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

Florian A Wenzl*, Simon Kraler*, Gareth Ambler, Clive Weston, Sereina A Herzog, Lorenz Räber, Olivier Muller, Giovanni G Camici, Marco Roffi, Hans Rickli, Keith A A Fox, Mark de Belder, Dragana Radovanovic†, John Deanfield†, Thomas F Lüscher†

Summary
Background The Global Registry of Acute Coronary Events (GRACE) 2.0 score was developed and validated in predominantly male patient populations. We aimed to assess its sex-specific performance in non-ST-segment elevation acute coronary syndromes (NSTE-ACS) and to develop an improved score (GRACE 3.0) that accounts for sex differences in disease characteristics.

Methods We evaluated the GRACE 2.0 score in 420781 consecutive patients with NSTE-ACS in contemporary nationwide cohorts from the UK and Switzerland. Machine learning models to predict in-hospital mortality were informed by the GRACE variables and developed in sex-disaggregated data from 386591 patients from England, Wales, and Northern Ireland (split into a training cohort of 309083 [80%] patients and a validation cohort of 77508 [20%] patients). External validation of the GRACE 3.0 score was done in 20727 patients from Switzerland.

Findings Between Jan 1, 2005, and Aug 27, 2020, 400054 patients with NSTE-ACS in the UK and 20727 patients with NSTE-ACS in Switzerland were included in the study. Discrimination of in-hospital death by the GRACE 2.0 score was good in male patients (area under the receiver operating characteristic curve [AUC] 0·86, 95% CI 0·86–0·86) and notably lower in female patients (0·82, 95% CI 0·81–0·82; p<0·0001). The GRACE 2.0 score underestimated in-hospital mortality risk in female patients, favouring their incorrect stratification to the low-to-intermediate risk group, for which the score does not indicate early invasive treatment. Accounting for sex differences, GRACE 3.0 showed superior discrimination and good calibration with an AUC of 0·91 (95% CI 0·89–0·92) in male patients and 0·87 (95% CI 0·84–0·89) in female patients in an external cohort validation. GRACE 3.0 led to a clinically relevant reclassification of female patients to the high-risk group.

Interpretation The GRACE 2.0 score has limited discriminatory performance and underestimates in-hospital mortality in female patients with NSTE-ACS. The GRACE 3.0 score performs better in men and women and reduces sex inequalities in risk stratification.

Funding Swiss National Science Foundation, Swiss Heart Foundation, Lindenhof Foundation, Foundation for Cardiovascular Research, and Theodor-Ida-Herzog-Egli Foundation.

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Introduction
Non-ST-segment elevation acute coronary syndromes (NSTE-ACS) account for about three quarters of acute coronary syndrome cases in women. The Global Registry of Acute Coronary Events (GRACE) score estimates mortality risk from widely available clinical, electrocardiographic, and biochemical variables and provides an established tool for personalised patient management. Based on evidence from clinical trials,14 selection of invasive treatment strategy, tailored monitoring during hospital stay, and assessment of prognosis according to the GRACE score are recommended across international NSTE-ACS guidelines (class 1a recommendation for guiding treatment).14 Even though the GRACE score was derived from and validated in predominantly male patient populations, it is used in both sexes alike, without accounting for sex-specific disease characteristics of NSTE-ACS.10 Women with NSTE-ACS display different plaque features and have a higher prevalence of plaque erosion as the primary causative mechanism.10 Moreover, female patients with NSTE-ACS present at an older age, have a higher comorbidity burden, have longer prehospital delays, and show higher unadjusted mortality risk than do male patients.11–14 Importantly, female patients are less likely to receive early invasive management.15 Despite the growing awareness of its differing discriminatory performance in specific patient groups,16 including female patients with ST-segment elevation myocardial infarction,16,17 the effect of sex differences on...
the performance of the GRACE score in patients with NSTE-ACS remains unclear. Emerging evidence on a distinct profile of baseline risk factors in women and men with NSTE-ACS, the unequal strength of association of individual GRACE components with adverse outcomes, and the hitherto uniform handling in the GRACE score suggest sex differences in score performance, which might promote structural inequities in the treatment of patients with NSTE-ACS.

In this study, we aimed to evaluate the performance of the GRACE 2.0 score in a sex-disaggregated manner and to redevelop the score in recently recruited populations using machine learning-based approaches to account for interindividual heterogeneity and phenotypic differences between female and male patients with NSTE-ACS.

Methods

Study design and participants

We used current data from 420,781 consecutive patients with NSTE-ACS in nationwide acute coronary syndrome cohorts from the UK and Switzerland. In the UK, patient data were retrieved from the Myocardial Ischaemia National Audit Project (MINAP), a prospective national registry of patients with acute coronary syndrome. The MINAP is the largest single health-care system acute coronary syndrome registry worldwide and covers the entire patient pathway from symptom onset to hospital discharge. Among 106,743 patients presenting with acute coronary syndrome to any of the participating hospitals in England, Wales, and Northern Ireland (appendix pp 6–8) between Jan 1, 2005, and March 31, 2017, 40,054 patients had a discharge diagnosis of NSTE-ACS, determined according to the consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee; of these patients presented to percutaneous coronary intervention (PCI)-capable university hospitals. In Switzerland, patient data were retrieved from the Acute Myocardial Infarction in Switzerland (AMIS) Plus national registry (NCT01305785) and the Special Programme University Medicine Acute Coronary Syndrome (SPUM-ACS) cohort (NCT01000701). AMIS Plus, a prospective national registry of patients with acute coronary syndrome in Switzerland, 45,797 patients were admitted.
to any of the participating hospitals (appendix p 9) between Jan 1, 2005, and Aug 27, 2020, of whom 20727 had a final diagnosis of NSTE-ACS. The prospective SPUM-ACS registry comprises 4787 consecutive patients with acute coronary syndrome admitted to one of the four major university hospitals in Switzerland who underwent coronary angiography between Dec 8, 2009, and Dec 31, 2017, of whom 2239 had a diagnosis of NSTE-ACS. The cohort profile and detailed inclusion and exclusion criteria of each cohort have been reported previously.21,25

Follow-up and assessment of outcomes
The primary study outcome was death in hospital. Additional outcomes were death between hospital admission and 6 months after admission, death between hospital admission and 1 year, death between hospital discharge and 6 months after hospital admission, and death between hospital discharge and 1 year after hospital admission. In-hospital mortality of patients in all cohorts was adjudicated by certified clinicians at the time of the event. Mortality at 6 months and at 1 year in MINAP was ascertained by data linkage to the UK Office for National Statistics using individual patient National Health Service (NHS) numbers. Patients enrolled in AMIS Plus who consented to long-term follow-up at hospital discharge had a scheduled follow-up interview by trained study personnel at 1 year after admission for the index event. In SPUM-ACS, all patients had follow-up visits at 1 month (telephone call) and at 1 year (clinical visit). Additionally, in SPUM-ACS, the 1-year mortality endpoint was reviewed by an external endpoint adjudication committee comprising three certified expert cardiologists who were masked to patient baseline characteristics using prespecified adjudication forms.25,26

Evaluation
We calculated the GRACE (version 2.0) score for in-hospital death, death at 6 months, and death at 1 year using the following variables at admission: age, heart rate, systolic blood pressure, Killip class, creatinine concentration, cardiac arrest, presence of ST-segment deviation, and presence of troponin elevation.7 We evaluated the score in pooled data from the UK and Switzerland; exact numbers of patients available in each analytical cohort at each endpoint are shown in the appendix (p 12). To account for distinct management characteristics of patients receiving a higher hospital level of care (ie, they were treated in a PCI-capable university hospital),25 we assessed the score performance in all patients and in patients admitted to PCI-capable university hospitals (appendix pp 6–9, 12). The discriminatory performance of the GRACE score was assessed for female and male patients by the area under the receiver operating characteristic (ROC) curve (AUC) and compared using the DeLong test for unpaired ROC curves. Calibration was evaluated graphically using calibration plots and locally weighted scatterplot smoothing-estimated calibration curves. Moreover, a range of performance metrics including the Brier score (average prediction error),7 accuracy, false omission rate, and the expected–observed ratio were calculated, as reported previously.25–27 Additionally, we compared mortality risks between female and male patients in predefined clinically meaningful GRACE risk categories for in-hospital deaths (ie, low-to-intermediate risk [≤3%; ≤140 points] and high risk [>3%; >140 points]).7 Given its broad use in clinical trials and endorsement by treatment guidelines,25–28 our analyses were primarily aimed at the in-hospital death endpoint of the score. Additional analyses were done for mortality endpoints at 6 months and at 1 year in all patients and in hospital survivors (ie, patients who survived the hospital stay) both on pooled data and at a national level.4 Further exploratory analyses were done on the patient subgroup receiving PCI treatment (appendix pp 13–14).

Model development and validation
We applied a supervised machine learning approach, called ensemble learning, to capture potential non-linear relationships between patient characteristics and mortality. Ensemble learning combines multiple prediction models to generate better predictions than a single model could.29,30 Specifically, we applied eXtreme Gradient Boosting (XGBoost; version 1.6.0.11), a widely used supervised tree-based learning algorithm, to predict in-hospital mortality in patients with NSTE-ACS. Given their high clinical availability and worldwide use, the eight GRACE variables (age, heart rate, systolic blood pressure, Killip class, creatinine concentration, cardiac arrest, presence of ST-segment deviation, and troponin elevation) were used as model features. Since the risk estimated by the GRACE 2.0 score derives from an unbiased global patient population with acute coronary syndrome and can be calculated internally without requiring additional variables, it was integrated as an additional feature, leading to increased model performance. The derivation cohort (MINAP) contained data from 386 591 patients recruited in England, Wales, and Northern Ireland and was randomly split into two datasets using the Mersenne-Twister random number generator implemented in R, comprising a training cohort (309 083 [80%] patients) that was used to train the machine learning models, and an internal validation cohort (77 508 [20%] patients; appendix pp 3, 5) that was used to test the developed models on unseen data and tune their hyperparameters. The external validation cohort (AMIS Plus) included 20727 patients from Switzerland. Separate models were trained on male and female patient data. Final models (termed the GRACE 3.0 score) were evaluated based on various performance metrics (including AUC) and calibration plots with a focus on the intermediate-to-high-risk patient population, for whom accurate calibration is most important for clinical risk stratification (appendix p 3). To aid interpretability, the Shapley Additive Explanations (SHAP) approach was used to evaluate the effect of each feature on the model output by assigning an importance value (ie,
| Variable                      | UK (2005–17) | p value | Switzerland (2005–20) | p value |
|-------------------------------|--------------|---------|-----------------------|---------|
| **Male (n=64,185)**          |              |         |                       |         |
| **Female (n=63,302)**        |              |         |                       |         |
| Age, years                   | 76 (66–84)   | <0·0001 | 74 (64–82)            | <0·0001 |
| Heart rate, beats per min    | 80 (69–95)   | <0·0001 | 78 (68–90)            | <0·0001 |
| Systolic blood pressure, mmHg| 142 (123–161)| <0·0001| 141 (123–161)        | <0·0001 |
| Creatinine, mg/dL            | 0·9 (0·7–1·1)| <0·0001| 0·8 (0·7–1·0)        | <0·0001 |
| Cardiac arrest               | 283 (260–315)| <0·0001| 192 (172–215)        | <0·0001 |
| ST-segment deviation         | 34·6 (31·8–37·4)| <0·0001| 2100·55·59 (1960–2280) | <0·0001 |
| Troponin >99th percentile     | 12·13 (12·0–12·2)| <0·0001| 7744·7958 (7500–8000) | <0·0001 |
| Killip class I               | 57·820 (54·0–61·0)| <0·0001| 432·54·61 (39·8–47·8) | <0·0001 |
| Killip class II              | 10·420 (9·4–11·4)| <0·0001| 126·00·14·76 (102–16·8) | <0·0001 |
| Killip class III             | 65·62 (62·0–69·0)| <0·0001| 127·00·14·76 (102–16·8) | <0·0001 |
| Killip class IV              | 73·07 (69·0–77·0)| <0·0001| 412·54·61 (37·8–41·7) | <0·0001 |

| **BMI, kg/m²**               | 25·6 (23·0–28·3)| <0·0001| 26·9 (25·7–28·3)    | <0·0001 |
| **Body surface area, m²**    | 1·7 (1·6–1·8)  | <0·0001| 1·7 (1·6–1·8)     | <0·0001 |
| **Current smoker**           | 22·75 (21·9–23·0)| <0·0001| 26·7 (25·7–27·7)   | <0·0001 |
| **Total cholesterol, mmol/L**| 4·8 (3·9–5·5)  | <0·0001| 5·3 (4·4–6·2)     | <0·0001 |
| **Type 2 diabetes**          | 5·38 (5·2–5·5) | <0·0001| 5·7 (5·4–6·2)    | <0·0001 |
| **HbA₁c, %**                 | 7·1 (6·8–7·3)  | <0·0001| 7·1 (6·8–7·3)     | <0·0001 |

| **Medical history**          |              |         |                       |         |
| Dyslipidaemia†               | 44·13 (39·3–43·0)| <0·0001| 30·88·54·78 (30·6–32·3) | <0·0001 |
| Hypertension†                | 7·85 (6·2–8·3) | <0·0001| 8·84·54·02 (8·6–8·8)  | <0·0001 |
| Previous percutaneous coronary intervention | 11·06 (9·8–12·3) | <0·0001| 8·84·54·02 (8·6–8·8)  | <0·0001 |
| Previous coronary artery bypass grafting | 6·23 (5·1–7·3) | <0·0001| 30·88·54·78 (30·6–32·3) | <0·0001 |
|                         | UK (2005-17) | Switzerland (2005-20) |
|-------------------------|--------------|-----------------------|
|                         | All patients (MINAP, n=400054) | All patients (AMIS Plus, n=20727) |
|                         | University hospitals (MINAP, n=97487) | University hospitals (SPUM-ACS, n=2239) |
|                         | Female (n=145730) | Male (n=254316) | p value | Female (n=5576) | Male (n=15151) | p value | Female (n=462) | Male (n=1777) | p value |
| Family history of coronary artery disease | 28.84/100.572 (27.1%) | 58.27/188.527 (30.9%) | <0.0001 | 153.45/482 (28.8%) | 414.16/87 (27.9%) | 0.87 | 141.42/7 (33.0%) | 428.16/165 (29.9%) | 0.0034 |
| Peripheral vascular disease | 55.71/129.959 (4.3%) | 12.49/22.151 (5.6%) | <0.0001 | 416.48/491 (7.6%) | 100.00/89 (6.7%) | 0.031 | 36.64/2 (8.7%) | 156.77/17 (8.8%) | 0.05 |
| Cardiovascular disease | 14.53/131.286 (11.1%) | 20.75/252.239 (9.2%) | <0.0001 | 405.54/521 (7.4%) | 100.89/189 (6.8%) | 0.13 | 19.46/2 (4.1%) | 46.77/17 (6.6%) | 0.082 |
| Depression | | | | | | | | | |
| Heart failure§ | 10.91/131.046 (8.3%) | 147.75/248.873 (6.6%) | <0.0001 | 218.89/2229 (7.5%) | 335.5/507 (6.1%) | <0.0001 | 601.49/69 (1.2%) | 875.13/330 (6.6%) | <0.0001 |
| Chronic kidney disease | 10.58/131.148 (8.1%) | 17.01/249.15 (7.6%) | <0.0001 | 237.89/2321 (7.1%) | 423.75/5009 (7.7%) | 0.026 | 65.65/415 (8.8%) | 128.14/720 (8.8%) | <0.0001 |

Clinical chemistry and haematology

C-reactive protein, mg/L | - | - | - | - | - | - | - | - | - |
N-terminal-pro BNP, mg/L | - | - | - | - | - | - | - | - | - |

Troponin, ng/L | 700 (350–252 000) | 10400 (400–240 000) | <0.0001 | 30500 (600–356 000) | 33 040 (610–391 350) | <0.0001 | 50 (2.4–1410) | 50 (2.9–110) | <0.0001 |
Haemoglobin, g/dL | 12.8 (11.5–13.9) | 14.6 (12.5–13.5) | <0.0001 | 12.7 (11.5–13.9) | 14.0 (12.5–15.0) | <0.0001 | 13.1 (12.0–141) | 14.5 (13.3–15.5) | <0.0001 |
Estimated glomerular filtration rate, mL/min/1.73 m² | 62.1 (43.7–81.1) | 72.1 (53.4–89.0) | <0.0001 | 64.8 (45.5–83.5) | 74.9 (55.1–90.6) | <0.0001 | 68.0 (50.0–86.0) | 80.8 (62.5–133) | <0.0001 |
Left ventricular ejection fraction ≤50% | 37.59/59.825 (62.8%) | 65.22/108.437 (60.2%) | <0.0001 | 87.62/138.18 (63.4%) | 166.52/278.86 (59.9%) | <0.0001 | 204.70/75 (66.6%) | 621.92/271 (67.0%) | 0.66 |

Medication at presentation

Aspirin | 66.68/130.718 (51.0%) | 124.35/240.181 (55.6%) | <0.0001 | 16.20/28252 (5.8%) | 33.30/53358 (6.4%) | <0.0001 | 236.59/296 (44.6%) | 629.14/157 (44.4%) | 0.087 |
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker | 5.67/126.213 (41.7%) | 90.95/155.996 (42.1%) | 0.021 | 116.61/26991 (42.2%) | 21.88/50.775 (43.1%) | 0.77 | 2527.57/56 (45.3%) | 39.07/1545 (39.2%) | <0.0001 |
β-blocker | 41.83/126.247 (33.1%) | 71.75/16.032 (33.2%) | 0.61 | 947.29/4611 (35.0%) | 1786.6/5066 (35.3%) | 0.46 | 2117.38/88 (39.3%) | 493.14/395 (34.3%) | <0.0001 |
P2Y12 receptor inhibitor | 0.16/414.161 (14.0%) | 28.46/136.722 (14.4%) | 0.0017 | 466.05/25348 (18.4%) | 890.44/48.34 (18.4%) | 0.91 | 5745.11/11 (12.1%) | 1649.13/52 (12.1%) | 0.007 |
Statin | 60.31/130.994 (46.0%) | 113.30/24.245 (50.6%) | <0.0001 | 1342.81/2653 (46.8%) | 2732/54 (70.4%) | <0.0001 | 1790.52/43 (34.1%) | 547.14/95 (38.8%) | <0.0001 |

Data are median (IQR) or n/N (%). AMIS=Acute Myocardial Infarction in Switzerland. GRACE=Global Registry of Acute Coronary Events. MINAP=Myocardial Ischaemia National Audit Project. SPUM-ACS=Special Programme University Medicine Acute Coronary Syndrome. *Estimated as coding to DuBois and DuBois.*† Defined as elevation in total cholesterol requiring dietary or drug treatment. ‡ Defined as already receiving treatment (drug, dietary, or lifestyle) for hypertension or consistently recorded blood pressure values exceeding 140/90 mm Hg before admission. §Refers to New York Heart Association class greater than III in AMIS Plus. ¶Refers to peak values in the UK. || Estimated according to Chronic Kidney Disease Epidemiology Collaboration creatinine equation.\(^\text{35}\)

Table 1: Baseline characteristics of patients with non-ST-segment elevation acute coronary syndromes in the UK and Switzerland, stratified by level of care and sex
### UK (2005–17)

| Feature | Value | p value | Female (n=145,738) | Male (n=254,316) |
|---------|-------|---------|--------------------|------------------|
| Death in hospital | 2.5 | <0.0001 | 2.3 | 1.4 |
| Death at 6 months | 100 | <0.0001 | 90 | 10 |
| Death at 1 year | 8.9 | <0.0001 | 7.2 | 5.4 |

### Switzerland (2005–20)

| Feature | Value | p value | Female (n=5576) | Male (n=115,151) |
|---------|-------|---------|-----------------|------------------|
| Death in hospital | 2.1 | <0.0001 | 2.4 | 1.0 |
| Death at 6 months | 8.0 | <0.0001 | 6.0 | 4.0 |
| Death at 1 year | 6.6 | <0.0001 | 4.6 | 3.1 |

### Management delay

| Feature | Value | p value |
|---------|-------|---------|
| Onset-to-door, min | 226 (112–669) | <0.0001 |
| Door-to-PCI, min | 242 (117–737) | <0.0001 |
| Onset-to-PCI, min | 345 (135–965) | 0.073 |

### Early invasive strategy (<24 h)

| Feature | Value | p value |
|---------|-------|---------|
| All | 345 (135–965) | 0.073 |
| Low-to-intermediate risk (according to GRACE 2.0 score) | 345 (135–965) | 0.073 |
| High-risk (according to GRACE 2.0 score) | 345 (135–965) | 0.073 |

### Type of intervention

| Feature | Value | p value |
|---------|-------|---------|
| Coronary angiography | 70.66/145,738 | 0.046 |
| PCI | 30.45/87,993 | 0.046 |
| Coronary artery bypass grafting | 22.98/87,993 | 0.046 |
| Thrombolysis | 22.98/87,993 | 0.046 |

### Procedural characteristics

| Feature | Value | p value |
|---------|-------|---------|
| Duration of PCI, min | 27.0 (17.0–40.5) | 0.046 |
| Intra-aortic balloon pump | 37.8/14,433 | 0.52 |
| Vasopressor use | 27.9/14,161 | 0.50 |
| Aspirin | 480.5/18,310 | 0.40 |
| P2Y12 receptor inhibitor | 392.5/18,310 | 0.40 |

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*Table 2 continues on next page*
|                     | UK (2005–17) | Switzerland (2005–20) |
|---------------------|--------------|-----------------------|
|                     | All patients (MINAP; n=400/54) | All patients (AMIS Plus; n=20,727) |
|                     | University hospitals (MINAP; n=33,847) | University hospitals (SPUM-ACS; n=2,239) |
|                     | Female (n=145,738) | Male (n=25,4316) | p value | Female (n=5,151) | Male (n=15,151) | p value |
| Female (n=462) | 26.1 | 15.9 | <0.0001 | 466/527 | 575/527 | 12.7% | 12.2% | <0.0001 |
| Male (n=1,777) | 29.0 | 28.5 | 0.92 | 3,285/5,176 | 3,385/5,176 | 19.7% | 19.7% | 0.92 |
| Female (n=556) | 26.8 | 16.2 | <0.0001 | 3,039/5,176 | 4,039/5,176 | 11.8% | 11.8% | <0.0001 |
| Male (n=1,502) | 29.5 | 28.7 | 0.92 | 3,556/5,176 | 4,556/5,176 | 19.6% | 19.6% | 0.92 |
| Duration of hospital stay, days† | 6 (3–10) | 5 (3–8) | <0.0001 | 5 (3–8) | 5 (3–8) | <0.0001 |
| Discharge destination | 1.0 | 0.24 | 0.0063 | 1.0 | 0.24 | 0.0063 |
| Rehabilitation or other hospital | 28.1% | 21.8% | 0.0001 | 29.5% | 23.8% | 0.0001 |
| Home | 71.9% | 78.2% | <0.0001 | 70.5% | 76.2% | <0.0001 |
| Discharge medication | 1.0 | 0.24 | 0.0063 | 1.0 | 0.24 | 0.0063 |
| Aspirin | 98.0% | 97.6% | <0.0001 | 97.9% | 97.6% | <0.0001 |
| Angiotensin- | 81.3% | 81.7% | <0.0001 | 81.1% | 81.7% | <0.0001 |
| converting enzyme inhibitor | 80.4% | 80.4% | <0.0001 | 80.4% | 80.4% | <0.0001 |
| β-blocker | 82.3% | 81.3% | <0.0001 | 82.4% | 81.3% | <0.0001 |
| P2Y12 receptor inhibitor | 79.4% | 79.5% | <0.0001 | 79.4% | 79.5% | <0.0001 |
| Statin | 46.9% | 46.3% | <0.0001 | 46.8% | 46.3% | <0.0001 |
| Outcomes | 1.0 | 0.24 | 0.0063 | 1.0 | 0.24 | 0.0063 |
| Major bleed in hospital | 4.2% | 4.3% | <0.0001 | 4.1% | 4.2% | <0.0001 |
| Death in hospital | 0.4% | 0.4% | <0.0001 | 0.4% | 0.4% | <0.0001 |
| Death at 6 months§ | 1.3% | 1.4% | <0.0001 | 1.3% | 1.4% | <0.0001 |
| Death at 1 year§ | 1.6% | 1.7% | <0.0001 | 1.6% | 1.7% | <0.0001 |

Data are median (IQR) or n/N (%) AMIS=Acute Myocardial Infarction in Switzerland. GRACE=Global Registry of Acute Coronary Events. PGU=percutaneous coronary intervention. SPUM-ACS=Special Programme University Medicine Acute Coronary Syndrome. *Based on complete cases. †Based on data retrieved from patients discharged home. §Defined as Bleeding Academic Research Consortium ≥3a. §Refers to post-discharge outcomes in AMIS Plus.

Table 2: GRACE 2.0 risk, management, and outcomes of patients with non-ST-segment elevation acute coronary syndromes in the UK and Switzerland, stratified by level of care and sex.
described previously. This approach is commonly used in game theory to estimate a player’s contribution to success. The ability to predict in-hospital death of the GRACE 3.0 score and the GRACE 2.0 score was compared on unseen data (ie, the internal and external validation cohort) using the DeLong test for paired ROC curves. Reclassification was assessed by comparing the risk groups assigned by GRACE 2.0 and GRACE 3.0, with individuals considered reclassified when groups were discordant. A calculator for GRACE 2.0 and GRACE 3.0, with individuals considered was assessed by comparing the risk groups assigned by data (ie, the internal and external validation cohort) using the binary outcome variables (in-hospital death, death at 6 months, and death at 1 year) as predictors (ie, no imputation was used for these variables in the analysis; appendix p 2). Results obtained in imputed datasets were combined using Rubin’s rule to derive an overall estimate and confidence interval (appendix p 2). Given that the XGBoost learning algorithm operates on single datasets, we used a single imputed dataset, generated as described, for training, testing, and external validation of the GRACE 3.0 score. Sensitivity analyses using complete cases were done to explore a potential effect of the imputation on the results (appendix pp 17–21, 23). Internal validation of the GRACE 2.0 score evaluation in complete cases was done in each cohort by using 300 bootstrap samples (appendix p 2). Sex differences in mortality and the importance of individual GRACE features for regression-based mortality predictions were assessed in generalised linear models (appendix p 2). Mortality endpoints with event counts below the predefined minimum of 30 were not considered for analysis. The results were reporte according to the framework for transparant reporting of prediction models summarised in the TRIPOD statement and comply with the STROBE statement (appendix pp 39–41). All p values and CIs are two-sided.

Data were analysed in R version 4.1 and IBM SPSS version 27.0.1. A detailed description of the statistical analyses is presented in the appendix (pp 2–4).

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.

Statistical analysis
Continuous variables are presented as median and IQR. Categorical data are shown as counts and percentages. Normally distributed variables were compared by Students t test, non-normally distributed variables by the Mann-Whitney test, and categorical variables by the χ² test, Fisher’s exact test, or Kruskal-Wallis test, as appropriate. Where data for the calculation of GRACE 2.0 risk estimates were missing, we applied multiple imputation using chained equations (20 imputations) for each cohort separately. We used predictive mean matching, proportional odds models, and logistic regression models using the binary outcome variables (in-hospital death, death at 6 months, and death at 1 year) as predictors (ie, no imputation was used for these variables in the analysis; appendix p 2). Results obtained in imputed datasets were combined using Rubin’s rule to derive an overall estimate and confidence interval (appendix p 2). Given that the XGBoost learning algorithm operates on single datasets, we used a single imputed dataset, generated as described, for training, testing, and external validation of the GRACE 3.0 score. Sensitivity analyses using complete cases were done to explore a potential effect of the imputation on the results (appendix pp 17–21, 23). Internal validation of the GRACE 2.0 score evaluation in complete cases was done in each cohort by using 300 bootstrap samples (appendix p 2). Sex differences in mortality and the importance of individual GRACE features for regression-based mortality predictions were assessed in generalised linear models (appendix p 2). Mortality endpoints with event counts below the predefined minimum of 30 were not considered for analysis. The results were reporte according to the framework for transparant reporting of prediction models summarised in the TRIPOD statement and comply with the STROBE statement (appendix pp 39–41). All p values and CIs are two-sided.

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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 Aug 27, 2020, 400054 patients with NSTE-ACS in the UK and 20727 patients with NSTE-ACS in Switzerland were included in the study (appendix p 25). At hospital admission, female patients showed marked differences in GRACE components and other baseline risk factors compared with male patients across all cohorts (table 1). Although creatinine concentrations, a component of the GRACE score, suggested better kidney function in female patients compared with male patients, the estimated glomerular filtration rate (eGFR), a sex-adjusted measure of renal function, indicated the opposite. Compared with male patients, the time elapsed between symptom onset and admission was longer and GRACE risk estimates calculated at presentation were consistently higher in female patients with NSTE-ACS (table 2). Paradoxically, female patients were less likely to receive coronary...
angiography and to undergo early invasive therapy than were male patients. The female patient population was characterised by longer hospital stays and lower rates of antiplatelet and statin treatment and had a higher crude but not multivariable-adjusted risk for in-hospital mortality compared with male patients (table 2; appendix p 10).

The AUC of the GRACE 2.0 score to predict in-hospital death was 0·86 (95% CI 0·86–0·86) in male patients and 0·82 (95% CI 0·81–0·82; p<0·0001) in female patients. Similar results were obtained in the UK and Switzerland, and for the 6-month and 1-year mortality endpoint across clinical settings of score calculation (figure 1; appendix pp 12, 15–16). Calibration of the GRACE 2.0 score was suboptimal in male and female participants, with higher average prediction errors and false omission rates and lower accuracy in female patients (figure 1; appendix pp 12–16). The GRACE 2.0 score underestimated the in-hospital mortality risk in female patients to a greater extent than in male patients (figure 1), favouring their incorrect stratification to the low-to-intermediate risk group where they were at an increased mortality risk (appendix p 22).

The importance of clinical features informing the GRACE 2.0 model to predict in-hospital death were differentially ranked in regression-based analyses in female and male patients with NSTE-ACS (appendix pp 2, 26), suggesting that sex-specific weighting of GRACE components improves overall model performance. By applying a machine learning algorithm to these features in sex-disaggregated cohorts, we developed and validated the GRACE 3.0 score that, based on an ensemble of decision trees, predicts in-hospital mortality separately in women and men with NSTE-ACS (appendix p 3). The relative feature importance to predict in-hospital death varied across sexes, with marked sex-specific effects of GRACE components on model output (figure 2). For example, baseline heart rate had a non-linear contribution to the model output in both sexes with a higher positive and negative effect on the prediction in male patients with NSTE-ACS.

The GRACE 3.0 score yielded AUCs of 0·89 (95% CI 0·89–0·90) and 0·86 (0·86–0·87) in the training cohort and an AUC of 0·88 (0·87–0·88) and 0·84 (0·83–0·85) in the internal validation cohort in male and female patients, respectively (figure 3). When applied to the external validation cohort, the GRACE 3.0 score showed AUCs of 0·91 (95% CI 0·89–0·92) and 0·87 (0·84–0·89) in male patients and female patients, respectively. Discrimination of in-hospital death by the GRACE 3.0 score exceeded that of the GRACE 2.0 score in both validation cohorts irrespective of sex (all p<0·0001). The GRACE 3.0 score showed good calibration (figure 3; appendix p 38), resulting in clinically meaningful differences in the proportion of female and male patients with NSTE-ACS stratified into the high-risk group (figure 4).

Sex-specific GRACE 3.0 risk estimates led to reclassification of women towards the high-risk group and of men towards the low-to-intermediate risk group (figure 4; appendix p 24). As a result, the proportion of patients in the high-risk group increased in female patients and decreased in male patients, without elevating the absolute mortality risk in the low-to-intermediate risk group for either sex.

**Discussion**

In this study, we report results from the largest investigation of the GRACE score to date. We evaluated the GRACE 2.0 score in 420781 patients with NSTE-ACS from four European countries and found limited discriminatory performance, suboptimal calibration, and underestimation of mortality risk in female patients, who were characterised by a distinct baseline risk profile. Applying a machine learning approach, we derived and externally validated a refined score (termed GRACE 3.0) that appreciates sex-specific relationships between GRACE components and in-hospital mortality, with excellent discriminative ability and good calibration, resulting in improved overall model performance, while relying on identical input variables.

Although sex differences in the clinical characteristics of patients with NSTE-ACS have been reported previously, current data from real-world patient populations in Europe were lacking. In the present study, female patients showed markedly reduced kidney function, evident from lower eGFR. However, creatinine concentrations, a surrogate of renal function used by the GRACE score without accounting for the different physiological range

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**Figure 2: Feature importance in the GRACE 3.0 score in female and male patients**

The clinical features and the internally calculated GRACE 2.0 risk estimates that inform the supervised machine learning model are ranked according to their contribution to the model output. Each point represents a patient, with colour indicating the feature value. For example, the effect of age on model output is positive when the patient is relatively old (purple) and negative when a patient is relatively young (yellow). Numbers next to the variables represent mean absolute SHAP values. GRACE=Global Registry of Acute Coronary Events. SHAP=Shapley Additive Explanations.
in women and men, were lower in female patients. Beyond differences in GRACE components, female patients were more likely to present with signs of congestion, had higher N-terminal prohormone of brain natriuretic peptide levels and did not have higher rates of cardiogenic shock (ie, Killip class IV), suggesting that worse Killip class in female patients might be partly related to non-acute coronary syndrome causes.

Female patients also differed in cardiometabolic risk factors, including BMI, cholesterol concentrations, and the prevalence of hypertension, which are not part of the GRACE score. In Switzerland, female patients were almost twice as likely as male patients to present with a history of depression, a patient characteristic with sex-specific association strength with fatal events after acute coronary syndrome. In the UK, female patients were more likely than male patients to have preserved ejection fraction at baseline, another factor with potentially different prognostic implications after acute coronary syndrome in women and men not included in the GRACE score. Despite their higher comorbidity burden and increased GRACE 2.0 risk estimates at baseline, female patients were less likely to undergo coronary angiography and to receive early invasive therapy. Although female patients with NSTE-ACS had a higher crude risk for in-hospital mortality relative to male patients, this association was not evident after adjusting for baseline characteristics, in line with observational data of independent cohorts.

Beyond the distinct patient risk profiles and management characteristics of female and male patients with NSTE-ACS, the present study unveiled clinically relevant sex-specific limitations of the GRACE 2.0 score. The GRACE 2.0 score showed lower discrimination and suboptimal calibration, as exemplified by a systematic underestimation of in-hospital mortality risk in female patients, thereby expanding on previous reports. The dissimilar association between individual GRACE variables and in-hospital mortality in female and male patients with NSTE-ACS in both regression and machine learning models was not considered by the GRACE 2.0 model. This fact might have, at least in part, contributed to diminished performance of the GRACE 2.0 score in female patients with NSTE-ACS, thereby promoting a systematic sex-dependent deviation in early risk stratification and guideline-directed care, probably preventing a subpopulation of female patients with NSTE-ACS from receiving early invasive therapy.

Female patients with NSTE-ACS were less likely to receive early invasive therapy, as reported in previous research. Although the management of patients with NSTE-ACS differs from country to country, with a more liberal use of PCI in Sweden and the USA versus the UK, the sex gap in the performance of the GRACE 2.0 score described in this study was evident across geographical boundaries. As diminished GRACE 2.0 score performance in women was independent of geographical region and results obtained in patients undergoing PCI also supported this finding, sex-specific differences in GRACE 2.0 score performance are unlikely to be driven by these factors.

Although the optimal treatment strategy for women with NSTE-ACS remains unclear, our results support the hypothesis that a subpopulation of female patients who were previously classified as low-to-intermediate risk by GRACE 2.0 might benefit from early invasive management. In fact, the updated GRACE 3.0 score stratified more female and less male patients with NSTE-ACS into the high-risk group, with potentially important therapeutic implications.

Although the GRACE score was developed in a predominantly male patient population, recruited until 2007, and is used in both sexes alike, its performance in current female patients with NSTE-ACS was understudied. We delineated sex differences in the importance of score variables and in baseline risk factors beyond the GRACE score, which was reflected in...
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and –, respectively. Percentages refer to patients of the indicated sex. GRACE=Global Registry of Acute Coronary 2.0 score. Increases and decreases of the patient population in the low-to-intermediate group are indicated by reclassification from the one risk group to another risk group by the GRACE 3.0 score compared with the GRACE validation cohort from the UK (A) and the external validation cohort from Switzerland (B). Arrows indicate Histograms showing the distribution of the patient population across 3% intervals of predicted risk in the internal non-ST-segment elevation acute coronary syndromes Figure 4: Effect of the GRACE 3.0 score on risk stratification in female patients and male patients with Events.

Figure 4: Effect of the GRACE 3.0 score on risk stratification in female patients and male patients with non-ST-segment elevation acute coronary syndromes Histograms showing the distribution of the patient population across 3% intervals of predicted risk in the internal validation cohort from the UK (A) and the external validation cohort from Switzerland (B). Arrows indicate reclassification from the one risk group to another risk group by the GRACE 3.0 score compared with the GRACE 2.0 score. Increases and decreases of the patient population in the low-to-intermediate group are indicated by + and –, respectively. Percentages refer to patients of the indicated sex. GRACE=Global Registry of Acute Coronary Events.

unequal score performance. By harnessing machine learning-based methods, we redeveloped the GRACE score, reaching superior performance in internal and external validation datasets, with clinically relevant implications.

Our study has several strengths. First, we analysed the largest patient cohorts in Europe, with a total sample size exceeding previous studies on the GRACE score. Indeed, along with the elegant study by Wilkinson and colleagues, which added an important layer of evidence on the sex gap in guideline-directed care in a cohort containing 418 177 patients with NSTE-ACS, to our knowledge the present study is among the largest investigations into NSTE-ACS. Second, we analysed patients that were enrolled between 2005–20, accounting for the evolution of the NSTE-ACS phenotype and treatment since the end of the recruitment periods of many landmark studies in terms of sex discrepancies in NSTE-ACS and in the derivation and validation cohorts of the GRACE score. Third, we applied resampling techniques to confirm the internal validity of the results. Fourth, we studied the GRACE score at 6 months and at 1 year mortality endpoints in different clinical settings (calculated at presentation and calculated for hospital survivors, respectively), and these findings were largely in line with the results obtained for the in-hospital death endpoint. Consistency of sex differences in the baseline risk profile and in the performance of the GRACE score in NSTE-ACS across independent prospective patient cohorts maximises the external validity of our findings. Despite markedly different mortality rates between the cohorts, probably due to various factors, including differences in management, study design, and unmeasured features of care, consistent underperformance of GRACE 2.0 in female patients with NSTE-ACS was observed. Finally, prospectively collected real-world data, as used in the current study, provides increased generalisability to the European patient population compared with clinical trial data.

There are some limitations inherent to the design of the study cohorts. First, the MINAP and AMIS Plus registries collect data via standardised electronic entry by health-care professionals without complete external event adjudication. Indeed, of the 400 054 patients recruited in MINAP, in-hospital outcomes were only available for 386 911 patients. Additionally, only in-hospital and postdischarge mortality data were available in AMIS Plus, and only a subset of patients were recruited for 1-year follow-up visits. Finally, only data on biological sex but not on the gender of study participants were available, precluding the exploration of sociocultural influences and transgender people.

In conclusion, the performance of the GRACE 2.0 score is limited by decreased discrimination and underestimation of in-hospital mortality in female patients with NSTE-ACS. The newly developed GRACE 3.0 score accounts for sex-specific weighting of individual GRACE components and shows excellent discrimination and good calibration. Awareness of sex differences in disease biology and the patient risk profile at the time of presentation is critical to improve outcomes in patients with NSTE-ACS. Further external validation is warranted to assess GRACE 3.0 score performance in other populations.

Contributors

FAW, SK, DR, JD, and TFL conceived the study. FAW, SK, SAH, and GA performed data queries, processing, and analyses. FAW and SK wrote the manuscript. FAW and SK have accessed and verified the underlying data reported in the manuscript. All authors had full access to the data and are responsible for the decision to submit for publication.

www.thelancet.com Vol 400 September 3, 2022
Declaration of interests
SK received travel support from the European Atherosclerosis Society and equipment and materials from Roche Diagnostics, outside the submitted work. MR declares institutional research grants from Terumo, Biotronik, Medtronic, Cordis/Cardinal Health, and Boston Scientific, outside the submitted work. LR received funding from Abbott, Biotronik, Boston Scientific, Sanofi, Regeneron, and Heartflow, consulting fees from Abbott, Aman, AstraZeneca, Canon, NovoNordisk, Medtronic, Sanofi, Oclutech, and Vifor, payment or honoraria from Abbott and Oclutech, and travel support from AstraZeneca. MD is Chair of the Data Monitoring and Ethics Committee of the UK GRIS Trial and part of the Steering Committee of the DAPA MI Trial. CW is the clinical lead of the MINAP registry. JD received consulting fees from GENInCode UK Ltd, honoraria or consulting fees from Aman, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk, and Bayer, and travel support from the Einstein Professorship Foundation (Berlin, Germany), outside the submitted work. JD holds unpaid leadership positions at Our Future Health and Public Health England. TFL declares institutional educational and research grants from Abbott, Aman, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novartis, and Vifor, and consulting fees from Daichi Sankyo, Philips, Pfizer, and Ineeo Inc. outside the submitted work. TFL holds leadership positions at the European Society of Cardiology, Swiss Heart Foundation, and the Foundation for Cardiovascular Research—Zürich 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 the data and additional documents related to the present study should be made to the corresponding author of each single registry (dragana.radovanovic@uzh.ch, j.deanfield@ucl.ac.uk, and cardio@tomluescher.ch).

Acknowledgments
The AMIS Plus registry is funded by unrestricted grants from the Swiss Heart Foundation and from Abbott AG, Aman, AstraZeneca AG, Bayer (Schweiz) AG, Biotronik AG, Boston Scientific AG, B Braun Medical AG, Daiichi-Sankyo/Lilly AG, Cordis Cardinal Health GmbH, Medtronic AG, Novartis Pharma Schweiz AG, Sanofi-Aventis (Schweiz) AG, SIS Medical AG, Terumo AG, and Vascular Medical GmbH, all in Switzerland, and the Swiss Working Group for Interventional Cardiology. The SPUM-ACS registry is primarily supported by the Swiss National Science Foundation (SPUM 33CM30-124112 and 32473B_163271) and the Science Foundation (SPUM 33CM30-124112 and 32473B_163271) and the Swiss Heart Foundation (through TFL). Additional support for the SPUM-ACS registry was received from Roche Diagnostics (Boehringer Mannheim; Indianapolis, IN, USA), Eli Lilly (Indianapolis, IN, USA), AstraZeneca (Baar, Switzerland), Medtronic (Münchenbuchsee, Switzerland), Merck Sharpe and Dohme (Lucerne, Switzerland), Sanofi-Aventis (Vernier, Switzerland), and St Jude Medical AG (Zürich, Switzerland). This work was further supported by the Foundation for Cardiovascular Research—Zürich Heart House (through FAW, SK, GGC, and TFL), the Lindenhofstiftung (through TFL and SK), and the Thedodor Ida Herzog-Egli Stiftung (through SK). We gratefully acknowledge the invaluable contribution of all health-care professionals who participate in the conduct of the national registries this study is based on. We further express our gratitude towards all administrative personnel and IT personnel involved in data entry and management. Finally, we are grateful to the Epidemiology, Biostatistics and Prevention Institute (University of Zurich, Zurich, Switzerland) for the productive discussions.

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