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**LEFT VENTRICULAR EJECTION FRACTION
ADDS VALUE OVER THE GRACE SCORE IN
PREDICTION OF 6-MONTH MORTALITY
AFTER ACS: THE MADDEC STUDY**

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Taustaa

Nykypäivän kansainvälisten hoitolinjojen mukaan GRACE (Global Registry of Acute Coronary Events) -pisteytys on suositeltu riskipisteytysjärjestelmä akuutin sepelvaltimotautikohtauksen (acute coronary syndrome, ACS) sairastaneiden potilaiden kuoleman riskin arvioinnissa. Alentunut vasemman kammion ejektiofraktio (left ventricular ejection fraction, LVEF) on tunnettu kuolleisuuden riskitekijä akuutin sepelvaltimotautikohtauksen jälkeen. Kuitenkaan LVEF ei sisälly GRACE-pisteytyksen laskemisessa käytettäviin parametreihin, eikä sen mahdollisesta prognostisesta hyödystä GRACE-pisteytykseen lisättynä tiedetä paljoa. Tämän tutkimuksen tarkoituksena on GRACE-pisteytyksen validointi Tays Sydänsairaalan potilasaineistossa sekä arvioida, onko ejektiofraktion lisäämisellä GRACE-pisteytykseen ennusteellista hyötyä arvioidessa kuuden kuukauden kuolemanriskiä.

Aineisto ja menetelmät

Aineistona on Tays Sydänsairaalan potilaat, joille tehtiin sepelvaltimoiden varjoainekuvaus ensimmäisen akuutin sepelvaltimotautikohtauksen yhteydessä aikavälillä 2015-2016. Retrospektiiviseen analyysiin valikoitui poissulkukriteerien jälkeen yhteensä 1576 potilasta. Coxin regressioanalyysin avulla arvioitiin ejektiofraktion ja GRACE-pisteytyksen yhteyksiä kuuden kuukauden kuolleisuuteen. Ejektiofraktion ennusteellista lisähyötyä arvioitiin C-statistiikan ja IDI-arvon (index of discrimination improvement) avulla.

Tulokset

LVEF ja GRACE-pisteytys olivat molemmat itsenäisesti yhteydessä kuuden kuukauden kuolleisuuteen ja yhdistettynä muuttajat samaan malliin, tulokset olivat merkittäviä (GRACE-pisteytys HR: 1.036, 95% CI 1.030-1.042; LVEF: HR: 0.965, 95% CI 0.948-0.982). GRACE-pisteytyksen kuolleisuuden arviointikyky oli hyvä (C-statistiikka: 0.833, 95% CI 0.795-0.871). LVEF:n lisääminen malliin GRACE-pisteytyksen lisäksi paransi mallin suorituskykyä merkittävästi (C-statistiikka: 0.848, 95% CI 0.813-0.883, parannuksen $p=0.029$ ja IDI 0.0171, 95% CI 0.0016-0.0327, $p=0.031$).

Yhteenveto

Vasemman kammion ejektiofraktion lisääminen malliin GRACE-pisteytyksen lisäksi paransi merkittävästi kuuden kuukauden kuolemanriskin ennustamiskykyä akuutin sepelvaltimotautikohtauksen jälkeen.

Avainsanat: akuutti sepelvaltimotautikohtaus, kuolleisuus, vasemman kammion ejektiofraktio

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Left ventricular ejection fraction adds value over the GRACE score in prediction of 6-month mortality after ACS: the MADDEC study

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ABSTRACT

Background

Reduced left ventricular ejection fraction (LVEF) is a risk marker for mortality after an acute coronary syndrome (ACS). Global Registry of Acute Coronary Events (GRACE) risk score, developed almost two decades ago, is the preferred scoring system for risk stratification in ACS. The aim of this study was to validate the GRACE score and evaluate whether LVEF has incremental predictive value over the GRACE in predicting 6-month mortality after ACS in a contemporary setting.

Methods

A retrospective analysis of all 1576 consecutive patients who were admitted to Tays Heart Hospital and underwent coronary angiography for a first episode of ACS (2015–2016). Clinical risk factors were extensively recorded. Adjusted Cox regression analysis was used to analyse the associations between LVEF and the GRACE score with 6-month all-cause mortality. The incremental predictive value was assessed by the change in C-statistic by Delong's method for paired samples and by index of discrimination improvement (IDI).

Results

In univariable analysis, both LVEF and the GRACE were associated with 6-month mortality, and after applying both variables into the same model, the results remained significant (GRACE score: HR: 1.036, 95% CI 1.030 to 1.042; LVEF: HR: 0.965, 95% CI 0.948 to 0.982, both HRs corresponding to a one unit change in the exposure variable). The GRACE score demonstrated good discrimination for mortality (C-statistic: 0.833, 95% CI 0.795 to 0.871). Adding LVEF to the model with the GRACE score improved model performance significantly (C-statistic: 0.848, 95% CI 0.813 to 0.883, $p=0.029$ for the improvement and IDI 0.0171, 95% CI 0.0016 to 0.0327, $p=0.031$).

Conclusions

Adding LVEF to the GRACE score significantly improves risk prediction of 6-month mortality after ACS.

INTRODUCTION

Acute coronary syndrome (ACS) represents one of the leading causes of death in the western countries.¹ ACS refers to a spectrum of clinical conditions ranging from ST-segment elevation myocardial infarction (STEMI) to non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina.² Numerous risk assessment instruments have been developed to quantify the risk of mortality among patients with ACS.^{3,4} Currently, the Global Registry of Acute Coronary Events (GRACE) clinical risk score is the most frequently used and recommended.⁴⁻⁷ According to previous studies, reduced left ventricular ejection fraction (LVEF) is associated with an increased risk of death in ACS.⁸⁻¹⁰ LVEF was not included in the development of the GRACE score and very little is known about possible improvement of prognostic evaluation in patients with ACS by adding LVEF to the GRACE score. Based on one retrospective registry of patients treated between 2004 and 2005, LVEF seems to have uncertain or little additional value over the GRACE score. However, the same study also demonstrated that among patients treated by percutaneous coronary intervention (PCI), the predictive value of GRACE was significantly diminished when compared with patients treated conservatively.¹¹ During the past few years, advances have been made in the treatment strategies and management of patients with acute myocardial infarction (MI).¹² For instance, the rates of different revascularisation modalities, such as coronary artery bypass grafting (CABG) and PCI, have increased; this is also the case for primary PCI in the management of STEMI. Similarly, LVEF-guided implantation of intracardiac defibrillators (ICD) has been introduced in the routine clinical work after the development of the GRACE score.¹³ Furthermore, the use of ultrasound in the assessment of LVEF has become main-stream in clinical work globally after the development of GRACE. Ultrasound is also used when assessing the need for LVEF-guided implantation of ICDs, a therapy aimed to reduce mortality in the long term. The objectives of this study were to evaluate the predictive value of the GRACE score with respect to 6-month mortality and to explore changes in the prognostic performance of the GRACE score when adding LVEF data in a contemporary setting among consecutive patients treated for ACS in a tertiary referral hospital (years 2015 and 2016). This cohort comprises patients treated according to the most recent guidelines with almost exclusive use of primary PCI for treatment of ST-elevation infarction, predominant use of radial access for angiography, use of newer generation drug-eluting stents, use of ticagrelor as a first-line adenosine diphosphate (ADP) blocker along with all other available emerged medical therapies recommended to reduce cardiovascular mortality after ACS.^{5,6} Due to many advances that have transformed the treatment of ACS during the last decade, it is important to determine whether the risk stratification should be updated.

METHODS

Study cohort

Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease (MADDEC) is an ongoing, retrospective registry study that integrates data from several electronic sources from patients treated in a single tertiary care centre, Tays Heart Hospital, which is the sole provider of specialised cardiac care for a population of approximately 0.5 million inhabitants (hospital district of Pirkanmaa, Finland).¹⁴ In this study, we investigated patients, who underwent coronary angiography for a first episode of ACS during a 2-year period (from January 1, 2015 to December 31, 2016). During this time period, altogether 1795 patients

underwent coronary angiography for suspected ACS. Patients who experienced a type 2 MI, or who were diagnosed with some other condition than ACS, were excluded from the study population (n=219). Accordingly, 1576 patients were included in the final analysis. Subjects (n=163) who were treated for ACS (unstable angina pectoris (UAP) or type I MI) but did not undergo invasive evaluation due to poor medical overall prognosis, refusal or for other medical reasons were not included in the study. These subjects were on average almost 10 years older (78 (11) vs 69 (12), $p<0.0001$) and had higher prevalence of dementia (10.5% vs 2.3%, $p<0.001$), active malignancy (6.8% vs 3.4%, $p=0.028$) and history of cerebrovascular accident (15.4% vs 8.3%, $p=0.002$). There was no significant difference in sex distribution between those undergoing invasive evaluation and those who did not ($p=0.224$). Due to the nature of this retrospective registry study, formal ethical approval was not required. However, the present study was approved by the local authority over-seeing the use of registry data as required by Finnish legislature. This study was conducted according to the ethical principles of the Declaration of Helsinki on the use of human data.

Data sources

Clinical cardiovascular phenotype data were collected from the KARDIO registry, which includes detailed information of patients undergoing invasive operations and treated in the coronary care unit and/or at the cardiac wards. The study data were collected and added into the KARDIO registry by the treating physicians during hospitalisation. Additional information, such as patient characteristics, laboratory values and length of hospital stay, were extracted from the hospital electronic health records. Data of prescribed medications at the time of discharge, transfer to secondary healthcare provider or before death were verified by checking all written patient records individually. The data of the main outcome—6-month mortality—was received from Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad.^{15 16} In this study, the coverage of follow-up for mortality was 100% (i.e., no loss to follow-up). All data collected was integrated into one structured query language database hosted in the PostgreSQL version 9.5.

Main outcome and main exposure variables

The main outcome in the present study was 6-month all-cause mortality, and the main exposure variables were the GRACE score and LVEF. The GRACE score was calculated for patients based on eight parameters: ST-segment deviation, age, heart rate, systolic blood pressure, creatinine value, Killip class, cardiac arrest at admission and elevated cardiac enzymes (troponin T -levels exceeding the 99th upper limit of the population (50 ng/L) on admission or within 24 hours of admission). For 35 patients (2.2%), the calculation was performed after imputation of missing values of individual components of the GRACE score using multiple imputation by chained equations (mice package for R). The echocardiographic LVEF was measured for 1556 patients (98.7%) during hospitalisation. Images were obtained from parasternal and apical views by treating physicians as a part of routine clinical evaluation. LVEF was usually measured from multiple views combining information from all areas of the left ventricle and the mean value of all measurements was combined to form a global estimate of LVEF. After the ultrasound, physicians recorded the measurement to the KARDIO registry. If the measurement was not recorded online, the results of the

ultrasound were later retrieved from written records and updated to the registry. Imputation was used to estimate the missing 20 values (1.3%).

Statistical analysis

Cox regression analysis was used to examine the association between the GRACE score and LVEF with prediction of 6-month mortality. The risk associated with the GRACE score and LVEF is reported as the hazard ratio (HR) related to a one-unit increase in the exposure variables. Testing of the proportional hazards assumption was based on the correlation of survival rankings with Schoenfeld residuals. All variables fulfilled this assumption. Successful model calibration for all models was verified with the Hosmer-Lemeshow test. The predictive value of different models was estimated by calculating C-statistic from the receiving operating characteristics (ROC) curves using predicted risk values for 6-month mortality. The incremental predictive value of adding LVEF to the GRACE score prediction was assessed by the significance of the change in C-statistic by the DeLong's method for paired samples (for same subjects of the same study population). The incremental predictive value was also assessed by the integrated discrimination improvement (IDI) depicting the average change in predicted risk between individuals with and without the outcome after including LVEF into the risk prediction and with continuous net reclassification index (NRI). A p value of 0.05 or below was considered statistically significant. All analyses were performed using IBM SPSS Statistics (V.21.0) and R-software (packages mice, miceadds, PredictABEL and pROC).

RESULTS

Baseline demographics and mortality during follow-up

A total of 1576 patients were treated for a first ACS, of these 554 (35.2%) had STEMI, 811 (51.5%) NSTEMI, while 211 (13.4%) had a final diagnosis of UAP. Demographic characteristics of the participants are shown in table 1. The majority of the patients were male (69.1%), and the mean age of the study sample was 69.3 years (SD 11.9 years). The majority of the patients underwent PCI (77.5%, n=1221), while the rates of patients treated by CABG (8.1%, n=127) or medical therapy only (14.5%, n=228) were substantially lower. Altogether, 106 (6.7%) patients died within 6-month follow-up time after ACS. A considerable proportion of deaths (n=42, 39.6%) occurred among patients with reduced LVEF (<40%). Details about the use of antithrombotic medications and invasive treatments are presented in the online supplement. Planned pharmacological therapies at discharge or at transfer are presented in online supplementary table 1.

Table 1. Baseline Characteristics of ACS patients evaluated and treated invasively in Tays Heart Hospital in 2015 and 2016.

	All (n=1576)	Dead (n=106)	Survivors (n=1470)	P-value*
Demographics				
Age (years)	69.26 ± 11.85	76.67 ± 10.17	68.73 ± 11.79	<.001
Men (%)	1089 (69.1%)	58 (54.7%)	1031 (70.1%)	<.001
Hypertension (%)	963 (61.1%)	68 (64.2%)	895 (60.9%)	0.048
Dyslipidemia (%)	935 (59.3%)	61 (57.5%)	874 (59.5%)	0.013
Diabetes (%)	389 (24.7%)	43 (40.6%)	346 (23.5%)	<.001
Previous MI (%)	309 (19.6%)	35 (33.0%)	274 (18.6%)	<.001
Peripheral artery disease (%)	119 (7.6%)	20 (18.9%)	99 (6.7%)	<.001

Previous PCI (%)	320 (17.8%)	21 (19.8%)	261 (17.8%)	0.594
Previous CABG (%)	165 (6.5%)	16 (15.1%)	122 (8.3%)	0.017
On admission data				
Type of ACS				<.001
UAP (%)	211 (13.4%)	4 (3.8%)	207 (14.1%)	
NSTEMI (%)	811 (51.5%)	49 (46.2%)	762 (51.8%)	
STEMI (%)	554 (35.2%)	53 (50.0%)	501 (34.1%)	
Killip class (%)				<.001
I	1267 (80.4%)	45 (42.5%)	1222 (83.1%)	
II	190 (12.1%)	21 (19.8%)	169 (11.5%)	
III	93 (5.9%)	22 (20.8%)	71 (4.8%)	
IV	26 (1.6%)	18 (17.0%)	8 (0.5%)	
Heart rate (beats per min)	79.11 ± 20.53	86.02 ± 22.71	78.63 ± 20.29	<.001
Systolic blood pressure (mmHg)	144.11 ± 29.04	128.27 ± 31.84	145.22 ± 28.51	<.001
Serum creatinine level (µmol/l)	90.91 ± 58.67	120.40 ± 71.37	88.79 ± 57.08	<.001
Cardiac arrest at admission	89 (5.6%)	21 (19.8%)	68 (4.6%)	<.001
TnT elevated (> 50ng/l)**	1335 (84.7%)	103 (97.2%)	1232 (83.8%)	<.001
ST-segment shift***	1036 (65.7%)	90 (84.9%)	946 (64.4%)	<.001
GRACE score	119.92 ± 33.67	163.36 ± 35.69	116.79 ± 31.29	<.001
Ejection fraction	50.61 ± 11.004	41.21 ± 11.92	51.29 ± 10.62	<.001

Categorical variables are expressed in frequency and percentage and continuous variables are presented as mean ± standard deviation.

*For comparison between patients who were dead at six months and survivors

**Exceeding the 99th percentile for general population

***Significant ST-elevation or ST-segment depression in two consecutive leads

Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, Acute Coronary Syndrome; UAP, Unstable Angina Pectoris; NSTEMI, Non-ST-elevation Myocardial Infarction; STEMI, ST-elevation Myocardial Infarction.

Prediction of 6-month mortality

Cox-regression analyses revealed that both the GRACE score and LVEF were independently associated with 6-month mortality. In univariate analysis, the GRACE score associated with the risk for mortality with a HR of 1.040 (95% CIs 1.034 to 1.046, $p < 0.0001$) corresponding to a one-unit change in the GRACE score. As expected, LVEF was inversely associated with mortality with a 1% (unit) change in LVEF corresponding to a HR of 0.927 (95% CIs 0.911 to 0.942, $p < 0.0001$). The unadjusted overall mortality rate across different clinical categories of LVEF (reduced: <40%, mildly reduced: 40%–49% and normal: ≥50%) are presented in table 2.

Table 2. The unadjusted over-all mortality rate and status upon admission across different clinical categories of left ventricular ejection fraction (LVEF) (reduced <40%, mildly reduced 40–49% and normal ≥50%)

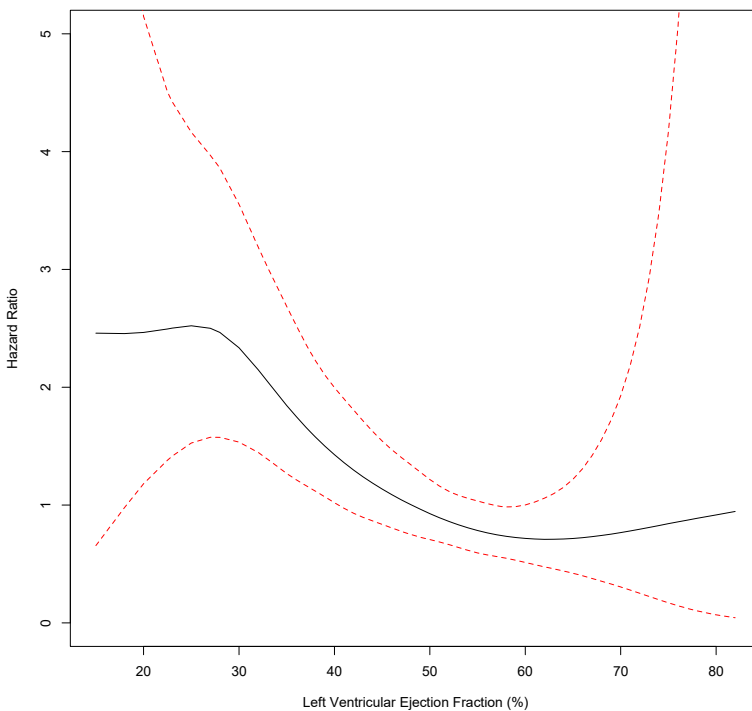
	LVEF < 40% (n=210)	LVEF 40-49% (n=357)	LVEF ≥ 50% (n=1009)	P-value
Dead at six-months, n	42 (20.0%)	31 (8.7%)	33 (3.3%)	<.001
Age	71.50 ± 12.06	70.23 ± 11.95	68.45 ± 11.70	<.001
Men, n	147 (70.0%)	250 (70.0%)	692 (68.6%)	0.839
GRACE-score	144.11 ± 34.12	128.55 ± 30.88	111.83 ± 31.30	<.001
Type of ACS				<.001
UAP	6 (2.9%)	29 (8.1%)	176 (17.4%)	
NSTEMI	99 (47.1%)	156 (43.7%)	556 (55.1%)	

STEMI	105 (50.5%)	172 (48.2%)	277 (27.5%)	
Killip class				<.001
I	92 (43.8%)	261 (73.1%)	914 (90.6%)	
II	62 (29.5%)	61 (17.1%)	67 (6.6%)	
III	41 (19.5%)	30 (8.4%)	22 (2.2%)	
IV	15 (7.1%)	5 (1.4%)	6 (0.6%)	

Abbreviations: LVEF, left ventricular ejection fraction; ACS, Acute Coronary Syndrome; UAP, Unstable Angina Pectoris; NSTEMI, Non-ST-elevation Myocardial Infarction; STEMI, ST-elevation Myocardial Infarction.

After applying both variables into the same model, the results remained significant: the GRACE score HR was 1.036 (95% CIs 1.030 to 1.042, $p < 0.0001$) and the LVEF HR 0.965 (95% CIs 0.948 to 0.982, $p < 0.0001$). The changes of mortality risk related to LVEF across the continuum of LVEF values after adjusting for the GRACE score is depicted in figure 1.

Figure 1 The association between left ventricular ejection fraction and six-month mortality after adjusting for patients' baseline risk as evaluated by GRACE score depicting patients' status upon admission for acute coronary syndrome.



There was no significant interaction between LVEF and the GRACE score ($p = 0.397$ for the interaction), suggesting that the association between LVEF and mortality was dependent on patient's baseline risk as evaluated by the GRACE score. Further adjustments for other comorbidities, such as previously suffered major health issues (history of MI, stroke, gastrointestinal bleed, anaemia, prior PCI or CABG), or prevalent conditions (cancer, valvular heart disease, diabetes or chronic obstructive pulmonary disease), did not change the adjusted association between LVEF and 6-month mortality (HR 0.967 with 95% CIs 0.951 to

0.984, $p=0.0001$). Additional adjustment with planned pharmacological therapies (at discharge, at transfer or before death in hospital, factors presented in online supplementary table 1) or with the type of ACS (UAP, NSTEMI or STEMI) did not result in significant change in the association (0.960 with 95% CIs 0.942 to 0.979, $p<0.0001$). Model discrimination was assessed by the C-statistic. A model with a C-statistic >0.75 is considered to have meaningful discriminatory ability. The GRACE score predicted mortality well with a resulting C-statistic value of 0.833 (95% CIs 0.795 to 0.871). Applying LVEF in the model, the resulting C-statistic was 0.848 (95% CIs 0.813 to 0.883). The difference in C-statistics was significant ($p=0.029$ for DeLong's test evaluating difference in C-statistic for paired samples). Estimates of continuous reclassification value showed a benefit in improving the current model: IDI 0.0171 (95% CIs 0.0016 to 0.0327, $p=0.031$) and NRI of 0.443 (95% CIs 0.252 to 0.635, $p=0.0001$).

DISCUSSION

According to the results of the present study, LVEF is an independent risk factor for mortality regardless of patient status at admission measured by the GRACE score. Adding LVEF to risk prediction with the GRACE score resulted in significant improvement in risk stratification. To the best of our knowledge, there is only one previous study published on the possible incremental predictive value of adding LVEF to risk prediction beyond the GRACE score in patients with ACS.¹¹ The retrospective MASCARA registry study by Abu-Assi et al¹¹ of 3,960 patients treated in 2004–2005 found no incremental benefit of adding LVEF to the GRACE score in predicting 6-month mortality post discharge or in-hospital mortality among patients with MI. The different study results might, at least partly, be explained by the many advances that have transformed the medical and invasive treatment of ACS during the last decade. In the MASCARA registry,¹¹ the revascularisation rate by any method was only 18%, which is in stark contrast with the corresponding figure of 86% in the present study. Furthermore, rather than using LVEF as a continuous variable as in the present study, LVEF was categorised in three risk categories in the MASCARA registry; this could result in diminished statistical power for detecting independent associations and incremental value of adding LVEF to the risk prediction. Supporting our findings, previous studies have shown that LVEF is an independent risk marker for mortality after ACS, even after accounting for other clinical risk factors related to comorbidities and status on admission. This was the case even after including Killip classification for heart failure, ST-segment abnormalities, cardiac enzyme levels and haemodynamic status, which are included in the GRACE score.^{8,9,17,18} Despite the fact that the GRACE score was introduced almost two decades ago, it still represents the best possible validated method for estimating the risk of mortality after ACS,³ and its use is recommended by current guidelines.^{5–7} After the onset of the new era of 'big data', the discovery of novel risk factors, which can add to risk prediction over clinically relevant risk markers, is important.¹⁹ Systematic recording of risk factors, such as LVEF, should be applied universally as the utilisation of registry information used to model patient survival becomes the norm.¹⁹ The limitation of the present study is that the GRACE score information was collected retrospectively and therefore was not available for all subjects. However, data were missing only for approximately 2.6% of the subjects. Retrospective collection can also be less accurate in capturing relevant information when compared with a dedicated online data collection protocol. Despite of these shortcomings, the GRACE score recorded in our study performed very well, with the C-statistic (0.83) very close to the value expected for prediction of 6-month mortality based on meta-analysis of

all previous observational studies (meta-analysed C-statistic of 0.84).³ The foremost strength of the present study is that it includes all consecutive patients diagnosed and treated invasively for ACS during the time of the study. Furthermore, due to the centralised nature of Finnish national registries, there was no loss of mortality data for follow-up. In conclusion, the GRACE score remains a good predictor of all-cause mortality in a contemporary setting. However, LVEF is an independent risk marker for death after ACS despite patient's comorbidities and status as measured by the GRACE score. LVEF can be used to improve risk prediction over the GRACE score.

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DECLARATIONS OF INTERESTS: None

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