (0·2%)	2239	0 (0·0%)
ST-segment deviation	384 738	15 316 (3·8%)	172 634	0 (0·0%)	24 673	272 (1·1%)	1817	217 (10·7%)	2113	34 (1·6%)	1061	0 (0·0%)	3949	0 (0·0%)	2175	64 (2·9%)
Killip class	201 438	198 616 (49·6%)	168 118	4516 (2·6%)	24 343	602 (2·4%)	2029	5 (0·2%)	2126	21 (1·0%)	1061	0 (0·0%)	3903	46 (1·2%)	2156	83 (3·7%)
Troponin elevation†	390 128	9926 (2·5%)	167 763	4871 (2·8%)	14 928	10 017 (40·2%)	2030	4 (0·2%)	2143	4 (0·2%)	1061	0 (0·0%)	3912	37 (0·9%)	2140	99 (4·4%)
Creatinine	348 007	52 047 (13·0%)	167 245	5389 (3·1%)	23 723	1222 (4·9%)	2030	4 (0·2%)	2127	20 (0·9%)	1052	9 (0·8%)	3929	20 (0·5%)	2057	182 (8·1%)
Outcomes																
Death in hospital	··§	··	172 634	0 (0·0%)	24 945	0 (0·0%)	2034	0 (0·0%)	2147	0 (0·0%)	1061	0 (0·0%)	3949	0 (0·0%)	2239	0 (0·0%)
Death at 1 year	400 054	0 (0·0%)	172 634	0 (0·0%)	2239¶	0 (0·0%)	1975#	0 (0·0%)	2147	0 (0·0%)	1061	0 (0·0%)	3949	0 (0·0%)	2239	0 (0·0%)
Composite primary endpoint‡	··	··	··	··	··	··	··	··	2147	0 (0·0%)	··	··	··	··	··	··

†Refers to values > 99th percentile. §The UK cohort was not included in analyses on in-hospital mortality. ¶Not documented in AMIS Plus. #Not documented in entire cohort. ‡Defined as the first occurrence of all-cause death, nonfatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure. Values in brackets are percentages.

Supplementary table 9: Hyperparameter tuning of one-year mortality model

Basic architecture	Hyperparameter	Description	Range explored	Final selected value
Computational engine: xgboost[34]	trees (nrounds)	No. of boosting rounds	1–2000	1570
No. of predictors: 9	tree_depth (max_depth)	Maximum depth of the tree (ie, number of splits)	1–15	10
	learn_rate (eta)	Rate at which the algorithm learns from each iteration (lower value prevent overfitting, while higher values speed up learning, but may lead to overfitting)	10^{-3}–10^{-1}	$8{\cdot}451 \times 10^{-3}$
	min_n (min_child_weight)	Minimum no. of data points in a node required for the node to be split further	2–40	35
	loss_reduction (gamma)	Minimum reduction in the loss function required to split further	10^{-10}–31·6	1·730
	sample_size (subsample)	Proportion of the data set used for modeling within an iteration.	0·1–1	0·499
	stop_iter (early_stopping_rounds)	No. of iterations without improvement in the objective function before training is halted.	3– 20	16
	mtry (colsample_bytree)	No. of features that are randomly sampled at each split.	1–16	2

Models were tuned using 10-fold cross validation employing an 80:20 data split at each fold. Initial hyperparameter combinations were obtained using grid search with Latin hypercube sampling (50 iterations). Based on these initial combinations we used Baysesian optimisation (50 iterations) to further optimise the hyperparameter combinations. The evaluation metric was the area under the receiver operating characteristic curve. L1 regularisation (alpha) was set to default (ie, 0). L2 regularisation (lamda) was set to default (ie, 2).

Supplementary table 10: Hyperparameter tuning of individualised treatment effect model

Basic architecture	Hyperparameter	Description	Base model 1	Base model 2	Base model 3	Base model 4	Base model 5
Computational engine: xgboost[34] No. of predictors: 9	trees (nrounds)	No. of boosting rounds	159	186	61	23	51
	tree_depth (max_depth)	Maximum depth of the tree (ie, number of splits)	5	3	6	8	18
	learn_rate (eta)	Rate at which the algorithm learns from each iteration (lower value prevent overfitting, while higher values speed up learning, but may lead to overfitting)	0·015	0·015	0·05	0·08	0·05
	min_n (min_child_weight)	Minimum no. of data points in a node required for the node to be split further	19	2	20	10	13
	loss_reduction (gamma)	Minimum reduction in the loss function required to split further	0·193	0·162	0·117	0·114	0·184
	sample_size (subsample)	Proportion of the data set used for modeling within an iteration.	0·5	1	0·5	0·5	1
	max_delta_step	Maximum delta step allowed for each tree's weight estimation.	1	3	6	7	5
	mtry (colsample_bytree)	No. of features that are randomly sampled at each split.	0·6	0·8	0·8	0·8	0·6

Each model was tuned using 100 search rounds with 5-fold cross validation. The evaluation metric was the root mean squared error. We used a maximum number of trees of 1000 and early stopping at 10 rounds. Default ranges specified by the rboost() function of the R package 'R-learner for Heterogeneous Treatment Effect Estimation' in R were explored for all other hyperparameters shown above.

Supplementary table 11: Evaluation of model performance on internal validation.

One-year mortality			
All patients			
	Estimate (95% CI)		
tAUC	0·84 (0·83–0·84)		
Slope	1·02 (1·00–1·04)		
Calibration-in-the-large	0·01 (-0·02–0·04)		
Sex-specific subgroups			
Female	Estimate (95% CI)	Male	Estimate (95% CI)
tAUC	0·82 (0·81–0·82)	tAUC	0·85 (0·84–0·85)
Slope	1·02 (0·99–1·05)	Slope	1·01 (0·99–1·03)
Calibration-in-the-large	0·04 (-0·01–0·08)	Calibration-in-the-large	-0·02 (-0·06–0·02)

Estimates derived from meta-analytic pooling from whole patient cohort. CI=confidence interval. tAUC=time-dependent area under the curve.

Supplementary table 12: Evaluation of model performance on external validation.

In-hospital mortality		One-year mortality	
	Estimate (95% CI)		**Estimate**
AUC	0·90 (0·89–0·91)	**tAUC**	0·84 (0·82–0·86)
Slope	1·06 (0·90–1·22)	**Slope**	1·09 (0·99–1·19)
Calibration-in-the-large	-0·15 (-0·86–0·57)	**Calibration-in-the-large**	-0·34 (-0·74–0·06)

Estimates derived from meta-analytic pooling from whole patient cohort. AUC=area under the curve. CI=confidence interval. tAUC=time-dependent area under the curve.

Supplementary table 13: Sex-stratified model performance on external validation.

In-hospital mortality		One-year mortality	
Female	**Estimate (95% CI)**	**Female**	**Estimate**
AUC	0·88 (0·88–0·89)	**tAUC**	0·83 (0·83−0·84)
Slope	1·20 (0·99–1·40)	**Slope**	1·10 (0·95−1·25)
Calibration-in-the-large	0·30 (-0·36–0·97)	**Calibration-in-the-large**	-0·36 (-0·90−0·18)
Male	**Estimate (95% CI)**	**Male**	**Estimate**
AUC	0·91 (0·90−0·93)	**tAUC**	0·85 (0·82–0·87)
Slope	1·00 (0·79−1·20)	**Slope**	1·10 (1·00−1·21)
Calibration-in-the-large	-0·18 (-1·06− 0·70)	**Calibration-in-the-large**	-0·29 (-0·67− 0·10)

Estimates derived from meta-analytic pooling from whole patient cohort. AUC=area under the curve. tAUC=time-dependent area under the curve.

Supplementary table 14: Improved performance of the GRACE 3.0 in-hospital mortality model and the GRACE 3.0 one-year mortality model above and beyond the previous score version upon external validation stratified by sex

In-hospital mortality			One-year mortality		
Female	**Estimate (95% CI)**	**p-value**	**Female**	**Estimate (95% CI)**	**p-value**
delta AUC	0·02 (0·01–0·03)	0·0046	**delta tAUC**	0·01 (0·00−0·01)	0·011
IDI	0·02 (-0·01–0·06)	0·15	**IDI**	0·03 (0·03−0·03)	<0·0001
NRI	0·25 (0·01–0·50)	0·047	**NRI**	0·33 (0·05−0·60)	0·026
Male	**Estimate (95% CI)**		**Male**	**Estimate**	
delta AUC	0·02 (0·02−0·02)	<0·0001	**delta tAUC**	0·01 (0·01–0·01)	<0·0001
IDI	0·04 (0·01−0·06)	0·017	**IDI**	0·03 (0·02–0·04)	<0·0001
NRI	0·84 (0·68−1·01)	<0·0001	**NRI**	0·45 (0·43–0·48)	<0·0001

AUC=area under the curve. CI=confidence interval. IDI=integrated discrimination improvement index. NRI=net reclassification improvement. tAUC=time-dependent area under the curve. Values refer to pooled estimates aggregated across all external validation cohorts using a random effects meta-analysis.
Comparison of GRACE 3.0 in-hospital mortality model with pervious score version (v.2.0).[74] Comparison of GRACE 3.0 one-year mortality model with previous score version (v.2.0).[74]

Supplementary table 15: Improved performance of the GRACE 3.0 in-hospital mortality model and the GRACE 3.0 one-year mortality model above and beyond the previous score version upon external validation

In-hospital mortality model			One-year mortality model		
	Estimate (95% CI)	**p-value**		**Estimate**	**p-value**
delta AUC	0·02 (0·02–0·02)	<0·0001	**delta tAUC**	0·01 (0·01–0·01)	<0·0001
IDI	0·02 (0·00–0·05)	0·045	**IDI**	0·03 (0·02–0·04)	<0·0001
NRI	0·47 (0·08–0·85)	0·025	**NRI**	0·46 (0·36–0·55)	<0·0001

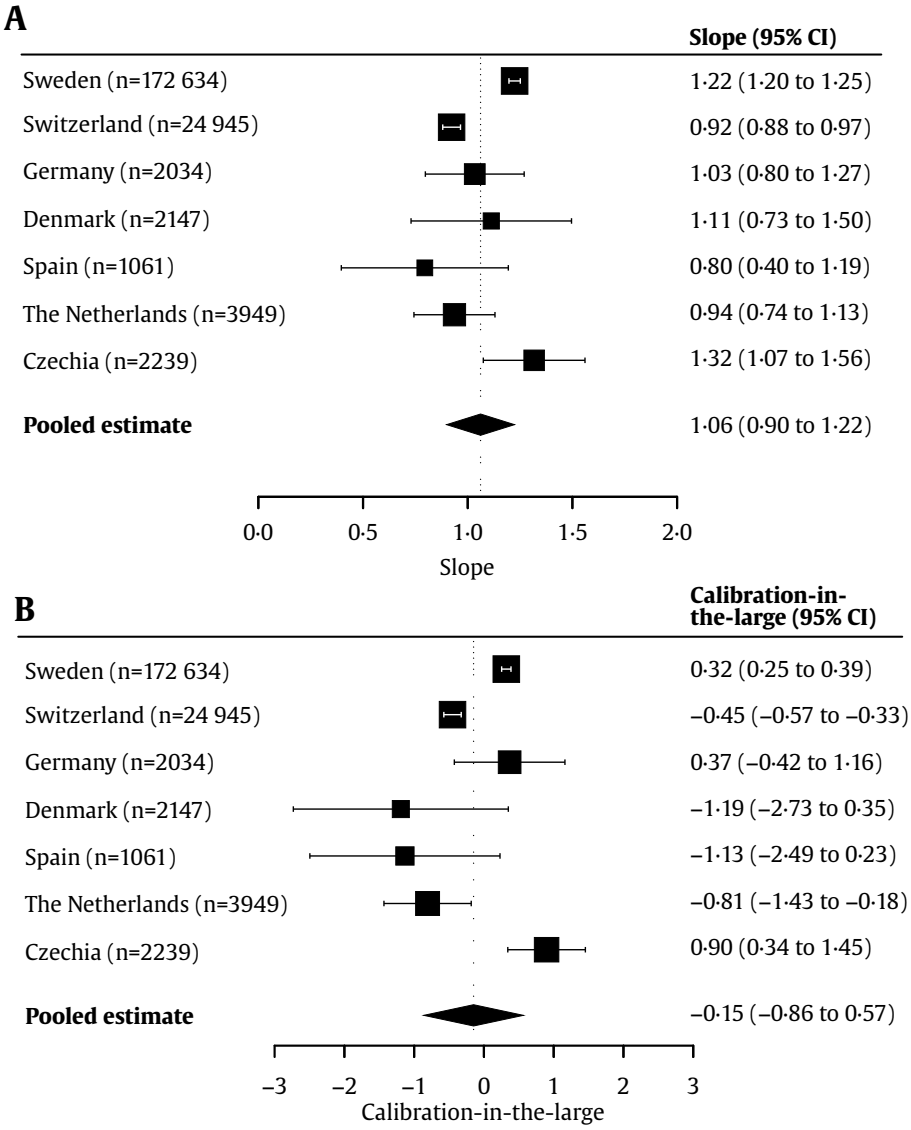
AUC=area under the curve. CI=confidence interval. IDI=integrated discrimination improvement index. NRI=net reclassification improvement. tAUC=time-dependent area under the curve. Values refer to pooled estimates aggregated across all external validation cohorts using a random effects meta-analysis.
Comparison of GRACE 3.0 in-hospital mortality model with pervious score version (v.2.0).[74] Comparison of GRACE 3.0 one-year mortality model with previous score version (v.2.0).[74]

Supplementary table 16: Sensitivity analyses on the effect of early invasive management across GRACE 3.0 individualised treatment effect model-benefit groups

	HR (95% CI)	ARR (95% CI)
Moderate-to-high benefit group	0·75 (0·58–0·97)	7·4% (2·8%–12·0%)
No-benefit group	1·35 (0·86–2·11)	-6·9% (-14·3% – 0·5%)

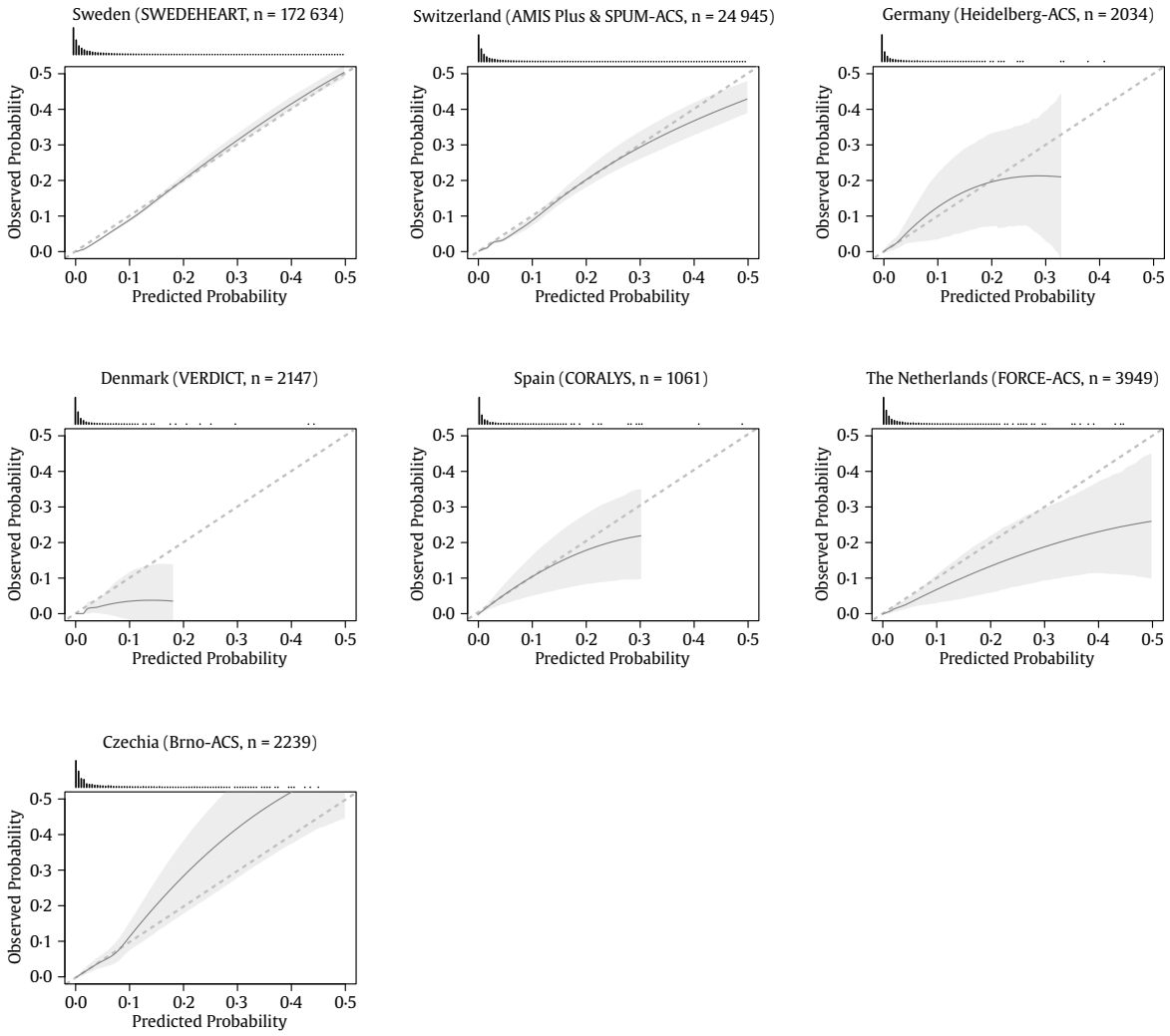
ARR=absolute risk reduction. CI=confidence interval. HR=hazard ratio. The $p_{interaction}$ of the zero-effect threshold and randomised trial group assignment is 0·026.

Supplementary figure 1: Calibration slope and calibration-in-the-large of the GRACE 3.0 in-hospital mortality model in unseen patient data stratified by country



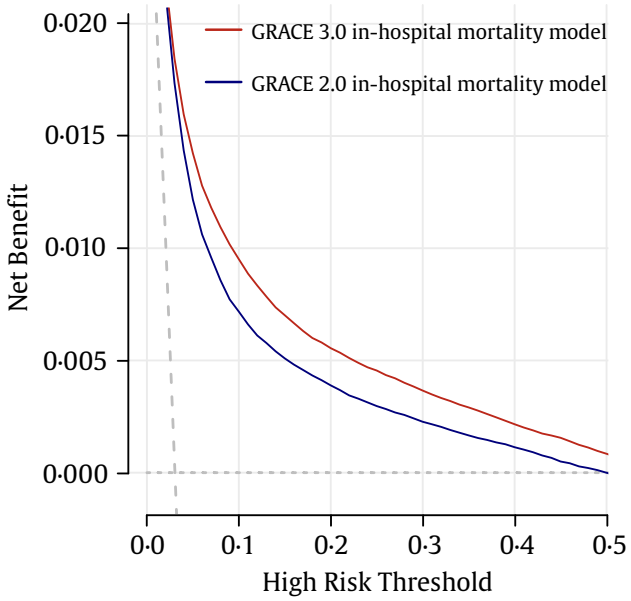
Calibration of the GRACE 3.0 in-hospital mortality model summarised as (A) calibration slope and (B) calibration-in-the-large. Plots display country-level estimates and 95% CI (squares with lines), and an overall pooled estimate and 95% CI (diamond). Square sizes correspond to relative weights. CI=confidence interval.

Supplementary figure 2: Calibration of the GRACE 3.0 in-hospital mortality model in unseen patient data stratified by country



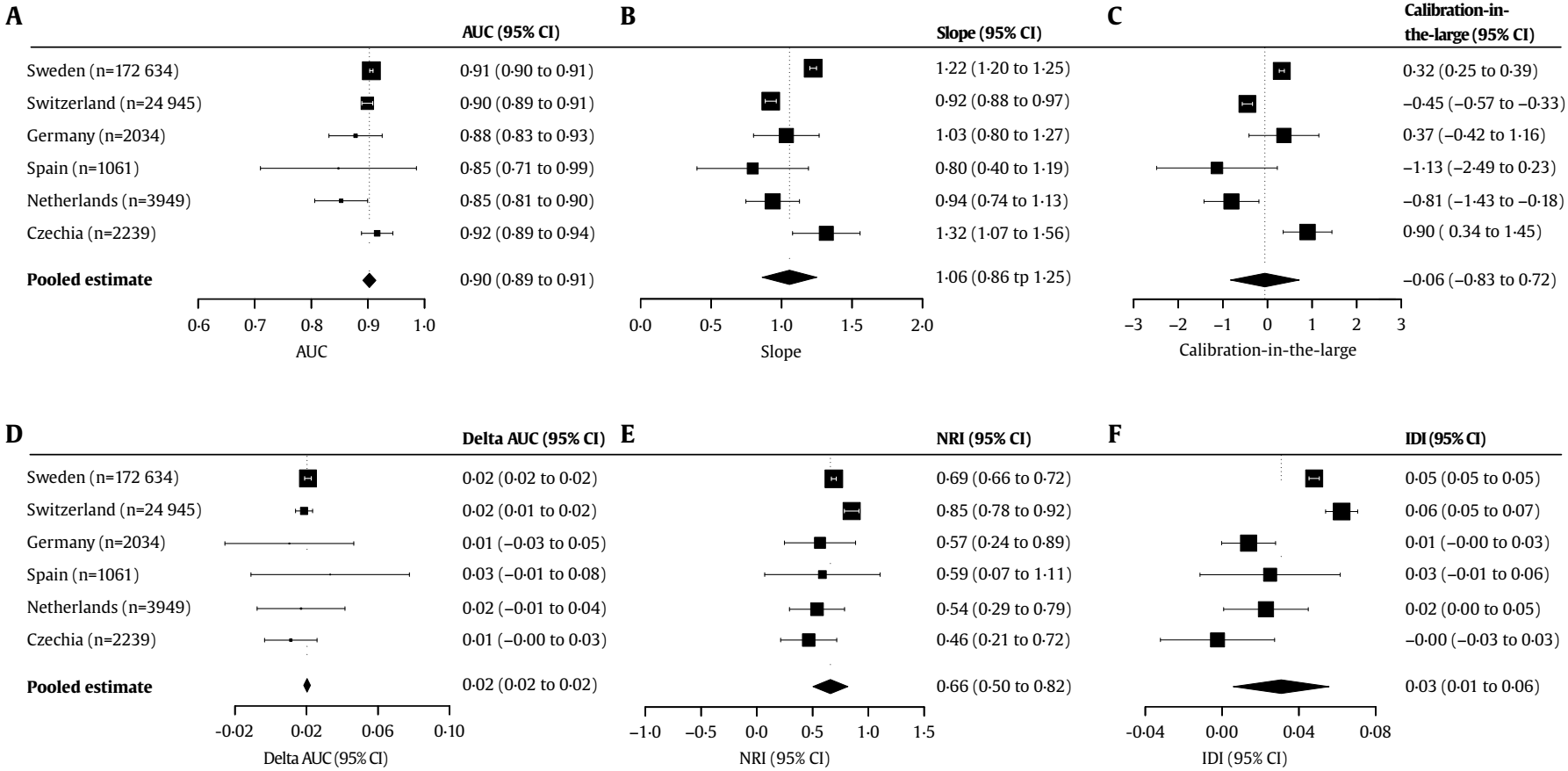
Predicted and observed risk of in-hospital mortality. Colour bands signify the 95% confidence interval (CI). Histograms on top of the graph show the distribution of model predictions in the population.

Supplementary figure 3: Decision curve analyses on the GRACE 3.0 in-hospital mortality model in unseen patient data of the external validation cohorts



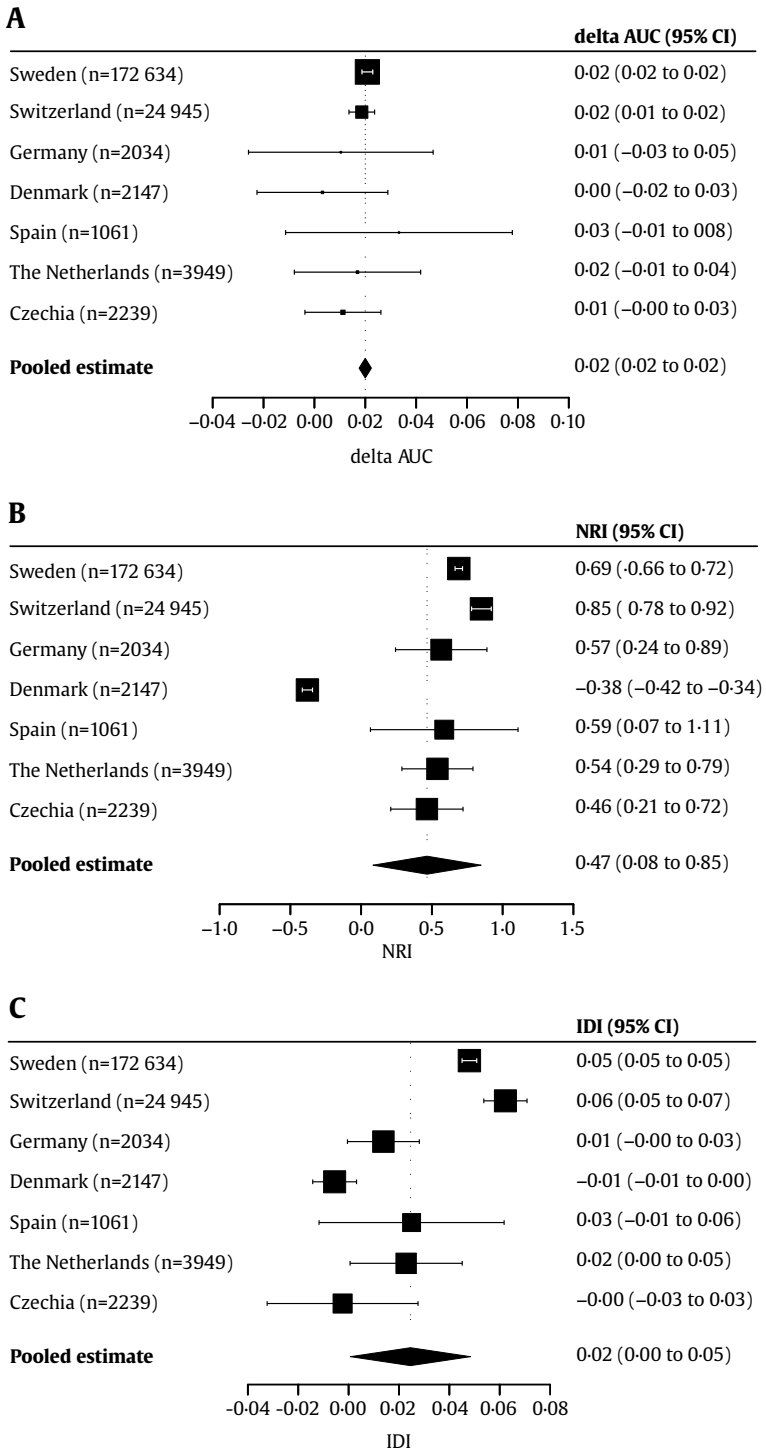
For each decision threshold, the net benefit of the GRACE 3.0 in-hospital mortality model and the GRACE 2.0 model for in-hospital mortality are shown. The net benefit assuming that all patients with ACS have an outcome risk higher than the threshold (dashed line) as well as the net benefit assuming that all patients with ACS have an outcome risk lower than the threshold (dotted line) are displayed. Across a range of clinically relevant decision thresholds, the GRACE 3.0 in-hospital mortality model was consistently positive and had substantial net benefit suggesting high clinical utility above and beyond the GRACE 2.0 in-hospital mortality model.

Supplementary figure 4: Sensitivity analysis of the performance of the in-hospital mortality model excluding patients from Denmark



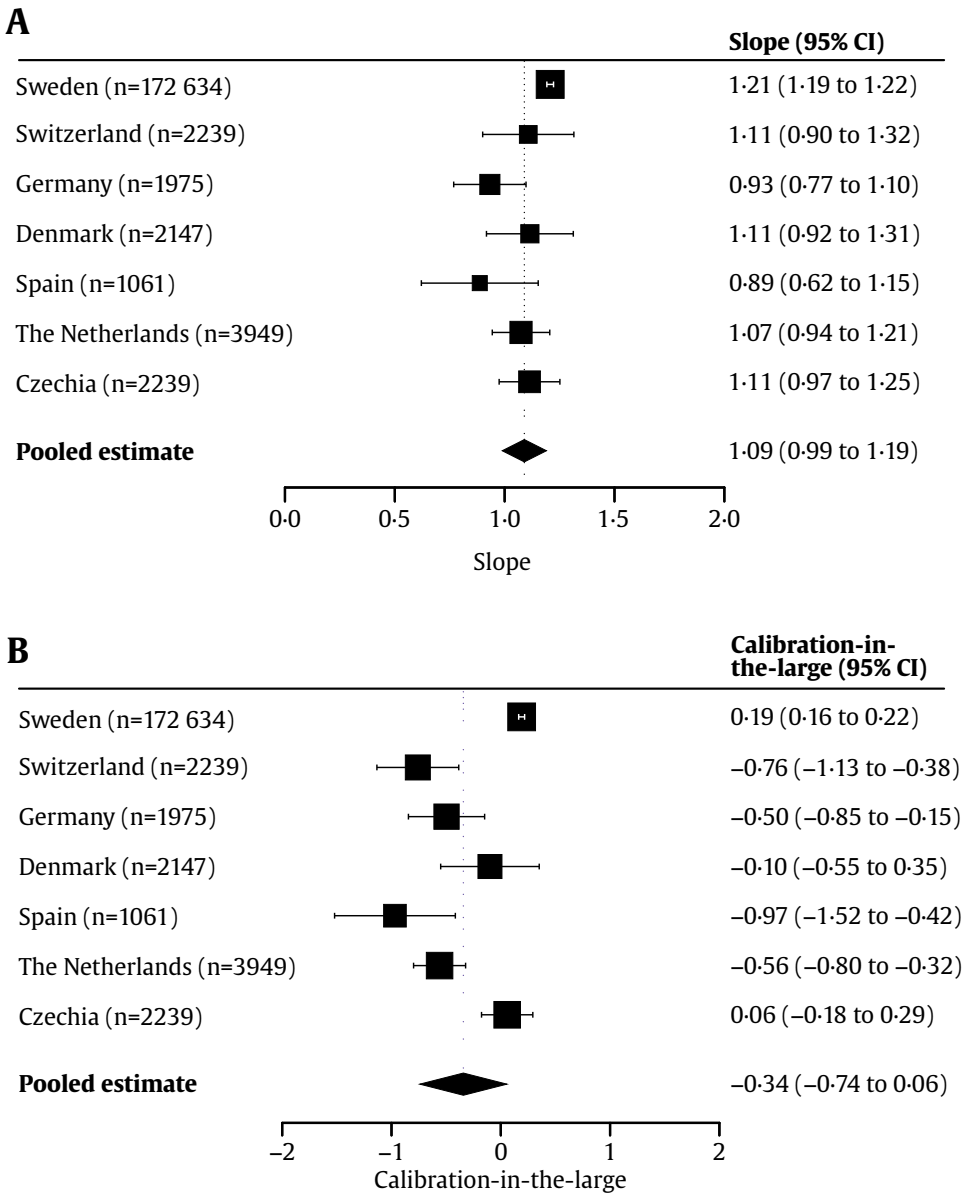
(A) Performance of the GRACE 3.0 in-hospital mortality model. Calibration of the GRACE 3.0 in-hospital mortality model summarised as (B) calibration slope and (C) calibration-in-the-large. Incremental performance of GRACE 3.0 in-hospital mortality model compared with the previous score version (v.2.0) in terms of (D) delta area under the receiver operating characteristic curve (AUC), (E) net reclassification improvement (NRI) and (F) integrated discrimination improvement index (IDI). Plots display country-level estimates and 95% CI (squares with lines), and an overall pooled estimate and 95% CI (diamond). Square sizes correspond to relative weights. Patients from Denmark were excluded from the analyses. CI=confidence interval.

Supplementary figure 5: Incremental discrimination and reclassification ability of the GRACE 3.0 in-hospital mortality model compared to the respective GRACE 2.0 model



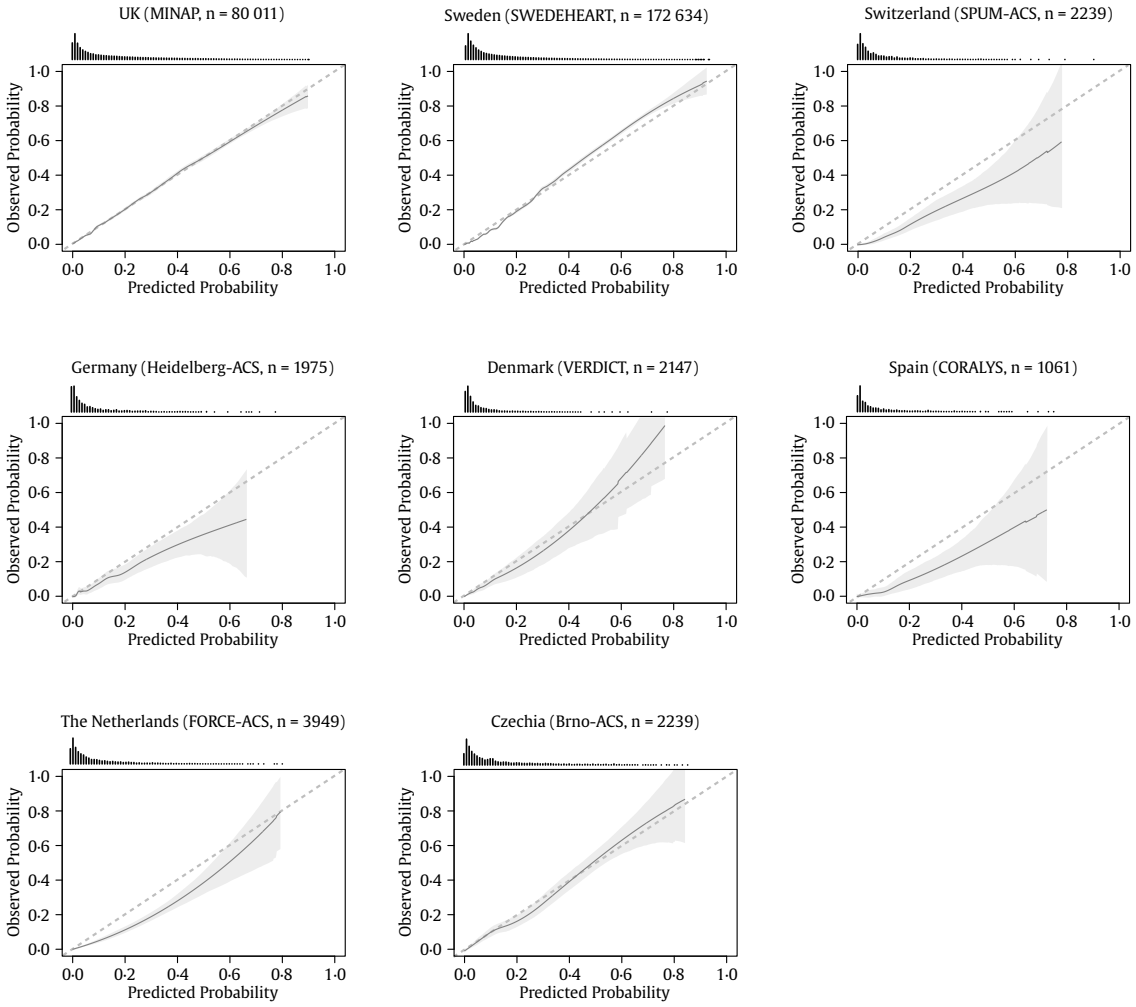
Incremental performance of GRACE 3.0 in-hospital mortality model compared with the previous score version (v.2.0)[74] in terms of (A) delta area under the receiver operating characteristic curve (AUC), (B) net reclassification improvement (NRI) and (C) integrated discrimination improvement index (IDI). Plots display country-level estimates and 95% CI (squares with lines), and an overall pooled estimate and 95% CI (diamond). Square sizes correspond to relative weights. CI=confidence interval.

Supplementary figure 6: Calibration slope and calibration-in-the-large of the GRACE 3.0 one-year mortality model in unseen patient data stratified by country



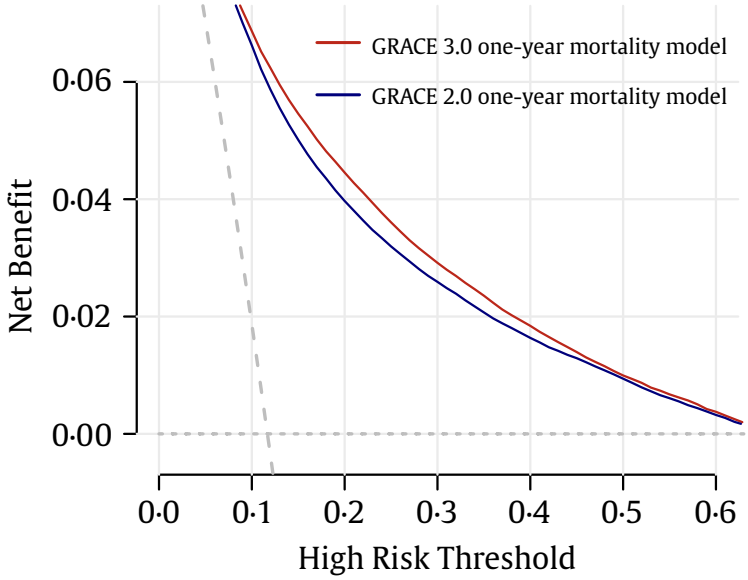
Calibration of the GRACE 3.0 one-year mortality model summarised as (A) calibration slope and (B) calibration-in-the-large. Plots display country-level estimates and 95% CI (squares with lines), and an overall pooled estimate and 95% CI (diamond). Square sizes correspond to relative weights. CI=confidence interval.

Supplementary figure 7: Calibration of the GRACE 3.0 one-year mortality model in unseen patient data form internal and external validation cohorts stratified by country



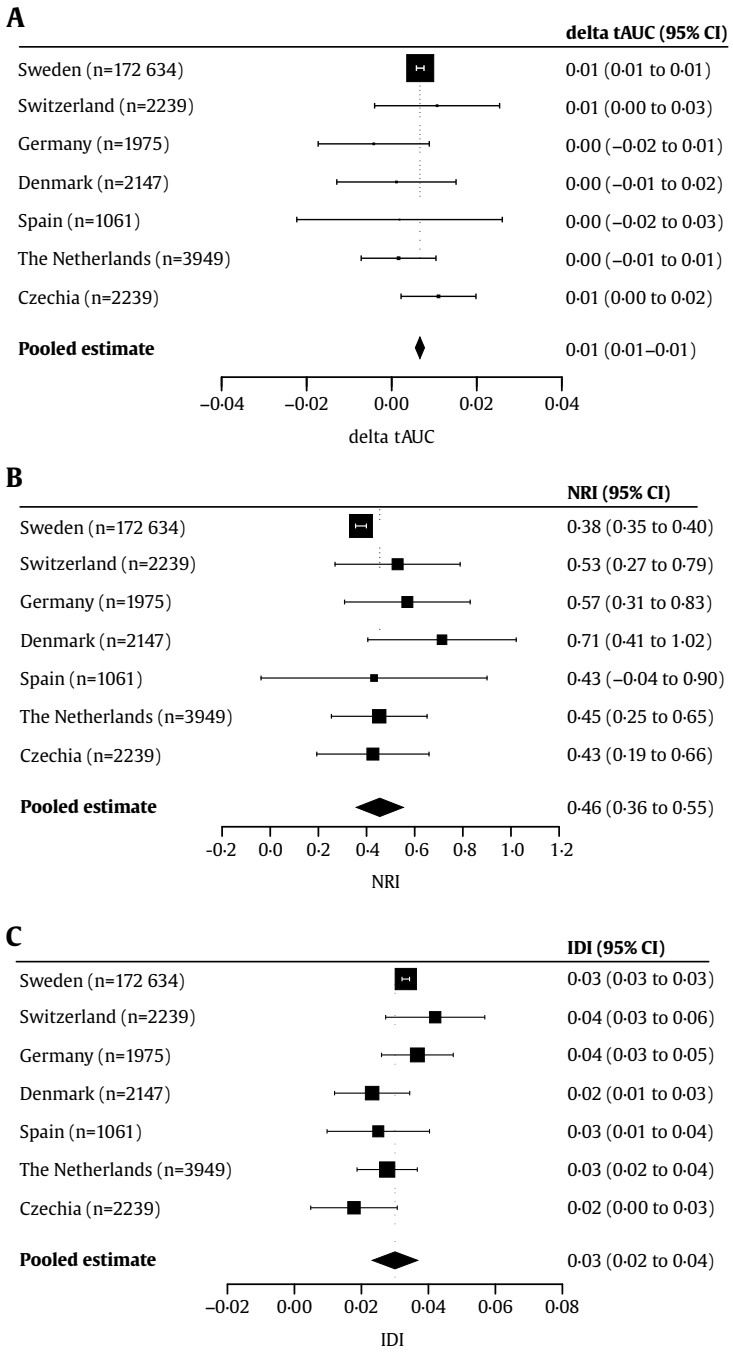
Predicted and observed risk of one-year mortality. Colour bands signify the 95% confidence interval (CI). Histograms on top of the graph show the distribution of model predictions in the population.

Supplementary figure 8: Decision analyses on the GRACE 3.0 one-year mortality model in unseen patient data of the external validation cohorts



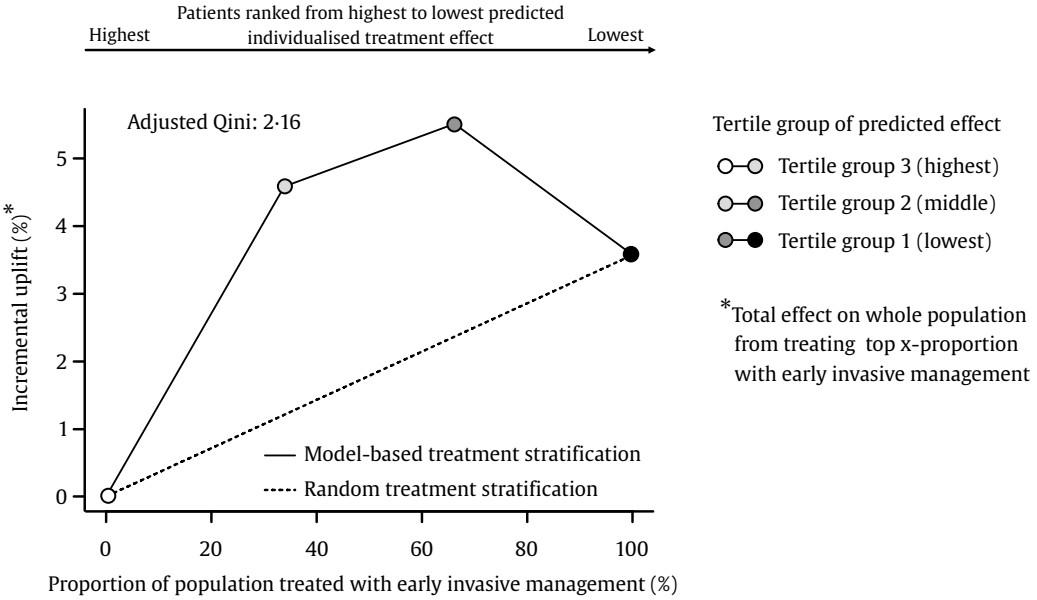
For each decision threshold, the net benefit of the GRACE 3.0 one-year mortality model and the GRACE 2.0 model for one-year mortality are shown. The net benefit assuming that all patients with ACS have an outcome risk higher than the threshold (dashed line) as well as the net benefit assuming that all patients with ACS have an outcome risk lower than the threshold (dotted line) are displayed. Across a range of clinically relevant decision thresholds, the GRACE 3.0 one-year mortality model was consistently positive and had substantial net benefit suggesting high clinical utility above and beyond the GRACE 2.0 one-year mortality model.

Supplementary figure 9: Incremental discrimination and reclassification ability of the GRACE 3.0 one-year mortality model compared to the respective GRACE 2.0 model



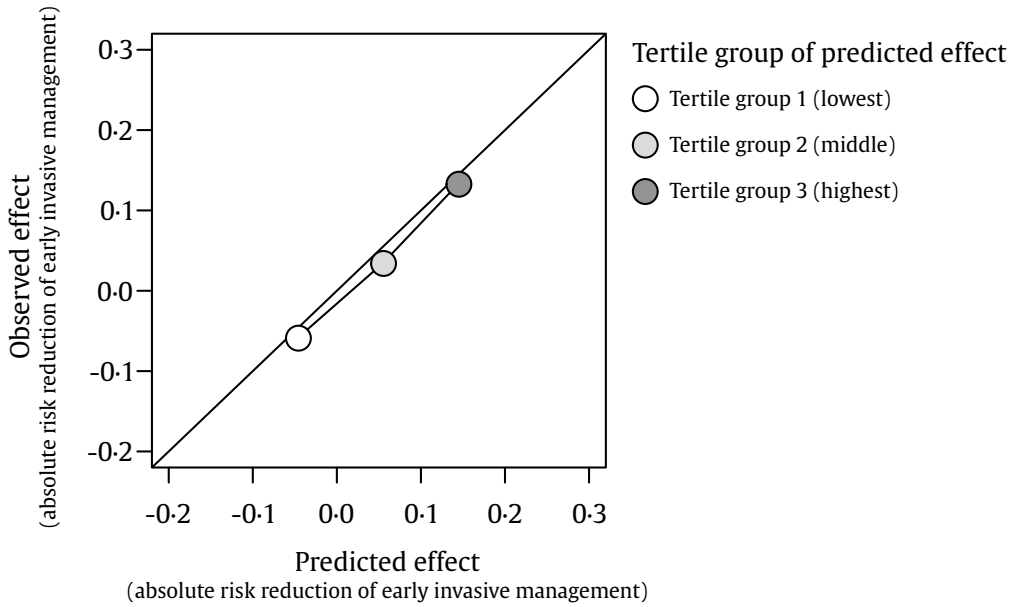
Incremental performance of GRACE 3.0 one-year mortality model compared with the previous score version (v.2.0)[74] in terms of (A) delta time-dependent area under the receiver operating characteristic curve (tAUC), (B) net reclassification improvement (NRI) and (C) integrated discrimination improvement index (IDI). Plots display country-level estimates and 95% CI (squares with lines), and an overall pooled estimate and 95% CI (diamond). Square sizes correspond to relative weights. CI=confidence interval.

Supplementary figure 10: Qini curve



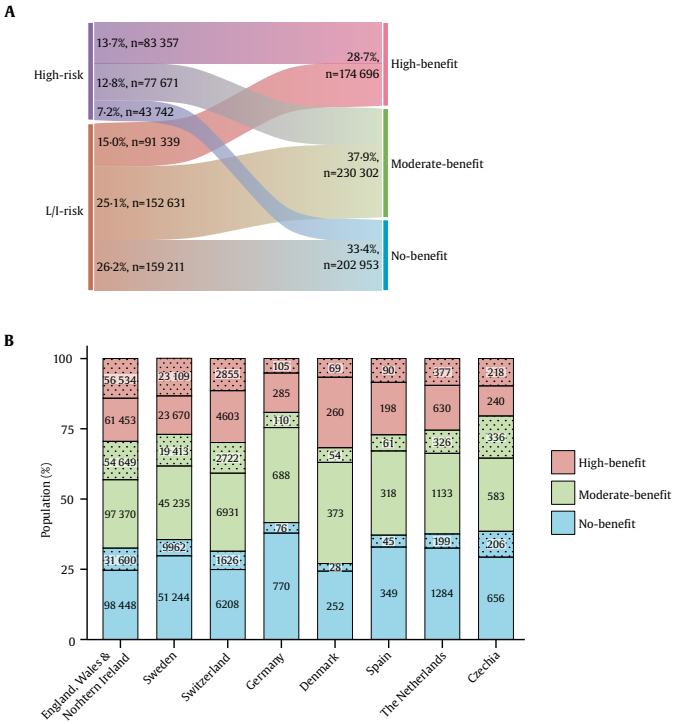
The figure depicts the discrimination of the individualised treatment effect model in the validation cohort. The x-axis displays the proportion of the population, ranked from highest to lowest predicted treatment effect, receiving early invasive management. The y-axis displays the total effect on the whole population from treating the top x-proportion with early, and the remaining patients with delayed invasive management. Consistent with the high discrimination of the model, the qini curve first increases (showing that patients for whom the model predicted the highest treatment effect experienced the largest benefit from the intervention), then plateaus (as the population begins to include patients with similar outcomes with early or delayed invasive management), and finally decreases (showing that patients for whom the model predicted the lowest treatment effect from early invasive management experienced no benefit from the intervention). The area between the solid line (early *vs* delayed invasive management based on predicted individualised treatment effect from the model) and the dotted line (random selection of patients for early invasive management) corresponds to the qini value.

Supplementary figure 11: Calibration of the GRACE 3.0 individualised treatment effect model in unseen patient data of the external validation cohort



Dots represent equally-sized patient groups based on tertiles of predicted effect. Tertile groups of predicted effect were created using the tertile cut-point of predicted treatment effect in the validation cohort: tertile group 1 (≤1·8 %), tertile group 2 (>1·8% and ≤9·2%), tertile group 3 (>9·2%). Both axes display the absolute risk reduction from early invasive management. The diagonal line indicates ideal calibration.

Supplementary figure 12: Modelling of hypothetical patient stratification according to individualised effect of early invasive management



(A) Re-stratification of patients with non-ST-elevation acute coronary syndrome from risk groups (according to in-hospital mortality risk predicted by GRACE 2.0) to benefit groups (according to the GRACE 3.0 individualised treatment effect model) for personalised selection of an early invasive management strategy using the individualised treatment effect model. The graph summarises aggregated results across all involved countries. (B) Patients were stratified to high-benefit, moderate-benefit and no-benefit groups according to country. Dotted areas correspond to patients classified as high-risk. The numbers in the bar segments refer to the corresponding absolute patient counts. Patients invoved in the development of the GRACE 3.0 individualised treatment effect model were excluded from the analyses. Low-to-intermediate (L/I)-risk: ≤3%, high risk: >3%, no-benefit: ≤0%, moderate-benefit: 0–9·5%, high-benefit: >9·5%

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