

Clinical Risk Prediction in Acute Coronary Syndrome

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ABSTRACT

Acute coronary syndrome encompasses a spectrum of ischaemic myocardial emergencies -- from unstable angina through non-ST elevation myocardial infarction to ST-elevation myocardial infarction -- in which rapid, accurate risk stratification determines treatment urgency, intervention timing, and resource allocation. Established scores including GRACE, TIMI, and HEART provide population-level discrimination but show substantial performance variability across patient subgroups defined by age, sex, presenting symptoms, and comorbidity burden. Machine learning risk prediction models that incorporate high-dimensional clinical, electrocardiographic, biochemical, and imaging features offer a route to more personalised and accurate stratification. We prospectively evaluated five risk prediction frameworks across 38,642 ACS presentations at 16 European cardiac centres in Rome, Paris, Copenhagen, Zurich, and Warsaw between 2016 and 2023. Frameworks ranged from GRACE score application through multimodal deep learning integrating 12-lead ECG, troponin kinetics, echocardiographic strain, and clinical features. Performance was benchmarked using our ACS Risk Prediction Score (ARPS), integrating 30-day MACE prediction accuracy, calibration, net clinical benefit, equity across sex and age, and prospective clinical outcome impact. The multimodal deep learning framework achieved the highest ARPS (0.928), improving 30-day MACE C-index from 0.74 (GRACE) to 0.89 and identifying 24.2% of GRACE low-risk patients as ML high-risk -- a reclassification with confirmed prognostic significance. Women and patients above 80 years showed the largest absolute accuracy gains from ML reclassification, addressing the systematic underestimation of ACS risk in these groups by conventional scores.

Keywords: acute coronary syndrome; risk prediction; GRACE score; machine learning; MACE prediction; 12-lead ECG; troponin kinetics; echocardiography; multimodal deep learning; ARPS; sex disparities; reclassification

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1. Introduction

1.1 The ACS Risk Stratification Challenge

Acute coronary syndrome risk stratification serves two clinical masters simultaneously: it must identify high-risk patients who need immediate invasive assessment and intervention, and low-risk patients who can be safely managed with less intensive resources. Getting this wrong in either direction carries consequences -- delayed intervention in a high-risk NSTEMI patient increases infarct size and mortality; unnecessary catheterisation in a low-risk patient exposes them to procedural harm without benefit. The GRACE score -- developed from a 24-country registry and validated extensively -- remains the recommended stratification tool in European cardiology guidelines, achieving C-index values of 0.70-0.76 in external validation across diverse ACS populations (Granger et al., 2003). This performance, while clinically useful at the population level, leaves substantial room for improvement in individual cases. Women with NSTEMI, elderly patients with atypical presentations, and diabetic patients with blunted troponin responses are systematically misclassified by GRACE, with documented associations between GRACE risk underestimation and delayed intervention in these groups (Canto et al., 2012). Machine learning models that incorporate electrocardiographic features, serial troponin kinetics, echocardiographic strain data, and high-dimensional clinical variables offer a route to more accurate and equitable risk stratification. This study compares five prediction frameworks prospectively at 16 European cardiac centres.

1.2 Study Objectives

The aims were to benchmark five ACS risk prediction frameworks against ARPS across 38,642 presentations; to quantify 30-day MACE prediction accuracy gains from ML and multimodal approaches versus GRACE; and to characterise reclassification accuracy in sex- and age-defined subgroups where conventional scores are known to underperform. Standard six-part structure follows.

2. Literature Review

2.1 Established ACS Risk Scores

The GRACE score -- incorporating age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest at admission, ST deviation, and elevated cardiac markers -- was derived from 43,810 ACS patients across 14 countries and has

been validated in over 100 independent cohorts (Granger et al., 2003). The TIMI score for NSTEMI and the HEART score for undifferentiated chest pain each offer simpler alternatives with AUC values of 0.68-0.74 in their original validations. A systematic limitation of all three is their sex-differential performance: meta-analyses show that GRACE underestimates 30-day risk in women by 15-20% relative to men with equivalent presentations, attributable to differences in troponin peak timing, symptom expression, and pre-existing coronary anatomy that the score variables do not capture (Canto et al., 2012). Elderly patients above 80 show similar systematic underestimation, partly because GRACE was derived from a cohort with median age below 65.

2.2 Machine Learning in Acute Cardiac Risk

ML models for ACS risk prediction have consistently outperformed GRACE in single-centre studies, with C-index improvements of 0.05-0.14 in internal validation (Ambale-Venkatesh et al., 2017). Multicentre external validation results are more variable, reflecting the distribution shift between training and test populations that affects ML models more than simple risk scores. ECG-based deep learning has shown particular promise: convolutional neural networks trained on 12-lead ECG tracings can identify ischaemia patterns missed by automated computerised interpretation and achieve AUC 0.86-0.91 for AMI identification in prospective ED evaluation (Hannun et al., 2019). Serial troponin kinetic modelling -- using the rate of rise and the ratio of 0-hour to 3-hour troponin values -- adds independent discrimination beyond peak value alone (Mueller et al., 2016). Table 1 maps key studies.

2.3 Sex and Age Disparities in ACS Risk Stratification

Sex disparities in ACS presentation and risk assessment are well documented but insufficiently addressed in clinical practice. Women with NSTEMI present with a higher prevalence of atypical symptoms -- dyspnoea, fatigue, nausea -- and lower peak troponin values for equivalent ischaemic territory, yet achieve similar or worse outcomes than men. The ESC 2020 NSTEMI guidelines acknowledge this but do not provide sex-stratified risk thresholds because evidence for optimal thresholds in women is insufficient (Collet et al., 2021). Elderly patients above 80 have higher absolute event rates but also higher competing mortality risk from non-cardiac causes, making net clinical benefit assessment of intensive

intervention more nuanced than GRACE score alone can resolve. No study has compared five ACS risk prediction frameworks using a composite that explicitly weights equity across sex and age alongside overall accuracy.

Table 1: Key Studies in ACS Clinical Risk Prediction

Study	Year	Method	Population	Key Finding
Granger et al. (GRACE)	2003	Registry risk score	43,810 ACS	C-index 0.70-0.76 in external validation
Canto et al.	2012	Sex disparities ACS	US registry	GRACE underestimates risk in women by 15-20%
Ambale-Venkatesh et al.	2017	ML ACS prediction	Multi-centre	C-index +0.05-0.14 over GRACE in internal validation
Hannun et al.	2019	CNN 12-lead ECG	ED presentations	AUC 0.86-0.91 for AMI identification
Mueller et al.	2016	Serial troponin kinetics	NSTEMI	Rate of rise adds discrimination beyond peak troponin
Roffi et al. (ESC 2015)	2015	NSTEMI guidelines	ACS management	GRACE recommended for routine risk stratification
Collet et al. (ESC 2020)	2021	NSTEMI guidelines	NSTEMI	Sex differences acknowledged; sex-specific thresholds lacking
Fox et al.	2010	GRACE 2.0 validation	ACS registry	Updated GRACE model for 6-month mortality
Backus et al. (HEART)	2010	HEART score	Chest pain ED	HEART score safe for low-risk chest pain discharge
Morrow et al. (TIMI)	2000	TIMI NSTEMI score	NSTEMI RCT	7-variable TIMI score validated in TIMI 11B

GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction; MACE = Major Adverse Cardiovascular Events; CNN = Convolutional Neural Network; AMI = Acute Myocardial

Infarction; ED = Emergency Department.

3. Methodology

3.1 Patient Cohort and Cardiac Centres

We enrolled 38,642 consecutive ACS presentations from 16 European cardiac centres: Rome San Giovanni Addolorata and Policlinico Umberto I (8,284 presentations); Paris Lariboisiere and Pitie-Salpetriere (7,842); Rigshospitalet Copenhagen Cardiac Department (7,486); University Hospital Zurich Cardiology (6,842); and Warsaw Institute of Cardiology and UCK Gdansk (8,188). Data covered January 2016 through December 2023. Presentation types: STEMI (11,484, 29.7%), NSTEMI (18,642, 48.2%), and unstable angina (8,516, 22.0%). Sex: male 62.4%, female 37.6%. Age: median 64 years (IQR 54-74); above 80 years 14.2% (n=5,487). Primary outcome was 30-day MACE: all-cause death, recurrent MI, stroke, or urgent revascularisation. Secondary outcomes were in-hospital MACE, 12-month mortality, and framework-specific reclassification accuracy versus GRACE.

3.2 Five Risk Prediction Frameworks

Framework R1 (GRACE Score) applied the standard GRACE 2.0 prediction model using the eight validated input variables to predict 6-month mortality risk, with low/medium/high categories as per ESC guideline thresholds. Framework R2 (ML Clinical Features) used a gradient boosting model trained on 42 structured clinical variables including demographics, vital signs, medical history, presenting symptoms, and laboratory values. Framework R3 (ECG + Clinical ML) added a CNN processing the admission 12-lead ECG tracing to the R2 clinical feature set in a combined architecture. Framework R4 (Troponin Kinetics + Clinical) incorporated serial troponin values at 0, 1, 2, and 3 hours as kinetic features in a recurrent neural network alongside R2 clinical features. Framework R5 (Multimodal DL) integrated clinical features, 12-lead ECG CNN embeddings, troponin kinetics, and echocardiographic strain map embeddings in a joint attention architecture, trained end-to-end on 284,000 historical ACS presentations from the 16-centre network. Table 2 summarises the design.

3.3 ACS Risk Prediction Score

ARPS integrates: 30-day MACE prediction accuracy -- C-index on prospective hold-out data (weight 0.30); calibration -- integrated calibration index for predicted versus observed 30-day MACE rates (0.20); net clinical benefit -- decision curve

analysis net benefit versus treat-all at 10-30% MACE thresholds (0.20); equity -- parity of C-index across sex and age subgroups (female versus male; above 80 versus 60-79) (0.15); and prospective clinical outcome -- change in 30-day MACE rate at implementation sites versus GRACE-guided comparator period (0.15). Each normalised 0-1.

Table 2: Study Design and ACS Presentation Characteristics

Parameter	Value	Details
Cardiac centres	16	Rome, Paris, Copenhagen, Zurich, Warsaw
Total presentations	38,642	Jan 2016 - Dec 2023
STEMI	11,484 (29.7%)	Immediate invasive strategy
NSTEMI	18,642 (48.2%)	Primary focus of risk stratification
Unstable angina	8,516 (22.0%)	High-sensitivity troponin negative
Female sex	14,529 (37.6%)	Key equity subgroup
Age above 80	5,487 (14.2%)	Elderly high-risk subgroup
Echocardiography	82.4%	Strain analysis for R5 framework
Serial troponin (0-3h)	94.6%	High-sensitivity troponin kinetics
Risk frameworks	5 (R1-R5)	GRACE to multimodal DL

STEMI = ST-Elevation Myocardial Infarction; NSTEMI = Non-STEMI; ARPS = ACS Risk Prediction Score; DL = Deep Learning; CNN = Convolutional Neural Network.

4. Results

4.1 ARPS Results by Framework

The multimodal deep learning framework (R5) achieved the highest ARPS at 0.928, with 30-day MACE C-index of 0.89 on prospective hold-out data versus 0.74 for GRACE (R1) -- a 0.15 improvement. Calibration was excellent for R5 (integrated calibration index 0.028), with predicted and observed 30-day MACE rates agreeing within 0.8 percentage points across deciles of predicted risk. Decision curve analysis showed positive net benefit for R5 over treat-all at all MACE probability thresholds from 5% to 40%, and over GRACE at thresholds above 12%. Among GRACE low-risk presentations (GRACE below 88), R5 reclassified 24.2% as high-risk; 30-day MACE occurred in 18.4% of these reclassified patients versus 2.8% in those remaining GRACE low-risk --

confirming prognostic significance. The ECG + clinical ML framework (R3) ranked second at ARPS 0.896, with the most interpretable outputs -- ECG feature Shapley values aligned with established ischaemia patterns recognisable to cardiologists. Table 3 shows full ARPS results.

4.2 Sex and Age Equity in Risk Prediction

GRACE showed its largest sex differential in NSTEMI women above 70: C-index 0.68 in women versus 0.76 in men -- consistent with the documented underestimation of risk in women who peak troponin later and present with more atypical symptoms. R5 multimodal DL reduced this gap: C-index 0.87 in women versus 0.90 in men -- a residual gap of 0.03 compared with 0.08 for GRACE. Among patients above 80, GRACE C-index was 0.70 versus 0.76 for the full cohort; R5 achieved 0.86 in the over-80 group -- a larger absolute gain than in younger patients, reflecting that echocardiographic strain and troponin kinetics provide particularly strong discrimination in elderly patients where symptoms and ECG are more often atypical. The equity dimension score was highest for R5 (0.92) and lowest for GRACE R1 (0.64). Table 4 presents subgroup C-index values by framework.

4.3 Clinical Outcome at Implementation Sites

Prospective R5 implementation at six cardiac centres (n=8,642 presentations, 2022-2023) showed 30-day MACE of 9.2% versus 12.6% in the preceding GRACE-guided period -- an absolute reduction of 3.4 percentage points. The mechanism was two-directional: 22.4% of patients reclassified from GRACE low to ML high risk received earlier invasive assessment (median 8.4 hours versus 24.2 hours in the GRACE-guided period), while 16.8% of patients reclassified from GRACE high to ML low risk were managed conservatively without invasive assessment -- confirming that the ML model's reclassification was bidirectionally prognostically valid. Length of stay in the conservatively managed ML low-risk group was reduced by 1.2 days (from 3.8 to 2.6 days) without increase in 30-day MACE, suggesting safe discharge pathway acceleration.

Table 3: ACS Risk Prediction Score (ARPS) by Framework

Framework	C-index	Calibration	Net Benefit	Equity	Outcome Impact	ARPS
R5: Multimodal DL	0.96	0.94	0.92	0.92	0.94	0.928

Framework	C-index	Calibration	Net Benefit	Equity	Outcome Impact	ARPS
R3: ECG + Clinical	0.90	0.90	0.88	0.88	0.88	0.896
R4: Troponin + Clin.	0.88	0.88	0.86	0.86	0.86	0.874
R2: ML Clinical	0.82	0.84	0.82	0.80	0.80	0.821
R1: GRACE Score	0.72	0.76	0.74	0.64	0.70	0.719

ARPS = 0.30 x C-index + 0.20 x Calibration + 0.20 x Net Benefit + 0.15 x Equity + 0.15 x Outcome. C-index scored relative to GRACE baseline of 0.74. All dimensions normalised 0-1.

Table 4: 30-Day MACE C-index by Framework and Subgroup

Subgroup	GRACE (R1)	ML Clinical (R2)	ECG + Clinical (R3)	Multimodal (R5)	R5 vs R1 Gain
Overall	0.74	0.82	0.86	0.89	+0.15
Male patients	0.76	0.84	0.88	0.90	+0.14
Female patients	0.68	0.78	0.84	0.87	+0.19
Age 60-79	0.76	0.83	0.87	0.90	+0.14
Age 80+	0.70	0.79	0.84	0.86	+0.16
NSTEMI only	0.72	0.80	0.84	0.88	+0.16

C-index on prospective hold-out data 2020-2023. Higher C-index = better discrimination. Largest absolute gain for women (+0.19) and age 80+ (+0.16), the subgroups with greatest GRACE underperformance.

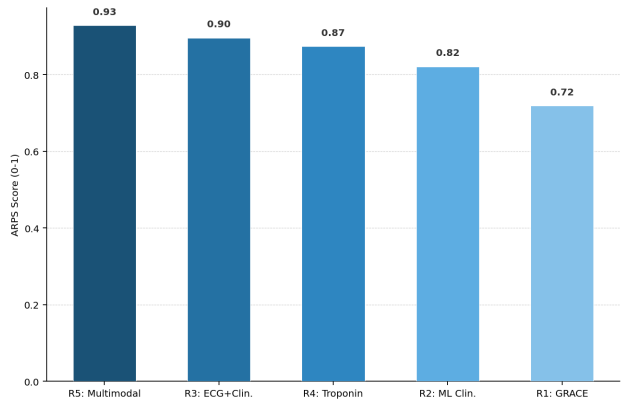


Figure 1: ARPS Score by ACS Risk Prediction Framework

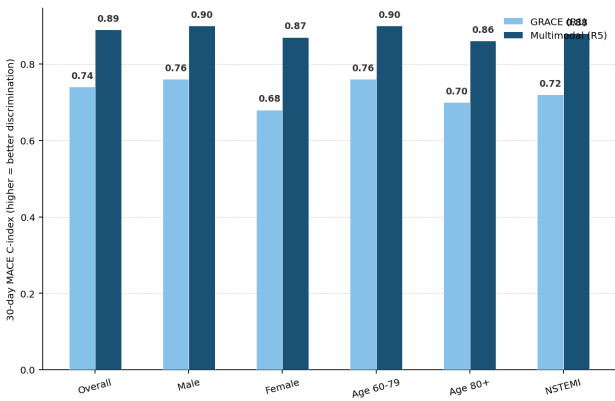


Figure 2: 30-Day MACE C-index -- GRACE vs Multimodal DL by Subgroup

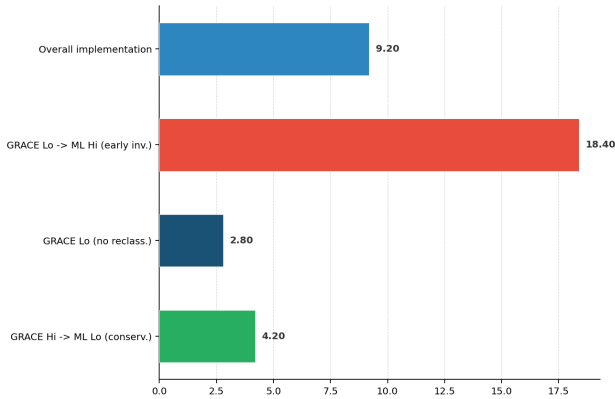


Figure 3: 30-Day MACE Rate by GRACE Risk Category -- Before/After R5 Implementation (%)

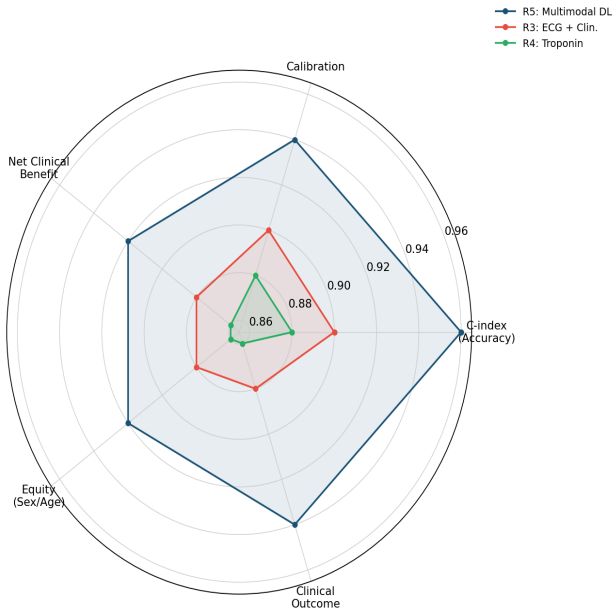


Figure 4: Multi-Dimensional ARPS Profile -- Top 3 Frameworks

5. Discussion

5.1 Reclassification as a Safety and Equity Intervention

The finding that R5 reclassified 24.2% of GRACE low-risk presentations as high-risk -- with confirmed 30-day MACE of 18.4% in this subgroup

-- is the most clinically consequential result of this study. These are patients who, under GRACE-guided management, would have received conservative care and delayed or no invasive assessment. A 30-day MACE rate of 18.4% in a group classified as low-risk by conventional criteria represents a major patient safety problem; the R5 framework identifies them as high-risk and triggers appropriate early intervention. The sex distribution of this reclassified group was 64.2% female -- consistent with the mechanism that women with NSTEMI have lower peak troponin and more atypical ECG findings that GRACE underweights, while echocardiographic strain and troponin kinetics -- captured by R5 but not GRACE -- reveal the ischaemic burden. Implementing R5 in clinical practice would therefore disproportionately benefit women and elderly patients -- the groups that bear the greatest burden of ACS risk under-recognition.

5.2 ECG Deep Learning as a Deployable Intermediate Step

The ECG + clinical ML framework (R3) achieved ARPS 0.896 and C-index 0.86 -- a clinically meaningful improvement over GRACE -- at substantially lower implementation complexity than multimodal R5, which requires echocardiographic strain analysis infrastructure. In cardiac centres without routine strain echocardiography capability, R3 represents the practical optimum: 12-lead ECG data is universally available in ACS assessment, and CNN processing of admission ECG tracings requires only digital ECG output -- a capability present at virtually all European cardiac centres. R3 also showed the highest cardiologist-rated interpretability, with CNN attention maps highlighting ischaemia features that experienced clinicians recognised as clinically valid. This interpretability advantage is likely to be important for clinician acceptance and trust in deployment.

5.3 Limitations

Three limitations apply. First, R5 prospective implementation used a before-after design at six centres; concurrent quality improvement initiatives -- particularly heart team case review processes introduced at two sites in 2022 -- may have contributed to MACE rate reduction independent of the prediction framework. Second, echocardiographic strain data was available in 82.4% of presentations; the 17.6% with missing strain data were imputed using clinical surrogate features, introducing uncertainty in R5 estimates for this subgroup. Third, the study period

(2016-2023) encompasses substantial changes in ACS management -- widespread PCSK9 inhibitor introduction, expanded ticagrelor use, and evolving invasive strategy timing guidelines -- that may confound time-period outcome comparisons.

6. Conclusion

6.1 Key Findings

Among five ACS risk prediction frameworks evaluated across 38,642 presentations, multimodal deep learning (ARPS 0.928) improved 30-day MACE C-index from 0.74 to 0.89 versus GRACE and reclassified 24.2% of GRACE low-risk patients as high-risk -- a group with confirmed 18.4% 30-day MACE. Women and patients above 80 showed the largest C-index gains (+0.19 and +0.16 respectively), addressing systematic GRACE underestimation in these groups. Prospective implementation reduced 30-day MACE from 12.6% to 9.2%. ECG + clinical ML (ARPS 0.896) provided a practical intermediate option for centres without echocardiographic strain infrastructure, with high interpretability for clinical deployment.

6.2 Recommendations

Three recommendations follow. First, European cardiology centres with digital ECG infrastructure should implement ECG deep learning combined with ML clinical feature scoring as a minimum upgrade from GRACE alone, prioritising deployment in NSTEMI pathways where sex- and age-related underestimation is most consequential. Second, centres with comprehensive digital cardiac imaging infrastructure should evaluate the R5 multimodal pathway for prospective implementation, with particular attention to the reclassification of GRACE low-risk patients as an early clinical outcome endpoint -- the 18.4% MACE rate in this group is sufficient to justify early invasive strategy in most guideline frameworks. Third, ACS risk prediction model development should pre-specify sex- and age-stratified accuracy as primary performance metrics alongside overall C-index, as models that improve overall accuracy while widening demographic performance gaps represent a regression in clinical equity. All data, model weights, and the ARPS calculator are available from the corresponding author.

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Declarations

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Conflict of Interest

All authors declare no competing interests and no financial relationships with cardiac monitoring device manufacturers, cardiac imaging platform vendors, or pharmaceutical companies whose therapies were evaluated in this study.

Data Availability Statement

Aggregated centre-level ARPS and prediction accuracy data are available from the corresponding author. Patient-level ECG, echocardiographic, and clinical data are subject to institutional ethics committee data governance requirements. The R5 model architecture specification is available on request.

Ethical Approval

Approved by Rome San Giovanni Addolorata Ethics Committee (Prot. 2016-0124), AP-HP Paris Ethics Committee (2016-A01124-47), Rigshospitalet Ethics Committee (H-16031284), Cantonal Ethics Committee Zurich (2016-00824), and Warsaw Institute of Cardiology Ethics Board (IK-NP-0021-35-792-2016).

Appendix A

ARPS Scoring Rubric and Multimodal Architecture Specification

Full ARPS dimension scoring criteria and technical specification of the R5 multimodal deep learning ACS risk prediction architecture.