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

Florian A Wenzl, Klaus F Kofoed, Moa Simonsson, Gareth Ambler, Niels M R van der Sangen, Erik Lampa, Francesco Bruno, Mark A de Belder, Jiri Hlasensky, Matthias Mueller-Hennessen, Maria A Smolle, Peizhi Wang, José P S Henriques, Wouter J Kikkert, Henning Kelbæk, Luboš Bouček, Sergio Raposeiras-Roubín, Emad Abu-Assi, Jaouad Azzahhafi, Matthijs A Velders, Konstantinos Stellos, Thomas Engstrøm, Dean R P P Chan Pin Yin, Clive Weston, David Adlam, Hans Rickli, Evangelos Giannitsis, Dragana Radovanovic, Jiri Parenica, Charalambos A Antoniades, Keith A A Fox, Fabrizio D'Ascenzo, Jurriën M ten Berg, Lars V Køber, Stefan James, John Deanfield*, Thomas F Lüscher**

Summary

Background The Global Registry of Acute Coronary Events (GRACE) scoring system guides the management of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) according to current guidelines. However, broad validation of the sex-specific GRACE 3.0 in-hospital mortality model, and corresponding models for predicting long-term mortality and the personalised effect of early invasive management, are still needed.

Methods We used data of 609 063 patients with NSTE-ACS from ten countries between Jan 1, 2005, and June 24, 2024. A machine learning model for 1-year mortality was developed in 400 054 patients from England, Wales, and Northern Ireland. Both the in-hospital mortality model and the new 1-year mortality model were externally validated in patients from Sweden, Switzerland, Germany, Denmark, Spain, the Netherlands, and Czechia. A separate machine learning model to predict the individualised effect of early versus delayed invasive coronary angiography and revascularisation on a composite primary outcome of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischaemia, or hospital admission for heart failure at a median follow-up of 4·3 years was developed and externally validated in participants from geographically different sets of hospitals in the Danish VERDICT trial.

Findings The in-hospital mortality model (area under the receiver operating characteristic curve [AUC] 0·90, 95% CI 0·89–0·91) and the 1-year mortality model (time-dependent AUC 0·84, 95% CI 0·82–0·86) showed excellent discriminative abilities on external validation across all countries. Both models were well calibrated and decision curve analyses suggested favourable clinical utility. Compared with score version 2.0, both models provided improved discrimination and risk reclassification. The individualised treatment effect model effectively identified patients who would benefit from early invasive management on external validation. Patients with high predicted benefit had reduced risk of the composite outcome when randomly assigned to early invasive management (hazard ratio 0·60, 95% CI 0·41–0·88), whereas patients with no-to-moderate predicted benefit did not (1·06, 0·80–1·40; $p_{interaction}$=0·014). The individualised treatment effect model suggested that the group of patients with NSTE-ACS who benefit from early intervention might be incompletely captured by current treatment strategies.

Interpretation The updated GRACE 3.0 scoring system provides a validated, practical tool to support personalised risk assessment in patients with NSTE-ACS. Prediction of an individual's long-term cardiovascular benefit from early invasive management could refine future trial design.

Funding Swiss Heart Foundation, University of Zurich Foundation, Kurt and Senta Herrmann Foundation, Theodor and Ida Herzog-Egli Foundation, and Foundation for Cardiovascular Research–Zurich Heart House.

Lancet Digit Health 2025

Published Online https://doi.org/10.1016/j.landig.2025.100907

*Joint study directors

National Health Service England, London, UK (F A Wenzl MD); **Center for Molecular Cardiology, University of Zürich, Zürich, Switzerland** (F A Wenzl, P Wang BMed, Prof T F Lüscher MD); **Department of Cardiovascular Sciences, University of Leicester, Leicester, UK** (F A Wenzl); **Department of Clinical Sciences, Karolinska Institute, Stockholm, Sweden** (F A Wenzl); **Department of Cardiology, The Heart Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark** (K F Kofoed DMSc, T Engstrøm MD, Prof L V Køber DSci); **Department of Radiology, The Diagnostic Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark** (K F Kofoed); **Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (K F Kofoed); **Department of Medicine Solna, Karolinska Institute, Solna, Sweden** (M Simonsson MD); **Department of Statistical Science, University College London, London, UK** (G Ambler PhD); **Department of Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands** (N M R van der Sangen MD, J P S Henriques MD); **Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden** (E Lampa PhD,

Introduction

The Global Registry of Acute Coronary Events (GRACE) scoring system guides the treatment of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).[1,2] NSTE-ACS represents the most common type of ACS and constitutes a major cause of morbidity and mortality globally. Current guidelines support an early invasive management strategy in patients with in-hospital mortality risk exceeding 3% according to GRACE.[1,2] However, the current score version (2.0)[2–4] and the current treatment threshold[1,2] derive from studies[3,5] that used non-specific cardiac markers and were conducted before crucial improvements in patient care, including modern drug-eluting stents, complete functional revascularisation, and

Prof S James MD); **Division of Cardiology, Cardiovascular and Thoracic Department, Molinette Hospital, Città della Salute e della Scienza di Torino, Turin, Italy** (F Bruno MD, F D'Ascenzo MD); **Heart Division, Royal Brompton and Harefield Hospitals, London, UK** (F Bruno, Prof T F Lüscher); **National Institute for Cardiovascular Outcomes Research, NHS Arden and Greater East Midlands Commissioning Support Unit, Leicester, UK** (M A de Belder MD); **Department of Internal Medicine and Cardiology, University Hospital Brno and Faculty of Medicine of Masaryk University, Brno, Czechia** (J Hlasensky PhD, J Parenica PhD); **Department of Internal Medicine III, Cardiology, University Hospital of Heidelberg, Heidelberg, Germany** (M Mueller-Hennessen MD); **Comprehensive Cancer Center Graz, Medical University of Graz, Graz, Austria** (M A Smolle MD); **Department of Cardiology, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China** (P Wang); **Department of Cardiology, Tergooi Hospital, Hilversum, Netherlands** (W J Kikkert MD); **Department of Cardiology, Zealand University Hospital, Roskilde, Denmark** (H Kelbæk DMSc); **Department of Laboratory Medicine, Division of Clinical Biochemistry, University Hospital Brno, Brno, Czechia** (L Bouček MD); **Cardiology Department, Hospital Álvaro Cunqueiro, Pontevedra, Spain** (S Raposeiras-Roubín MD, E Abu-Assi MD); **Department of Cardiology, St Antonius Hospital, Nieuwegein, Netherlands** (J Azzahhafi MD, D R P P Chan Pin Yin MD; J M ten Berg MD); **Department of Clinical Physiology, Västmanland County Hospital, Västerås, Sweden** (M A Velders PhD); **Department of Medicine VI, University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany** (Prof K Stellos MD); **Department**

Research in context

Evidence before this study

The Global Registry of Acute Coronary Events (GRACE) scoring system guides the treatment of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) according to international guidelines. The machine learning-based GRACE 3.0 model for in-hospital mortality considers sex-specific differences and accounts for distinct characteristics of patients with NSTE-ACS rather than drawing on features of a broad ACS population, thereby attaining improved performance. We systematically searched PubMed for studies published from database inception up to Oct 5, 2024, using the search terms: "Global Registry of Acute Coronary Events", "GRACE", "ST-segment", and "acute coronary syndrome", with no language restrictions. No articles were excluded. Broad validation of the GRACE 3.0 in-hospital mortality model, and corresponding prediction models for longer-term mortality and individualised treatment effect, have not been reported but hold promise to improve the personalised management of patients with NSTE-ACS.

Added value of this study

Using data from 609 063 patients with NSTE-ACS from ten countries, we extended the GRACE scoring system by machine learning-based sex-specific and disease-specific 1-year mortality and individualised treatment effect models. In this study, we (1) substantiated the excellent performance of the GRACE 3.0 in-hospital mortality model upon large-scale external validation; (2) developed and externally validated a GRACE 3.0 1-year mortality model; and (3) developed and externally validated a GRACE 3.0 individualised treatment effect model to predict the individualised effect of early invasive management on long-term cardiovascular outcomes in patients with NSTE-ACS. By restricting the analyses to patients with NSTE-ACS, rather than a broad ACS population, the newly developed prediction models account for the substantial differences in patient characteristics, disease features, treatment strategies, and outcomes across the clinical spectrum of ACS. We leveraged participant-level trial data and applied, for the first time, an effect modelling approach considering complex non-linear relationships between baseline characteristics and individualised benefit in patients with NSTE-ACS. In contrast to conventional treatment selection algorithms for early invasive management, our study shows that the value of clinical characteristics is different for the prediction of risk and for the prediction of treatment effect. This approach highlights the potential of individual-level inference from randomised clinical trials to refine personalised care and suggests that current treatment strategies might incompletely capture the subset of patients with NSTE-ACS who benefit from early intervention.

Implications of all the available evidence

The updated GRACE 3.0 scoring system provides a validated, practical tool for clinical risk assessment. Based on nine clinical variables, GRACE 3.0 accurately predicts short-term and long-term mortality. In the context of a comprehensive clinical evaluation, GRACE 3.0 can support clinical decision making on patient triage and in personalising secondary prevention regimens. Prediction of the individualised, rather than the average, effect of early invasive management in patients with NSTE-ACS could refine future trial design and optimise management strategies.

intensified lipid-lowering therapy. Moreover, current treatment stratification according to GRACE does not incorporate the evolution of clinical NSTE-ACS phenotypes.[6]

Combined analyses including randomised controlled trials (RCTs) showed no interaction of current risk groups with the effect of early invasive management in patients with NSTE-ACS, bringing their clinical utility for present-day patients into question.[7,8] Better characterisation of individuals with NSTE-ACS who benefit from early invasive management is an unmet medical need.[2,8]

Recently, the GRACE 3.0 in-hospital mortality model was developed in patients undergoing contemporary treatment approaches.[9] The GRACE 3.0 in-hospital mortality model accounts for sex differences and for the clinical characteristics of patients with NSTE-ACS rather than drawing on features of a broad ACS population, thereby attaining improved performance. Large-scale validation of the GRACE 3.0 in-hospital mortality model and the development of a corresponding prediction model for longer-term mortality are needed. In parallel, the application of machine learning algorithms to RCT data provides a novel means to estimate heterogeneity of the effect of early invasive management in patients with NSTE-ACS.[10] Indeed, personalised prediction of individualised treatment effects, rather than basing treatment decisions on the average effect across a patient population, holds promise to guide future trial design and optimise management strategies.

Here, we sought to validate the GRACE 3.0 in-hospital mortality model in contemporary patients with NSTE-ACS and to extend the GRACE scoring system by sex-specific and disease-specific 1-year mortality and individualised treatment effect models.

Methods

Study design

In this multicentre development and validation study, we used data from large patient registries and an RCT to complete large-scale external validation of the GRACE 3.0 in-hospital mortality model and to develop and externally validate a 1-year mortality model and an individualised treatment effect model to predict the effect of early invasive management in patients with NSTE-ACS. We used data of 609 063 patients with NSTE-ACS from ten countries: England, Wales, Northern Ireland, Sweden, Switzerland, Germany, Denmark, Spain, the Netherlands, and Czechia

(figure 1). Only patients with NSTE-ACS, rather than a broad ACS population, were included due to marked differences in patient characteristics,[2] disease features,[11] treatment,[2,11] and outcomes[11] across the clinical spectrum of ACS.

The GRACE 3.0 in-hospital mortality model was externally validated in patients from Sweden, Switzerland, Germany, Denmark, Spain, the Netherlands, and Czechia. To refine the assessment of longer-term mortality risk, a novel sex-specific prediction model for 1-year mortality (GRACE 3.0 1-year mortality model) was developed in contemporary patients from England, Wales, and Northern Ireland, and externally validated in patients from the other seven countries. To estimate the personalised benefit of early invasive management on long-term outcomes on an individual level, we used an effect modelling approach and developed a prediction model for the individualised effect of early invasive management (GRACE 3.0 individualised treatment effect model), harnessing participant-level data from the randomised controlled Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography (VERDICT) trial.[12] A geographical split of hospitals participating in VERDICT was used to define a development cohort (n=1111) and a spatially separated external validation cohort (n=1036), as reported previously (appendix pp 2–4, 12, 15).[13] The potential impact of the GRACE 3.0 individualised treatment effect model on patient stratification was estimated in all countries. Ethical approval was obtained from the respective institutional review boards and participant consent was obtained or waived in accordance with the prevailing local policy (appendix p 6).

Participants

In the UK, patient data were retrieved from the Myocardial Ischaemia National Audit Project (MINAP), a prospective nationwide registry of patients with ACS. Between Jan 1, 2005, and March 31, 2017, 400 054 patients with NSTE-ACS presenting to any of the participating hospitals in England, Wales, and Northern Ireland were included (appendix pp 7–9).[9] 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 nationwide registry of patients with ACS, and included 172 634 patients with NSTE-ACS presenting between Jan 1, 2005, and Jan 16, 2022 (appendix p 10). In Switzerland, we used data from the prospective nationwide ACS registry (Acute Myocardial Infarction in Switzerland [AMIS] Plus, NCT01305785) and from the prospective multicentre Special Programme University Medicine Acute Coronary Syndromes (SPUM-ACS) cohort (NCT01000701),[14] including a total of 24 945 patients with NSTE-ACS between Jan 1, 2005, and Sept 30, 2023 (appendix p 11). In Germany, patient data were retrieved from the prospective Heidelberg ACS cohort study (Heidelberg-ACS),[15] including 2034 patients with NSTE-ACS presenting to Heidelberg University Hospital between June 9, 2009, and May 10, 2014 (appendix pp 2, 12). In Denmark, we used data from the VERDICT trial (NCT02061891),[12] which comprises 2147 patients presenting with NSTE-ACS to participating hospitals in Denmark between Nov 26, 2010, and April 29, 2016 (appendix p 12). In Spain, patient data were retrieved from the Incidence and Predictors of Heart Failure after Acute Coronary Syndrome (CORALYS) registry (NCT04895176),[16] including 1061 patients with NSTE-ACS recruited between Jan 1, 2014, and Sept 27, 2020 (appendix pp 2, 12). 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),[17] and included 3949 patients with NSTE-ACS presenting to participating hospitals (appendix p 12) between Jan 1, 2015, and March 18, 2023 (appendix p 12). In Czechia, we used data from two prospective registries at University Hospital Brno (Brno-ACS),[18] and included 2239 patients with NSTE-ACS between July 24, 2009, and June 24, 2024 (appendix pp 3, 12). Data on sex for all participants were collected from medical records with two options available (male and female).

Outcomes

Mortality during hospitalisation and at 365 days after admission were the primary outcomes of the GRACE 3.0 in-hospital mortality model and the GRACE 3.0 1-year mortality model, respectively. The composite primary outcome of the VERDICT trial—first occurrence of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischaemia, or hospital admission for heart failure—was used as a binary outcome for the development of the GRACE 3.0 individualised treatment effect model.

In MINAP, SWEDEHEART, and Brno-ACS, mortality was obtained by linkage of unique patient identifiers to the UK Office for National Statistics, the Swedish Population registry, and the Czech National Health Information System, respectively. In SPUM-ACS, Heidelberg-ACS, VERDICT, Brno-ACS, and FORCE-ACS, fatal events were prospectively recorded by the investigators. In CORALYS, deaths were assessed by review of electronic and hard copy medical files. Event data were verified by an independent event adjudication committee in SPUM-ACS, VERDICT, Brno-ACS, and FORCE-ACS.

Development of 1-year mortality model

Consistent with the in-hospital mortality model,[9] we applied a machine learning approach to predict mortality at 1 year in patients with NSTE-ACS. We used eXtreme Gradient Boosting (XGBoost),[9,19] a well established and widely used tree-based ensemble learning algorithm capturing complex and non-linear relationships, which leverages advanced regularisation to reduce overfitting. The model was developed in 400 054 patients from England, Wales, and Northern Ireland. We used Bayesian optimisation with ten-fold cross-validation and an 80:20 split into a training

of Cardiovascular Research, European Center for Angioscience, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (Prof K Stellos); **German Centre for Cardiovascular Research (DZHK), Partner Site Heidelberg/Mannheim, Mannheim, Germany** (Prof K Stellos); **Helmholtz-Institute for Translational AngioCardioScience (HI-TAC) of the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) at the Heidelberg University, Heidelberg, Germany** (Prof K Stellos); **Glangwili General Hospital, Carmarthen, UK** (C Weston MRCP); **Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Biomedical Research Centre, Leicester, UK** (D Adlam DPhil); **Cardiology Division, Kantonsspital St Gallen, St Gallen, Switzerland** (Prof H Rickli MD); **Department of Cardiology, University Hospital Heidelberg, Heidelberg, Germany** (E Giannitsis MD); **AMIS Plus Data Center, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland** (D Radovanovic MD); **Acute Multidisciplinary Imaging and Interventional Centre, British Heart Foundation Centre of Research Excellence, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK** (Prof C A Antoniades PhD); **NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK** (Prof C A Antoniades); **Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK** (Prof K A A Fox MB ChB); **Department of Cardiology, University Medical Center Maastricht, Maastricht, Netherlands** (J M ten Berg); **Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden** (Prof S James); **Institute of Cardiovascular Science, University College London,**

London, UK (Prof J Deanfield FMedSci); National Heart and Lung Institute, Imperial College London, London, UK (Prof T F Lüscher); School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, London, UK (Prof T F Lüscher); Department of Cardiology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China (P Wang)

Correspondence to:
Dr Florian A Wenzl, National Health Service England, London SE1 8UG, UK
florian.wenzl1@nhs.net

or

Prof Thomas F Lüscher, Royal Brompton and Harefield Hospitals, London SW3 6NP, UK
cardio@tomluescher.ch

For the **GRACE 3.0 score** see https://www.grace-3.com/

See **Online** for appendix

For **MINAP** see https://www.nicor.org.uk/national-cardiac-audit-programme/heart-attack-audit-minap

For **SWEDEHEART** see https://www.ucr.uu.se/swedeheart

For **AMIS Plus** see https://amis-plus.ch

cohort (n=320 043) and an internal validation cohort (n=80 011; appendix p 3) to identify the optimal configuration of hyperparameters. Tuned hyperparameters, ranges explored, and final configurations are available in the appendix (pp 3, 18). The final model (GRACE 3.0 1-year mortality model) was then evaluated on unseen data of the external validation cohorts. Given their broad availability and worldwide use, the GRACE variables (age, sex, heart rate, systolic blood pressure, Killip class, creatinine concentration, cardiac arrest, presence of ST-segment deviation, and troponin elevation) were used as model features. The importance of individual model features was evaluated using the Shapley additive explanations (SHAP) approach (appendix p 4).

Development of individualised treatment effect model

In a post-hoc analysis of the VERDICT trial, we developed a machine learning model (GRACE 3.0 individualised treatment effect model) to predict the benefit of early invasive management. VERDICT is a prospective, multicentre, open-label, parallel-group RCT evaluating the optimal timing of invasive coronary angiography and revascularisation in terms of long-term outcome in patients with NSTE-ACS.[12] In VERDICT, patients were randomly assigned (1:1) to receive either early invasive management within 12 h from the time of diagnosis or delayed invasive management within 48–72 h. Among all RCTs on the optimal timing of invasive management to date, 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. VERDICT is the only large-scale trial on the optimal timing of invasive management in contemporary patients with NSTE-ACS. We applied Rboost, an XGBoost implementation of the R-learner framework, to predict the individualised treatment effect as a function of baseline characteristics, as described previously (appendix pp 3–4).[20] Overfitting was minimised by using the GRACE variables as prespecified model features, as recommended.[21] Rboost has proven efficient in the accurate prediction of individualised treatment effects using randomised clinical trial data in other clinical settings.[20] Given the low number of patients in VERDICT, we used differential seed initialisation in sequential runs and trained five different base models to improve stability.[20,22] Hyperparameters were tuned using five-fold cross-validation. The tuned hyperparameter configurations of the five base models for treatment effect are available in the appendix (p 19).[20] Final predictions were means of the five different base model estimates and represent the expected absolute risk reduction in the primary outcome for early invasive management compared with delayed invasive management.[20,22] The contribution of individual features to the model output was assessed using an effect modelling-based adaptation of the SHAP approach, as reported previously (appendix p 4).[20]

Performance of mortality models

The discrimination performance of the GRACE 3.0 in-hospital mortality and GRACE 3.0 1-year mortality models was assessed by the area under the receiver operating characteristic curve (AUC) and the time-dependent AUC (tAUC) at 365 days, respectively. The tAUC was derived using inverse probability of censoring weighting estimates of time-dependent receiver operating characteristic curves. Calibration was evaluated by constructing smoothed calibration curves and by calculating the calibration slope and the calibration-in-the-large.[9] The calibration slope quantifies the spread of predicted risks, with an ideal value of one. Calibration-in-the-large measures whether a model systematically overpredicts or underpredicts risk, and the optimal value is zero. Clinical utility of the in-hospital mortality and 1-year mortality models was assessed using decision curve analyses. This analysis assesses the trade-off between correctly identifying true positives (occurrence of the event) and incorrectly identifying false positives across a range of threshold probabilities. We evaluated potential performance heterogeneity in sex-specific subgroup analyses. We compared the GRACE 3.0 in-hospital and 1-year mortality models with the respective 2.0 models,[4] and assessed the improvement in risk discrimination and reclassification by calculating (1) the difference in AUC and tAUC, respectively (delta AUC and delta tAUC, respectively), (2) the integrated discrimination improvement (IDI) index, and (3) the continuous net reclassification improvement (NRI). All three metrics suggest improved performance if values are positive.

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 discrimination performance of the GRACE 3.0 individualised treatment effect model was evaluated in the validation cohort by calculating the C-for-benefit, which describes the concordance between predicted and observed treatment benefit.[20,23] The C-for-benefit of individualised treatment effect prediction models 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. The C-for-benefit commonly ranges from 0·5 (chance) to 0·6 in clinical trial data,[20,23] with higher values indicating better discrimination and values higher than 0·6 considered unusual.[23] In addition, we calculated the adjusted Qini value, where values greater than zero indicate discrimination that is better than chance.[24] The Qini value corresponds to the total effect on the whole population from intervention assignment based on model predictions compared with random ordering of patients for intervention assignment and can be derived from the Qini curve (appendix 35). We also calculated the concentration of benefit (Cb) of the predicted individualised treatment effect

values, which ranges from zero to one, with increasing values indicating higher value for informing treatment selection.[25] 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. The calibration of the GRACE 3.0 individualised treatment effect model was evaluated by comparing the observed benefit with the predicted benefit across tertiles of predicted effect (appendix p 36).[20,23]

We defined a threshold for high predicted benefit of early invasive management at the second tertile cut point of predicted treatment effect in the development cohort (ie, 9·5% absolute risk reduction), as reported previously,[20] to derive high-benefit (>9·5%), moderate-benefit (0 to 9·5%), and no-benefit (<0%) groups. This high-benefit threshold was then applied to the external validation cohort to form a high-benefit group and a no-to-moderate-benefit group.[20] To assess heterogeneity in the effect of early versus delayed invasive management on the primary composite outcome across predicted benefit groups in the external validation cohort, we used Cox regression and tested the significance of the interaction term between benefit group and randomised treatment allocation. Next, the effect of early versus delayed invasive management on the primary composite outcome in patients in the high-benefit and no-to-moderate-benefit groups was estimated. The absolute risk reduction in long-term cardiovascular outcomes was calculated as the difference in event incidence rates between patients randomly assigned to early invasive management versus those randomly assigned to delayed invasive management. Cumulative incidence curves were constructed according to benefit group and randomised treatment allocation. 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.

Treatment stratification

Current GRACE 2.0 risk categories[1,2] stratify patients according to their predicted risk of in-hospital death into groups at low-to-intermediate risk (≤3%; ≤140 points) and high risk (>3%; >140 points), with early invasive management recommended in the group at high risk.[2] To estimate the potential impact of the GRACE 3.0 individualised treatment effect model on patient stratification, we assessed the proportion of individuals stratified into discordant treatment groups using GRACE 3.0 individualised treatment effect groups compared with standard stratification based on GRACE 2.0.[4]

Statistical analysis

A detailed description of the statistical analyses is presented in the appendix (pp 3–6). Continuous variables are presented as median and IQR. Categorical data are shown as counts and valid percentages. Analyses were conducted using multiply imputed data (ten imputations) and results were pooled

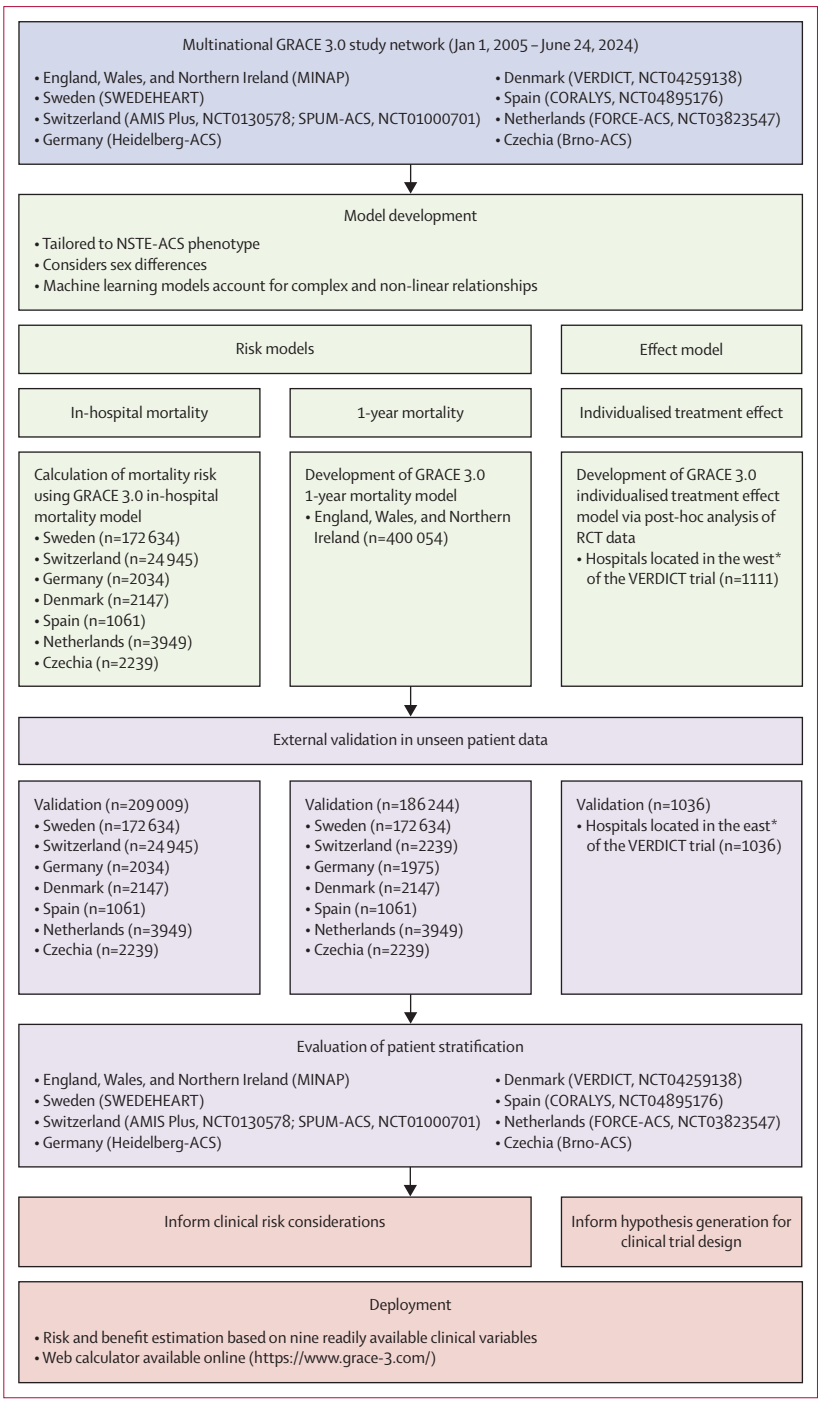

Figure 1: **Study design**
Study cohorts, model development, external validation, and deployment of the GRACE 3.0 score. AMIS Plus=Acute Myocardial Infarction in Switzerland Plus. Brno-ACS=two prospective registries at University Hospital Brno. CORALYS=Incidence and Predictors of Heart Failure after Acute Coronary Syndrome. FORCE-ACS=Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome. GRACE=Global Registry of Acute Coronary Events. Heidelberg-ACS=prospective Heidelberg ACS cohort study. MINAP=Myocardial Ischaemia National Audit Project. NSTE-ACS=non-ST-elevation acute coronary syndrome. RCT=randomised controlled trial. SPUM-ACS=Special Programme University Medicine Acute Coronary Syndromes. SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. VERDICT=Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography. *Hospitals located in the geographical west and east of the VERDICT trial are given in the appendix (pp 4, 7–12).

using Rubin's rules, as appropriate (appendix pp 6, 17). Performance metrics were pooled across countries using a random-effects meta-analysis based on the Hartung-Knapp-Sidik-Jonkmann method[26] to derive overall point estimates and 95% CIs. This approach ensures that between-country differences are appropriately considered when summarising performance estimates. Data reporting follows the principles as outlined by the TRIPOD AI statement, the STROBE statement, and the PATH statement. All p values and CIs are two-tailed. Results were deemed to be statistically significant at a p value lower than 0·05. Data were analysed in R (version 4.3 or later), Stata (version 14.0 or later), and IBM SPSS (version 28.0.1.1). A web calculator for all GRACE 3.0 models is available online.

For the **GRACE 3.0 web calculator** see https://www.grace-3.com

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2005, and June 24, 2024, 609 063 patients with NSTE-ACS were included (figure 1). There were 61 741 deaths at 1 year in the development cohort from England, Wales, and Northern Ireland alongside 6373 deaths during hospitalisation, and 21 904 deaths at 1 year in Sweden, Switzerland, Germany, Denmark, Spain, the Netherlands, and Czechia. Patient characteristics across the involved countries are shown in the table and in the appendix (pp 13–14).

The GRACE 3.0 in-hospital mortality model showed excellent discrimination performance on external validation (AUC 0·90, 95% CI 0·89–0·91), with AUC values ranging from 0·85 (0·71–0·99) in Spain to 0·92 (0·89–0·94) in Czechia (figure 2; appendix p 29). The GRACE 3.0 in-hospital mortality model was well calibrated (slope 1·06, 95% CI 0·90–1·22; calibration-in-the-large –0·15, 95% CI –0·86 to 0·57) with decision curve analyses suggesting high utility across a range of clinically relevant thresholds beyond GRACE 2.0 (figure 2; appendix pp 26–28).

For the prediction of mortality at 1 year, old age and high creatinine had the highest relative importance (figure 3). The novel GRACE 3.0 1-year mortality model showed high performance on internal validation (tAUC 0·84, 95% CI 0·83–0·84) and on external validation (0·84, 0·82–0·86), with tAUC values ranging from 0·79 (0·71–0·87) in Spain to 0·86 (0·85–0·86) in Sweden (figure 3; appendix pp 20–21). The GRACE 3.0 1-year mortality model showed acceptable calibration (slope 1·09, 95% CI 0·99–1·19; calibration-in-the-large -0·34, 95% CI –0·74 to 0·06) and favourable clinical utility across clinically relevant thresholds on decision curve analysis (figure 3; appendix pp 31–33). The in-hospital mortality and 1-year mortality models provided helpful predictive performance across sex-specific subgroups (appendix p 22).

Both models surpassed the respective GRACE 2.0 models, leading to improved risk discrimination and reclassification in the whole population. For in-hospital mortality, the models showed a significant improvement (delta AUC 0·02, 95% CI 0·02–0·02, p<0·0001; IDI 0·02, 95% CI 0·00–0·05, p=0·045; NRI 0·47, 95% CI 0·08–0·85, p=0·025). Similarly, for 1-year mortality, there were significant improvements (delta tAUC 0·01, 95% CI 0·01–0·01, p<0·0001; IDI 0·03, 95% CI 0·02–0·04, p<0·0001; NRI 0·46, 95% CI 0·36–0·55, p<0·0001). Detailed results are available in the appendix (pp 24, 30, 34). Similar improvements were observed for in-hospital mortality and 1-year mortality when patients were stratified according to sex (appendix p 23).

The novel GRACE 3.0 individualised treatment effect model effectively identified patients who would benefit from early invasive management (C-for-benefit 0·56, 95% CI 0·52–0·60; adjusted Qini value 2·16, 95% CI 0·19–3·61; Cb 0·55, 95% CI 0·21–0·94). There was good agreement between predicted and observed treatment effect (appendix p 36). Patients for whom the GRACE 3.0 individualised treatment effect model predicted high benefit from early invasive management were younger, more likely to be female, and had lower creatinine levels, more signs of myocardial ischaemia, and worse haemodynamic status (figure 4; appendix p 16). Patients with high predicted benefit from early invasive management had lower risk of the composite outcome when randomly assigned to early invasive management than when randomly assigned to delayed invasive management (hazard ratio [HR] 0·60, 95% CI 0·41–0·88; absolute risk reduction 14·4%, 95% CI 7·3–21·5, $p_{interaction}$=0·014), whereas patients with no-to-moderate predicted benefit did not (HR 1·06, 95% CI 0·80–1·40; absolute risk reduction –1·3%, 95% CI –6·0% to 3·3%). Sensitivity analyses using alternative groups yielded consistent results (appendix p 25). Across all countries, the GRACE 3.0 individualised treatment effect model would lead to substantial re-stratification of patients with NSTE-ACS compared with the current risk-based treatment stratification based on GRACE 2.0, suggesting that the group of patients who benefit from early intervention in terms of long-term cardiovascular outcomes might be incompletely captured by current treatment strategies (appendix p 37).

Discussion

The GRACE scoring system guides the management of patients with NSTE-ACS according to international guidelines. Here, we (1) externally validated the recently introduced GRACE 3.0 in-hospital mortality model; (2) developed and externally validated a GRACE 3.0 1-year mortality model; and (3) developed and externally validated a GRACE 3.0 individualised treatment effect model to predict the effect of early invasive management in contemporary patients with NSTE-ACS.

Whereas score version 2.0[2,4] is not specifically tailored to the NSTE-ACS patient population, does not account for potential complex, non-linear relationships, and ignores sex differences, the GRACE 3.0 models incorporate these aspects. Compared with GRACE 2.0, both the GRACE 3.0

	England, Wales, and Northern Ireland (MINAP; n=400 054)	Sweden (SWEDEHEART; n=172 634)	Switzerland (AMIS Plus and 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)
Age, years	72 (61–81)	72 (63–81)	68 (58–78)	69 (58–77)	64 (54–73)	67 (57–77)	70 (60–77)	69 (61–77)
Sex								
Female	145 738/400 054 (36·4%)	59 806/172 634 (34·6%)	6549/24 944 (26·3%)	618/2034 (30·4%)	735/2147 (34·2%)	310/1061 (29·2%)	1197/3947 (30·3%)	645/2239 (28·8%)
Male	254 316/400 054 (63·6%)	112 828/172 634 (65·4%)	18 395/24 944 (73·7%)	1416/2034 (69·6%)	1412/2147 (65·8%)	751/1061 (70·8%)	2750/3947 (69·7%)	1594/2239 (71·2%)
BMI, kg/m^2	27·2 (24·1–30·8)	26·6 (24·1–29·7)	27·0 (24·0–30·0)	..	26·3 (23·9–29·5)	27·7 (25·0–31·0)	27·0 (24·5–30·1)	28·1 (25·5–31·2)
Current smoker	77 255/355 326 (21·7%)	27 351/160 963 (17·0%)	7325/21 963 (33·4%)	769/1910 (40·3%)	665/2147 (31·0%)	269/1061 (25·4%)	881/3836 (23·0%)	487/1778 (27·4%)
Heart rate, bpm	78 (66–92)	78 (66–92)	75 (65–88)	73 (64–84)	74 (65–78)	72 (61–85)	74 (63–88)	72 (64–83)
Systolic blood pressure, mm Hg	140 (122–159)	150 (131–170)	140 (122–159)	150 (135–166)	143 (129–161)	144 (129–160)	146 (130–164)	140 (125–160)
Cardiac arrest	3675/389 378 (0·9%)	2712/172 539 (1·6%)	691/24 888 (2·8%)	1/2030 (0·0%)	0/2147 (0·0%)	8/1061 (0·8%)	56/3941 (1·4%)	32/2239 (1·4%)
ST-segment deviation	96 187/384 738 (25·0%)	57 254/172 634 (33·2%)	8096/24 697 (32·8%)	341/1817 (18·8%)	825/2113 (39·0%)	275/1061 (25·9%)	1107/3949 (28·0%)	946/2175 (43·5%)
Left ventricular ejection fraction ≥50%	102 776/168 262 (61·1%)	86 842/127 923 (67·9%)	10 175/15 200 (66·9%)	..	1371/1834 (74·8%)	839/1032 (81·3%)	1362/1733 (78·6%)	1204/1864 (64·6%)
Killip class								
I	157 040/201 438 (78·0%)	150 127/168 118 (89·3%)	20 732/24 343 (85·2%)	1906/2029 (93·9%)	2038/2126 (95·9%)	963/1061 (90·8%)	3365/3903 (86·2%)	1837/2156 (85·2%)
II	31 690/201 438 (15·7%)	14 866/168 118 (8·8%)	2370/24 343 (9·7%)	99/2029 (4·9%)	70/2126 (3·3%)	64/1061 (6·0%)	498/3903 (12·8%)	194/2156 (9·0%)
III	11 588/201 438 (5·8%)	2199/168 118 (1·3%)	713/24 343 (2·9%)	21/2029 (1·0%)	18/2126 (0·8%)	25/1061 (2·4%)	30/3903 (0·8%)	100/2156 (4·6%)
IV	1120/201 438 (0·6%)	926/168 118 (0·6%)	528/24 343 (2·2%)	3/2029 (0·2%)	..	9/1061 (0·8%)	10/3903 (0·3%)	25/2156 (1·2%)
Medical history								
Diabetes	90 940/369 833 (24·6%)	44 477/172 634 (25·8%)	5745/23 909 (24·0%)	479/1896 (25·3%)	331/2147 (15·4%)	307/1061 (28·9%)	1013/3917 (25·9%)	841/2239 (37·6%)
Hypertension	198 372/360 354 (55·1%)	70 883/172 634 (41·1%)	16 790/23 954 (70·1%)	1537/1903 (80·8%)	1121/2147 (52·2%)	710/1061 (66·9%)	2486/3838 (64·8%)	1545/2239 (69·0%)
Previous PCI	43 824/357 051 (12·3%)	30 308/172 634 (17·6%)	5159/24 378 (21·2%)	806/1877 (42·9%)	314/2147 (14·6%)	196/1061 (18·5%)	1089/3949 (27·6%)	61/368 (16·6%)
Previous coronary artery bypass graft	30 317/357 808 (8·5%)	14 501/172 634 (8·4%)	1969/24 641 (8·0%)	262/1882 (13·9%)	114/2147 (5·3%)	60/1061 (5·7%)	490/3949 (12·4%)	21/368 (5·7%)
Family history of coronary artery disease	87 122/295 099 (29·5%)	..	6765/20 290 (33·3%)	680/1778 (38·3%)	..	..	1513/3761 (40·2%)	140/2156 (6·5%)
Peripheral vascular disease	17 999/352 873 (5·1%)	11 387/172 634 (6·6%)	1756/24 945 (7·0%)	..	..	107/1061 (10·1%)	397/3949 (10·1%)	209/2239 (9·3%)
Cerebrovascular disease	35 302/356 525 (9·9%)	17 046/172 634 (9·9%)	1649/24 945 (6·6%)	..	176/2147 (8·2%)	75/1061 (7·1%)	458/3949 (11·6%)	170/2239 (7·6%)
Heart failure	25 651/355 919 (7·2%)	22 177/172 634 (12·8%)	886/24 461 (3·6%)	420/1708 (24·6%)	214/2147 (10·0%)	0/1061 (0·0%)	140/3949 (3·5%)	184/2239 (8·2%)
Chronic kidney disease	27 596/356 063 (7·8%)	9414/172 634 (5·5%)	2172/22 444 (9·7%)	..	198/2147 (9·2%)	292/1061 (27·5%)	187/3949 (4·7%)	..

(Table continues on next page)

	England, Wales, and Northern Ireland (MINAP; n=400 054)	Sweden (SWEDEHEART; n=172 634)	Switzerland (AMIS Plus and 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)
(Continued from previous page)								
Clinical chemistry and haematology								
White blood count, 10^9/L	..	..	8·7 (7·0–11·0)	..	10·0 (7·5–11·5)	7·8 (5·9–9·8)	8·3 (6·7–10·3)	9·4 (7·5–11·7)
Haemoglobin, g/L	135 (120–148)	138 (126–149)	142 (129–153)	..	139 (129–148)	142 (130–152)	140 (129–150)	142 (130–152)
C-reactive protein, mg/L	..	5·0 (2·0–10·0)	4·7 (2·0–11·0)	3·3 (2·0–11·0)	..	..	..	16·4 (5·7–54·2)
Total cholesterol, mmol/L	4·6 (3·7–5·6)	..	5·0 (4·2–5·9)	..	..	..	4·6 (3·7–5·5)	4·6 (3·8–5·6)
Low-density lipoprotein cholesterol, mmol/L	..	2·8 (2·0–3·7)	3·2 (2·3–4·0)	..	..	2·6 (1·9–3·4)	2·8 (2·0–3·6)	2·7 (2·0–3·5)
HbA_{1c}, %	..	5·8 (5·4–6·5)	6·0 (5·5–6·1)	5·8 (5·5–6·4)	..	..	..	4·2 (3·7–5·1)
Troponin elevation*	351 510/390 128 (90·1%)	152 438/167 763 (90·9%)	14 453/14 928 (96·8%)	1348/2030 (66·4%)	1718/2143 (80·2%)	968/1061 (91·2%)	3608/3912 (92·2%)	2140/2157 (99·2%)
NT-proBNP, ng/L	..	..	846 (258–2757)	531 (163–2020)	..	828 (204–3622)	..	1706 (780–3784)
Creatinine, µmol/L	89 (74–112)	80 (71–106)	83 (70–100)	83 (69–103)	74 (63–88)	78 (65–94)	83 (71–99)	93 (79–115)
Estimated glomerular filtration rate, mL/min per 1·73 m^2†	74 (53–91)	80 (60–94)	83 (63–96)	83 (62–96)	93 (79–102)	73 (57–85)	79 (64–94)	76 (57–93)
Medication at admission								
ASS‡	191 319/354 736 (53·9%)	71 582/170 661 (41·9%)	10 291/22 674 (45·4%)	..	..	322/1061 (30·3%)	..	123/368 (33·4%)
$P2Y_{12}$ receptor inhibitor	44 452/311 089 (14·3%)	16 692/170 688 (9·8%)	2649/13 433 (19·7%)	..	..	31/1061 (2·9%)	..	..
β blocker	113 587/342 279 (33·2%)	75 078/170 485 (44·0%)	8278/22 490 (36·8%)	..	..	..	..	1135/2239 (50·7%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	143 595/342 209 (42·0%)	74 873/170 263 (44·0%)	10 279/22 503 (45·7%)	..	..	..	..	1363/2239 (60·9%)
Vitamin K antagonist or direct oral anticoagulant	..	15 734/170 682 (9·2%)	1752/6354 (27·6%)	..	..	91/1061 (8·6%)	..	10/368 (2·7%)
Statin	173 819/355 239 (48·9%)	65 015/170 627 (38·1%)	8825/22 531 (39·2%)	..	..	..	..	1222/2239 (54·6%)

Data are median (IQR) or n/N (%). Count data are shown as n/N with n referring to the number of participants in which the feature is present and N referring to the number of patients with available information on this particular variable. AMIS Plus=Acute Myocardial Infarction in Switzerland Plus. ASS=acetyl salicylic acid. bpm=beats per min. Brno-ACS=two prospective registries at University Hospital Brno. CORALYS=Incidence and Predictors of Heart Failure after Acute Coronary Syndrome. FORCE-ACS=Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome. Heidelberg-ACS=prospective Heidelberg ACS cohort study. MINAP=Myocardial Ischaemia National Audit Project. NSTE-ACS=non-ST-elevation acute coronary syndrome. NT-proBNP=N-terminal pro-BNP. PCI=percutaneous coronary intervention. SPUM-ACS=Special Programme University Medicine Acute Coronary Syndromes. SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. VERDICT=Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography. *Refers to values >99th percentile. †Estimated according to the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation. ‡Refers to any antiplatelet therapy in Czechia.

Table: **Baseline characteristics of patients with NSTE-ACS**

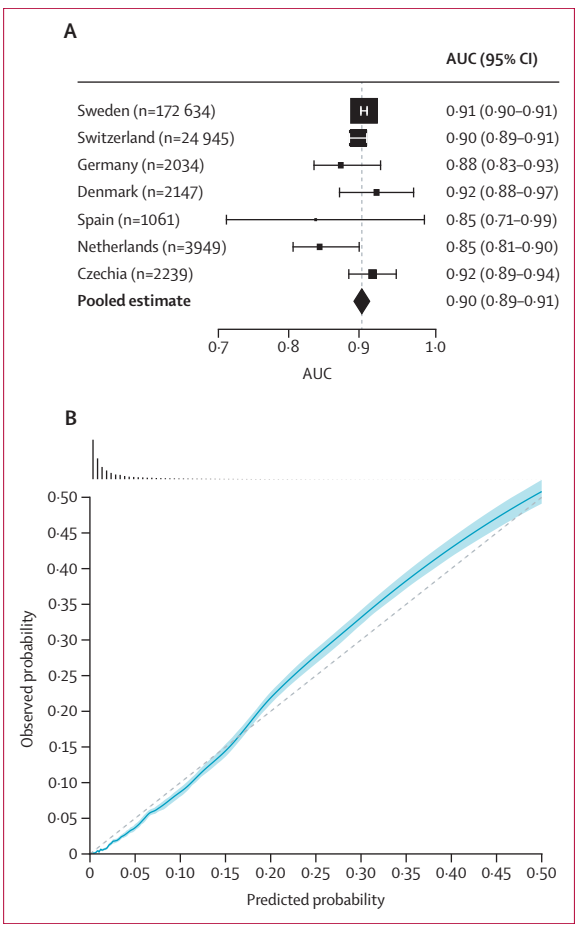

Figure 2: **Performance of the in-hospital mortality model**
(A) Results from the external validation of the GRACE in-hospital mortality model for the AUC. The plot displays country-level point estimates (squares) with 95% CIs (lines), and an overall pooled estimate with 95% CI (diamond). Square sizes correspond to relative weights. (B) Predicted and observed risk of in-hospital mortality on external validation. Colour bands signify the 95% CI. The distribution of predicted risks is summarised as a histogram on top of the graph. AUC=area under the receiver operating characteristic curve. GRACE=Global Registry of Acute Coronary Events.

in-hospital mortality model and the GRACE 3.0 1-year mortality model had improved performance.

Short-term mortality in patients with NSTE-ACS is mainly due to acute sequelae such as mechanical complications, arrhythmias, and cardiogenic shock. We performed a broad external validation of the GRACE 3.0 in-hospital mortality model that confirmed its excellent performance in patients presenting with NSTE-ACS. Our results verify the GRACE 3.0 in-hospital mortality model as a highly accurate tool for early assessment of short-term mortality risk. These findings are in line with the results from a single-centre study[27] reporting excellent performance of the GRACE 3.0 in-hospital mortality model in patients who have undergone percutaneous coronary intervention (PCI) for NSTE-ACS. Accurate assessment of in-hospital mortality risk could support preclinical and in-hospital triage, and patient monitoring during hospitalisation. In addition, the newly developed GRACE 3.0 1-year mortality model enables the prediction of longer-term mortality risk, above and beyond the score version 2.0, considering sex differences in the risk factor profile. Refined assessment of longer-term mortality risk following the acute event could help to personalise secondary prevention regimens and standardise outcome research in these patients.

Invasive management is recommended for most patients with NSTE-ACS, yet the optimal timing is uncertain.[2,7,8] Early invasive management does not improve outcomes in the overall NSTE-ACS population.[7] Hence, the rapid identification of individuals who benefit from early invasive management is of high clinical importance.[7,8] The assumption that the effect of early invasive management increases with increasing baseline risk has led to risk-based patient stratification in NSTE-ACS guided by the estimated in-hospital mortality risk according to the GRACE score.[1,2] However, the current risk threshold showed no interaction with treatment effect in combined patient-level analyses of randomised trials, warranting a re-evaluation of treatment stratification for patients with NSTE-ACS.[8]

Here, we explored a benefit-based approach without assuming that the treatment effect increases linearly with baseline risk. Potential complex and non-linear relationships between baseline characteristics and treatment effect are now considered. Moreover, the GRACE 3.0 individualised treatment effect model was derived from randomised trial data and thus is not subject to confounding bias.[21] Our results agree with existing evidence that machine learning-based effect modelling can outperform the high-risk approach.[10]

The GRACE 3.0 individualised treatment effect model indicates that patients with NSTE-ACS who benefit from early invasive management present with clinical characteristics different from those previously described. Indeed, the clinical profile of patients with predicted benefit from early invasive management is characterised by more signs of myocardial ischaemia, worse haemodynamics, and a higher likelihood of being female, but younger age and better renal function. These findings appear clinically plausible, given that timely revascularisation is also indicated in patients with acute myocardial ischaemia due to ST-elevation myocardial infarction, and in patients with cardiogenic shock. Younger age might predispose individuals to higher potential long-term benefit from early invasive management due to longer remaining life expectancy. These findings align with observational data[28] and results from a randomised controlled trial[29] published in 2024 that reported no benefit of invasive management over a conservative strategy in terms of long-term cardiovascular outcomes in older patients (ie, aged ≥75 years) with NSTE-ACS and showed a nominally lower effect in the GRACE group at high risk of death. Of note, in conventional risk-based treatment selection, young age favours patient stratification towards delayed invasive management. Collectively, the individualised treatment effect model

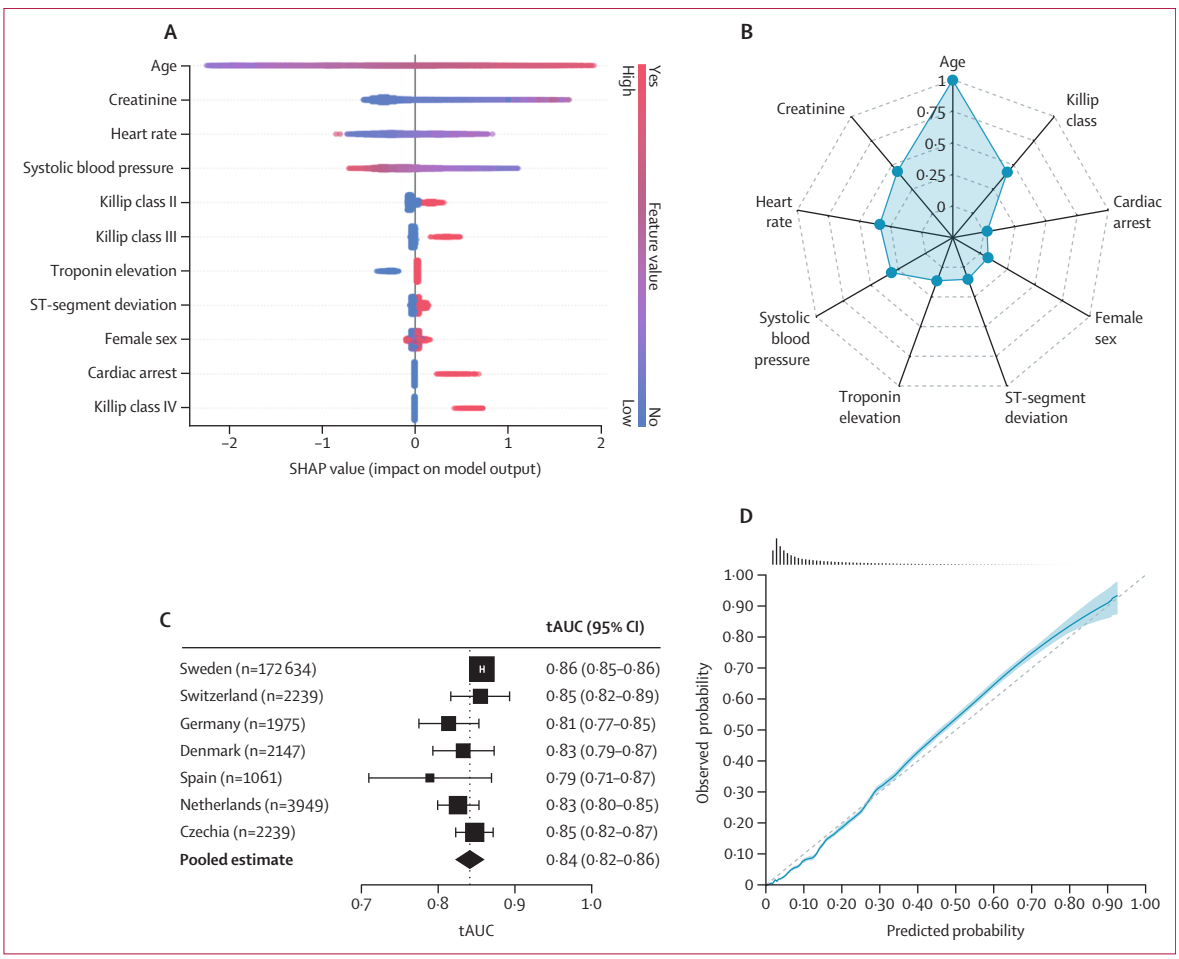

Figure 3: **Feature importance and performance of the 1-year mortality model**
(A) The clinical features of the model are ranked by their contribution to the model output. Each dot corresponds to a patient, with its colour indicating the feature value. For example, the effect of age on the model output is positive, leading to increased predicted risk, when the patient is relatively old (red) and negative, leading to decreased predicted risk, when the patient is relatively young (blue). (B) Radar plot for the importance of each clinical predictor variable according to the mean of the absolute SHAP value scaled to the feature with the highest value. The SHAP value of a feature represents its contribution to the difference between the actual prediction and the average prediction. The mean absolute SHAP value for a feature is the average of the absolute values of its SHAP values across all patients and reflects the magnitude of a feature's effect on predictions, without regard to whether it increases or decreases the prediction. (C) Results from the external validation of the GRACE 1-year mortality model for the tAUC. The plot displays country-level point estimates (squares) with 95% CIs (lines), and an overall pooled estimate with 95% CI (diamond). Square sizes correspond to relative weights. (D) Predicted and observed risk of 1-year mortality on external validation. Colour bands signify the 95% CI. The distribution of predicted risks is summarised as a histogram on top of the graph. GRACE=Global Registry of Acute Coronary Events. SHAP=Shapley additive explanations. tAUC=time-dependent area under the receiver operating characteristic curve.

suggests that current treatment strategies might incompletely capture the subset of patients with NSTE-ACS who benefit from an early intervention in terms of long-term cardiovascular outcomes. Our analyses indicate that early invasive management can substantially reduce long-term major adverse cardiovascular events in patients with high predicted benefit. However, additional prospective validation of the individualised treatment effect model is warranted before clinical implementation can be considered, given the paucity of data from large RCTs with long-term outcomes currently available.

Our study has several strengths. First, according to our knowledge, the study design includes the largest worldwide NSTE-ACS cohorts with thorough clinical documentation. Prospective nationwide registries from different countries allowed us to account for the geographical and sociocultural diversity of the patient population, which enhances the validity of the results. Second, we restricted the enrolment to contemporary patients (Jan 1, 2005, to June 24, 2024) to account for the evolution of clinical NSTE-ACS phenotypes and changes in management. Third, the developed prediction models are specific to the NSTE-ACS patient population and account for sex-specific differences. Importantly, the individualised treatment effect model was developed in the only available clinical trial on the timing of early invasive management with long-term follow-up, and thus estimates the effect of treatment on long-term outcomes. Furthermore, the developed prediction

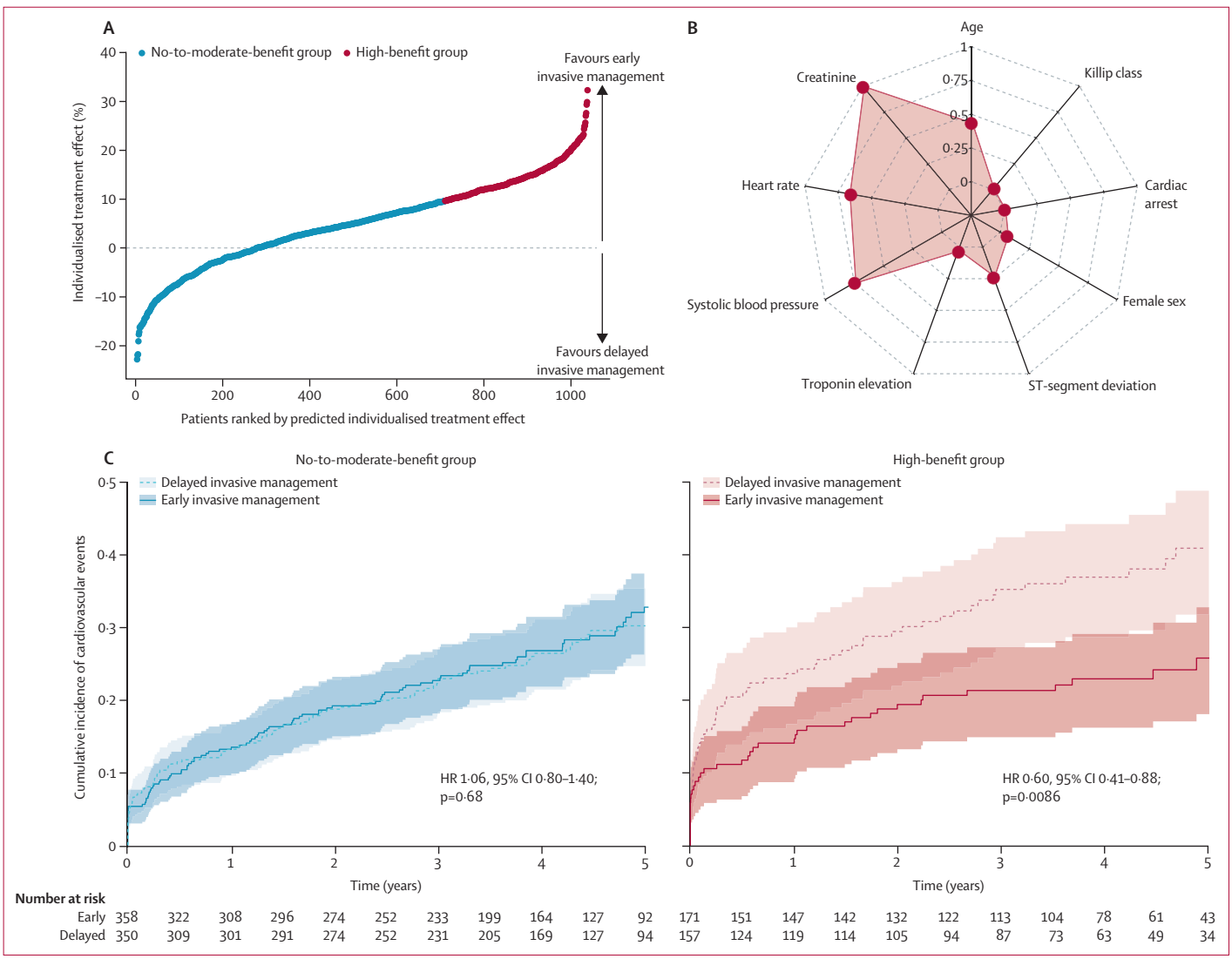

Figure 4: **Prediction of individualised treatment effect**

(A) Predicted individualised effect of early invasive management generated by the GRACE 3.0 individualised treatment effect model for each of the 1036 unseen patients with NSTE-ACS in the external validation cohort (those from the geographical east of the VERDICT trial). Patients were ranked from the lowest value on the left to the highest value on the right. Colours signify low and high predicted treatment effect. (B) Feature importance in the individualised treatment effect model scaled to the feature with the highest value in the development dataset (n=1111). (C) Cumulative incidence of the composite primary outcome in patients with no-to-moderate predicted benefit (left) and high predicted benefit (right) according to randomisation in unseen data (n=1036). The p value of the interaction term between the benefit group and the randomly assigned treatment group in the external validation cohort is 0·014. Colour bands signify the 95% CI. GRACE=Global Registry of Acute Coronary Events. HR=hazard ratio. NSTE-ACS=non-ST-elevation acute coronary syndrome. VERDICT=Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography.

models are easily applicable using a single set of nine variables that are routinely available in clinical care settings.

There are also some limitations of this study. First, due to restricted availability of, and limited access to, large-scale high-quality NSTE-ACS cohorts, our study does not include patient cohorts outside of Europe. Extrapolation of our findings to other geographies requires caution, and additional external validation of the in-hospital mortality and 1-year mortality models in other areas is warranted. Next, the low number of events in the patient cohorts from Spain and Denmark precludes definitive conclusions on the performance of the in-hospital mortality model. Indeed, performance evaluation in the presence of very low event counts is challenging and requires cautious interpretation. In addition, data on ethnicity were not consistently available in the involved cohorts and were therefore not reported. Moreover, all results including those related to short-term and long-term clinical outcomes should be viewed in the context of differences in treatment received across the involved cohorts, including the notable variation in the proportion of patients who were treated with PCI. Furthermore, we note that any post-hoc analysis of RCT data beyond the primary analysis is exploratory and can only provide suggestive evidence. Thus, the presented evidence regarding treatment benefit should not be considered

definitive but could inform hypothesis generation for clinical trial design. Prospective evaluation of the GRACE 3.0 individualised treatment effect model is warranted.

In conclusion, the GRACE 3.0 scoring system provides a validated, practical tool for the individualised assessment of short-term and long-term mortality risk in patients with NSTE-ACS. In the context of a comprehensive clinical evaluation, GRACE 3.0 can inform clinical treatment considerations. The individualised treatment effect model could refine the design of future clinical trials regarding the timing of invasive management.

Contributors

FAW and TFL conceived the study. FAW, EL, GA, FB, MS, LVK, DR, MM-H, NMRvdS, and JP performed data queries, data curation, and gathered the data. FAW and EL accessed, verified, and analysed the data. FAW, EL, FB, PW, and NMRvdS generated descriptive summary statistics of patient baseline characteristics. FAW wrote the first draft of the manuscript. FAW and MAS were involved in the visualisation of the results. FAW, JD, and TFL jointly directed the study. Due to data protection policies, co-authors accessed the data from their local institutions, but did not access data from other contributing institutions. All authors provided important intellectual input in the interpretation of the data, revised the work critically, approved the final version of the manuscript to be published, and agreed to be accountable for the content and the decision to submit for publication. FAW and TFL were responsible for the final decision to submit.

Declaration of interests

FAW declares no competing interests related to this manuscript but reports research grant support for the present work from the research fund for excellent research of the University of Zurich Foundation, the Kurt and Senta Herrmann Foundation, the Theodor and Ida Herzog-Egli Foundation, and the Foundation for Cardiovascular Research—Zurich Heart House. Outside of the present work, FAW reports research support from the Swiss Heart Foundation, the Swiss Society of Cardiology, the European Society of Cardiology, the Fund for Fostering Young Scientists at the University of Zurich, the Medical University of Graz, Amgen Switzerland, 4TEEN4 Pharmaceuticals, PAM Theragnostics, and Sphingotec; personal support for attending meetings or travel from the Foundation for Cardiovascular Research—Zurich Heart House, the Swiss Society of Cardiology, the European Society of Cardiology, the Critical Care Clinical Trialists Workshop, 4TEEN4 Pharmaceuticals, PAM Theragnostics, and Sphingotec; equipment, materials, drugs, medical writing, gifts, or other services from Roche Diagnostics, 4TEEN4 Pharmaceuticals, PAM Theragnostics, and Sphingotec; and membership of the Steering Committee of the National Registry of Acute Myocardial Infarction in Switzerland–AMIS Plus and the European Society of Cardiology Digital Cardiology and Artificial Intelligence Committee. KFK has received funding from the Danish Agency for Science, Technology and Innovation by the Danish Council for Strategic Research and the AP Møller og hustru Chastine McKinney Møllers Fond; grants from Novo Nordisk Foundation, Sygeforsikringen Danmark, Canon Medical Corporation, GE HealthCare, and Novo Nordisk; and honoraria for lectures from the speaker's bureau of Canon Medical Corporation and GE HealthCare. MS has received honoraria for lectures from Amgen, Boehringer Ingelheim, Bayer, Novo Nordisk, and Novartis, and has participated on an advisory board for AstraZeneca. EL has received consulting fees from Biogen outside of the submitted work. MAdB is a member of the Steering Committee of the DAPA MI Trial for AstraZeneca and chair of the Data Monitoring and Ethics Committee of the UK GRIS Trial. MM-H has received grants from Roche Diagnostics and consulting fees from Zoll Cardiac Management Solutions. MAS has received travel grants from Alphamed Fischer, ImplanTec, Implantcast, and PharmaMar outside of the submitted work. JPSH has received institutional research grants from Abbott Vascular, AstraZeneca, B. Braun, Getinge, Ferrer, Infraredx, and ZonMw. KS has received grants from the European Research Council under the EU's Horizon 2020 Research and Innovation Programme and from the German Research Foundation (Deutsche Forschungsgemeinschaft), the Health + Life Science Alliance Heidelberg Mannheim, and the Helmholtz Association. KS is chair of the Professional/Public Education and Publications Committee of the Council of Genomic and Precision Medicine of the American Heart Association; a member of the Brain and Heart Committee, Heart Failure Association; an ex-officio member of the Working Group of Atherosclerosis and Vascular Biology, European Society of Cardiology; a principal investigator of the German Centre for Cardiovascular Research partner site Heidelberg Mannheim; a principal investigator of the Helmholtz Institute for Translational Angio-Cardiac-Science; and an associate editor of the *European Heart Journal*, an associate editor of *Cardiovascular Research*, an editorial board member of *Circulation: Genomic and Precision Medicine*, and an associate editor of *Frontiers in Immunology*. TE has received honoraria for lectures from Novo Nordisk, Abbott, and Boston Scientific, and is member of advisory boards for Abbott and Novo Nordisk. CW has received honoraria for educational meetings from AstraZeneca and is the Clinical Lead of the Myocardial Ischaemia National Audit Project registry. DA has received research grants from Cancer Research UK and the British Heart Foundation for the submitted work; has received research grants from the UK National Institute for Health and Care Research (NIHR), Abbott Vascular, and Beat SCAD outside of the submitted work; has received royalties from Elsevier; holds patents (cardiac arrest device [EP3277337A1] and heart failure shunt device [patent application number 2211616.4]); and is a member of the Phoenix trial, a member of the advisory board of Beat SCAD, and chair of the ESC-EORP SCAD Registry. EG has received consulting fees from Roche Diagnostics, BRAHMS Deutschland, Boehringer Ingelheim, and AstraZeneca; honoraria for lectures from AstraZeneca, Roche Diagnostics, Lilly Deutschland, Daiichi Sankyo, Amgen, and Bayer Vital; and is a member of the Advisory Board for Cancer Therapy of Boehringer Ingelheim. JP received research grants from the Ministry of Health of the Czech Republic, Roche, and Siemens; declares consulting fees from AstraZeneca and Boehringer Ingelheim; and declares payments and honoraria from Amgen, Bayer, and Novartis. CAA has received grants from the British Heart Foundation (CH/F/21/90009, TG/19/2/34831, and RG/F/21/110040, Oxford CRE) and the NIHR Oxford Biomedical Research Centre (Cardiovascular and Imaging Themes) for the submitted work; has received grants from the US National Institutes of Health (HSR01920), the British Heart Foundation (FS/CRTF/23/24460), the British Heart Foundation Oxford Centre of Research Excellence (RG/18/3/34214), Innovate UK (grant 104688), The Secretary of State for Health and Social Care (UK National Health Service artificial intelligence award AI_AWARD02443 and AI_AWARD02013), and EU MAESTRIA (grant agreement number 965286) outside of the submitted work; holds patents (as inventor US10695023B2, PCT/GB2017/053262, GB2018/1818049.7, GR20180100490, and GR20180100510 [patents licensed to Caristo Diagnostics and royalties paid to Oxford University Innovation]; as co-inventor US10695023B2 [patent licensed to Caristo Diagnostics and royalties paid to Oxford University Innovation]); has received personal consulting fees from Caristo Diagnostics, Silence Therapeutics, Abcentra, and Amgen; has received personal fees for lectures from Amarin, Covance, and Hunan University; is past chair of the British Atherosclerosis Society, vice chair of several Marie Curie Panels, and a member of several national committees in the UK and the British Heart Foundation; and holds stock options of Caristo Diagnostics. JMtB has received institutional research grants from ZonMw (Dutch government) and AstraZeneca. LVK has received speaker's honoraria from AstraZeneca, Boehringer, Novartis, and Novo Nordisk. SJ reports research contracts of his institution with AstraZeneca, Jansen, Amgen, Medtronic, and Edwards; has received honoraria for lectures from Medtronic JD; has received grants from Alzheimer's Research UK and the British Heart Foundation; has received consulting fees from Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer; and has received honoraria for lectures from Amgen, AstraZeneca, Boehringer

Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer. TFL declares no competing interests related to this manuscript, but declares support from the Swiss National Science Foundation (Special Programme University Medicine Acute Coronary Syndromes [SPUM] 33CM30-124112 and 32473B_163271), the Swiss Heart Foundation, Abbott, Amgen, Anylam, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Cytokinetics, Daichi_Sankyo, Eli Lilly, Novartis, Novo Nordisk, Pfizer, Sanofi, and Vifor. TFL does no longer accept any honoraria from industry, but holds leadership positions at the European Society of Cardiology, the Swiss Heart Foundation, the Foundation for Cardiovascular Research—Zurich Heart House, and the London Heart House. All other authors declare no competing interests.

Data sharing

Due to data protection regulations related to the different study cohorts involved in this study, the authors do not have authorisation to provide unrestricted data access. Requests for study materials, including statistical analysis code, additional information on the involved cohorts, and software should be made to the corresponding authors (FAW and TFL).

Acknowledgments

This work was supported by funds from the Swiss Heart Foundation, the Kurt and Senta Herrmann Foundation, the University of Zurich Foundation, the Theodor and Ida Herzog-Egli Foundation, and the Foundation for Cardiovascular Research–Zurich Heart House (all to FAW). The AMIS Plus registry is funded by unrestricted grants from the Swiss Heart Foundation and from Abbot, Amgen, AstraZeneca, Bayer (Schweiz), Biotronik, Boston Scientific, B. Braun Medical, Daiichi Sankyo/Lilly, Cordis Cardinal Health, Medtronic, Novartis Pharma Schweiz, Sanofi-Aventis (Schweiz), SIS Medical, Terumo, and Vascular Medical, all in Switzerland, and the Swiss Working Group for Interventional Cardiology. The SPUM-ACS registry was primarily supported by the Swiss National Science Foundation (SPUM 33CM30-124112 and 32473B_163271) and the Swiss Heart Foundation, and by unrestricted grants from AstraZeneca (Baar, Switzerland), Eli Lilly (Indianapolis, IN, USA), Medtronic (Münchenbuchsee, Switzerland), Sanofi-Aventis (Vernier, Switzerland), and St Jude Medical (Zurich, Switzerland) and donated assays by Roche Diagnostics. We gratefully acknowledge the invaluable contribution of all health-care professionals and patients who participated in the conduct of the registries and the randomised controlled trial, VERDICT, on which this study is based. We further express our gratitude to all administrative personnel and IT personnel involved in data entry and management, and to all patients and research personnel involved in previous studies within the GRACE programme.

References

1 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **64:** e139–228.

2 Byrne RA, Rossello X, Coughlan JJ, et al, and the ESC Scientific Document Group. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023; **44:** 3720–826.

3 Granger CB, Goldberg RJ, Dabbous O, et al, and the Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. *Arch Intern Med* 2003; **163:** 2345–53.

4 Fox KA, Fitzgerald G, Puymirat E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open* 2014; **4:** e004425.

5 Mehta SR, Granger CB, Boden WE, et al, and the TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; **360:** 2165–75.

6 Ruff CT, Braunwald E. The evolving epidemiology of acute coronary syndromes. *Nat Rev Cardiol* 2011; **8:** 140–47.

7 Jobs A, Mehta SR, Montalescot G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet* 2017; **390:** 737–46.

8 Kite TA, Gershlick AH. High-risk NSTE-ACS: high time for robust data. *Eur Heart J* 2021; **42:** 352.

9 Wenzl FA, Kraler S, Ambler G, et al. Sex-specific evaluation and redevelopment of the GRACE score in non-ST-segment elevation acute coronary syndromes in populations from the UK and Switzerland: a multinational analysis with external cohort validation. *Lancet* 2022; **400:** 744–56.

10 Inoue K, Athey S, Tsugawa Y. Machine-learning-based high-benefit approach versus conventional high-risk approach in blood pressure management. *Int J Epidemiol* 2023; **52:** 1243–56.

11 Roe MT, Parsons LS, Pollack CV Jr, et al, and the National Registry of Myocardial Infarction Investigators. Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction. *Arch Intern Med* 2005; **165:** 1630–36.

12 Kofoed KF, Kelbæk H, Hansen PR, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. *Circulation* 2018; **138:** 2741–50.

13 Ganna A, Ingelsson E. 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. *Lancet* 2015; **386:** 533–40.

14 Wenzl FA, Wang P, Arrigo M, et al. Proenkephalin improves cardio-renal risk prediction in acute coronary syndromes: the KID-ACS score. *Eur Heart J* 2025; **46:** 38–54.

15 Stamatelopoulos K, Mueller-Hennessen M, Georgiopoulos G, et al. Cathepsin S levels and survival among patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2022; **80:** 998–1010.

16 De Filippo O, D'Ascenzo F, Wańha W, et al. IncidenCe and predictOrs of heaRt fAiLure after acute coronarY Syndrome: the CORALYS registry. *Int J Cardiol* 2023; **370:** 35–42.

17 Chan Pin Yin DRPP, Vos GA, van der Sangen NMR, et al. Rationale and design of the Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) registry: towards "personalized medicine" in daily clinical practice. *J Clin Med* 2020; **9:** 3173.

18 Arrigo M, Parenica J, Ganovska E, Pavlusova M, Mebazaa A. Plasma bio-adrenomedullin is a marker of acute heart failure severity in patients with acute coronary syndrome. *Int J Cardiol Heart Vasc* 2019; **22:** 174–76.

19 Oikonomou EK, Spatz ES, Suchard MA, Khera R. Individualising intensive systolic blood pressure reduction in hypertension using computational trial phenomaps and machine learning: a post-hoc analysis of randomised clinical trials. *Lancet Digit Health* 2022; **4:** e796–805.

20 Buell KG, Spicer AB, Casey JD, et al. Individualized treatment effects of oxygen targets in mechanically ventilated critically ill adults. *JAMA* 2024; **331:** 1195–204.

21 Dorresteijn JA, Visseren FL, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. *BMJ* 2011; **343:** d5888.

22 Sinha P, Spicer A, Delucchi KL, McAuley DF, Calfee CS, Churpek MM. Comparison of machine learning clustering algorithms for detecting heterogeneity of treatment effect in acute respiratory distress syndrome: a secondary analysis of three randomised controlled trials. *EBioMedicine* 2021; **74:** 103697.

23 van Klaveren D, Steyerberg EW, Serruys PW, Kent DM. The proposed 'concordance-statistic for benefit' provided a useful metric when modeling heterogeneous treatment effects. *J Clin Epidemiol* 2018; **94:** 59–68.

24 Seitz KP, Spicer AB, Casey JD, et al. individualized treatment effects of bougie versus stylet for tracheal intubation in critical illness. *Am J Respir Crit Care Med* 2023; **207:** 1602–11.

25 Sadatsafavi M, Mansournia MA, Gustafson P. A threshold-free summary index for quantifying the capacity of covariates to yield efficient treatment rules. *Stat Med* 2020; **39:** 1362–73.

26 IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014; **14:** 25.

27 Molenaar MA, Selder JL, Schmidt AF, et al. Validation of machine learning-based risk stratification scores for patients with acute coronary syndrome treated with percutaneous coronary intervention. *Eur Heart J Digit Health* 2024; **5:** 702–11.

28 Eggers KM, James SK, Jernberg T, Lindahl B. Timing of coronary angiography in patients with non-ST-elevation acute coronary syndrome: long-term clinical outcomes from the nationwide SWEDEHEART registry. *EuroIntervention* 2022; **18:** 582–89.

29 Kunadian V, Mossop H, Shields C, et al, and the British Heart Foundation SENIOR-RITA Trial Team and Investigators. Invasive treatment strategy for older patients with myocardial infarction. *N Engl J Med* 2024; **391:** 1673–84.