New insights in management and prognosis in acute myocardial infarction

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Multiple biomarkers for the prediction of short and long-term mortality after ST-segment elevation myocardial infarction: the Amsterdam Groningen collaboration

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Abstract

Multiple biomarkers improve prognostication for long-term mortality in ST-segment elevation myocardial infarction (STEMI). However, one-third of mortality after STEMI occurs within initial discharge. Our objective was to determine whether multiple biomarkers (glucose, N-terminal pro-brain natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR)) predict both short-term as long-term mortality in STEMI. We used a patient-pooled dataset of consecutive STEMI patients, with complete biomarkers, who underwent primary percutaneous coronary intervention (PCI) in two single centers (Amsterdam and Groningen). With a previously developed multimarker risk score, based on three biomarkers, patients were indicated as low-, intermediate- or high risk. Cumulative 4-year mortality was estimated with the Kaplan–Meier method and compared with a log-rank test. We compared short-term and long-term mortality with a land- mark set at 30 days because previous studies have shown that mortality largely occurs within 30 days. A total of 2,355 STEMI-patients were treated with primary PCI. The mortality rates in the low- (n=1,531), intermediate- (n=403), and high-risk (n = 421) groups were 4.8%, 16.1%, and 43.9%, respectively. The differences were observed at a follow-up up to 30 days (log-rank p<0.001) as well as after 30 days (log-rank p<0.001). A multimarker risk score, based on admission levels of glucose, NT-proBNP, and eGFR identifies STEMI patients at low-, intermediate-, and high-risk for short-term and long-term mortality.

Introduction

Several clinical risk scores have been developed to aid in early risk stratification of patients with ST-elevation myocardial infarction (STEMI).[1,2] These risk scores have been shown to identify patients at high risk for (recurrent) events, and may therefore significantly influence therapeutic decision-making. However, the risk scores are mainly based on readily available clinical symptoms and signs. Recently we have shown that multiple biomarkers sampled at admission significantly improve prognostication regarding mortality on top of established clinical risk factors derived from the thrombolysis in myocardial infarction (TIMI) score; age, body mass index, diabetes, hypertension, systolic blood pressure, heart rate, anterior MI, and time to treatment.[2,3] Furthermore, a simplified integer risk score was developed based on the strongest predicting biomarkers, including glucose, N-terminal pro-brain natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR). With this multimarker risk score, we were able to identify low-, intermediate- and high-risk subgroups of STEMI-patients for long-term mortality. We validated the prognostic value of the biomarkers in a separate cohort.[4] It has previously been described that one-third of long-term mortality after STEMI occurs within initial discharge.[5] To evaluate whether the prognostic value of the bio- marker risk score is mainly driven by short-term mortality, we assessed the prognostic value of the score for 30-day mortality and for 30-day to 4-year mortality in a STEMI patient-pooled dataset from Amsterdam and Groningen, The Netherlands.

Methods

Study design

For the current study, we pooled individual STEMI patient data from the Dutch Academic Medical Center (AMC) Amsterdam and the University Medical Center Groningen (UMCG) PCI registries. Details of the original Amsterdam source and study populations, procedures and data collection have been reported previously.[3] In short, the study concerned consecutive STEMI patients undergoing primary PCI, patients with cardiogenic shock were excluded. Regarding the Groningen data, this concerned a cohort treated with primary PCI in a large single center in Groningen, The Netherlands. We analyzed data of all 1,645 consecutive STEMI patients treated with primary PCI from 2006 to 2010. A STEMI cohort of 1,321 patients was in consensus with the criteria of the original cohort.

Biomarkers and multimarker risk score

Blood samples were obtained before primary PCI as part of routine clinical care. Blood samples were centrifuged without undue delay and analyzed. NT-proBNP was measured

using a Hitachi modular E-170 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Glucose and plasma creatinine were measured with an enzymatic assay on a Hitachi modular P-800 analyzer (Roche Diagnostics GmbH). The sample analyses were performed locally using the same analyzers. The eGFR was calculated according to the Cockcroft and Gault formula.[6] The multimarker risk score is calculated as follows: a glucose <8 mmol/l, NT-proBNP <150 ng/l, and eGFR <60 ml/min are assigned 0 points, a glucose 8–9 mmol/l, NT-proBNP 150–599 ng/l, and eGFR 60–90 ml/min are assigned two points, a glucose >10 mmol/l, and NT-proBNP >600 ng/l are assigned three points, and an eGFR >60 ml/min is assigned four points. The multimarker low-risk group is defined as a score <4, the intermediate-risk group as score 5 or 6, and the high-risk group as score >6.

Outcome

The main outcome of the current study was all-cause mortality. Data on mortality was collected using the Dutch national population registry, which has completeness of vital status of all residents registered in The Netherlands.

Statistical analysis

Normally distributed continuous variables are presented as mean with standard deviation (SD). Skewed distributed continuous variables are presented as median with inter- quartile range (IQR). Trends in continuous variables were assessed in linear regression. Categorical variables are presented as number and percentage and were compared using the χ^2testfor trend. Cumulative mortality was estimated with the Kaplan–Meier method and compared with the log-rank test. Patients were censored at 4 years or the last known date of follow-up, whichever came first. We compared short-term and long-term mortality across the multimarker risk categories with a landmark set at 30 days. Long-term mortality was from 30 days up to the end of follow-up. The discriminative value of the risk score was assessed with C-statistics that were calculated with logistic regression models. Furthermore, the prognostic value of the biomarker risk score for short-term and long-term mortality was assessed in. Two sets of Cox proportional-hazards analyses: univariable analyses of single biomarkers and multivariable analysis including the biomarker risk score and established prognostic factors for mortality from the TIMI risk score. These included age, body weight (body mass index), history of diabetes or hypertension, systolic blood pressure and heart rate, anterior myocardial infarction (MI), and time to treatment (symptom onset to first balloon inflation).[2]

Results

Patients

A total of 2,355 STEMI patients were treated with primary PCI in the AMC (n = 1,034) and UMCG (n = 1,321). The baseline characteristics of the study patients are presented in Table 1. In short, the mean age was 63 years, 13.1% were diabetics and 42.5% presented with an anterior MI. Of the patients, 1,531 were indicated as low-risk, 403 as intermediate-risk, and 421 as high-risk based on our multimarker risk score. With increasing risk as assessed by the risk score, patients were older, more often female, and had a lower body mass index. Regarding risk factors, hypertension, diabetes mellitus and history of MI were observed

Table 1 | Baseline patient characteristics

Characteristics	Total population (n=2355)	Low-risk group (n=1531)	Intermediate-risk group (n=403)	High-risk group (n=421)	p-value*
Demographics					
Age, year	63 (13)	57 (11)	69 (11)	77 (9)	<0.001
Male gender	1707 (72.5%)	1124 (79.9%)	270 (67.0%)	213 (50.6%)	<0.001
Body mass index, kg/m2	26.8 (4.3)	27.2 (4.4)	26.8 (4.2)	25.5 (3.6)	<0.001
Risk factors and history					
Current smoking	1081 (46.3%)	830 (54.4%)	144 (36.2%)	107 (25.9%)	<0.001
Hypertension	848 (36.5%)	461 (30.4%)	173 (43.9%)	214 (51.6%)	<0.001
Hypercholesterolemia	583 (26.7%)	394 (27.7%)	98 (26.7%)	91 (23.4%)	0.10
Diabetes mellitus	291 (12.4%)	109 (7.1%)	78 (19.4%)	104 (27.4%)	<0.001
Myocardial infarction	272 (11.6%)	143 (9.4%)	46 (11.5%)	83 (19.8%)	<0.001
Laboratory assessments					
Glucose, mmol/l	8.2 (7.0-10.0)	7.6 (6.7-8.9)	9.5 (7.8-11.1)	10.1 (8.4-12.3)	<0.001
NT-proBNP, ng/l	149 (59-540)	88 (50-178)	383 (162-1114)	990 (377-3155)	<0.001
eGFR, ml/min	103 (40)	119 (35)	90 (34)	56 (18)	<0.001
Time to treatment, min	186 (130-283)	177 (126-258)	200 (132-310)	177 (126-259)	<0.001
Other risk identifiers					
Anterior myocardial infarction	1000 (42.5%)	608 (39.7%)	201 (49.9%)	191 (45.4%)	<0.01
Systolic blood pressure	131 (27)	130 (25)	133 (28)	133 (30)	0.01
Heart rate	78 (18)	77 (17)	80 (19)	80 (20)	<0.001

Data are presented as absolute numbers (%), mean ± SD, or median (interquartile range).
eGFR: estimated glomerular filtration rate, NT-proBNP: N-terminal pro-brain natriuretic peptide.
*for comparison of three risk groups.

more frequently with higher risk categories, while current smoking, hypercholesterolemia were observed less frequently.

Table 2 | Unadjusted and adjusted Cox proportional-hazards models for mortality

Multimarker risk score group	Unadjusted models		p-value	Adjusted models*		p-value
	Hazard ratio	95% confidence interval		Hazard ratio	95% confidence interval	
Short-term mortality						
Low risk	Reference		-	Reference		-
Intermediate risk	4.43	(2.11-9.32)	<0.001	3.22	(1.19-8.75)	0.02
High risk	18.00	(9.88-32.78)	<0.001	11.63	(4.46-30.32)	<0.001
Long-term mortality						
Low risk	Reference		-	Reference		-
Intermediate risk	3.58	(2.23-5.74)	<0.001	1.70	(0.96-3.00)	0.07
High risk	8.20	(5.48-12.26)	<0.001	2.33	(1.31-4.14)	<0.01

*Adjusted for age, BMI, history of diabetes or hypertension, systolic blood pressure and pulse, anterior myocardial infarction, and time to treatment.

Short-term and long-term mortality

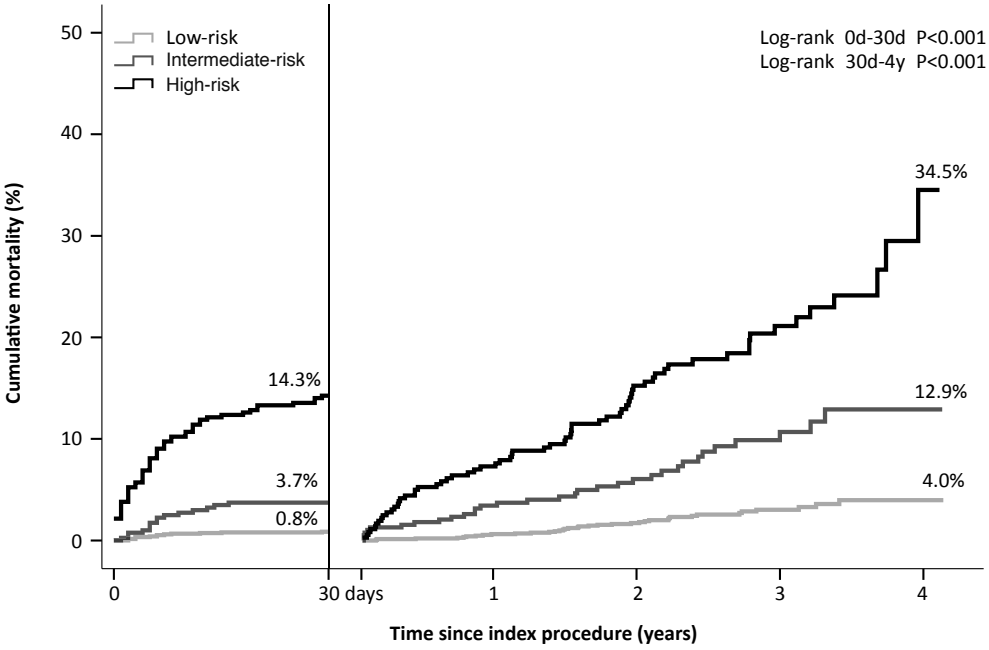
Follow-up was complete in 100% of the patients, with a median duration of 889 days (IQR 614–1,133). The estimated cumulative mortality at 4-year follow-up in the total cohort was 14.6%. The mortality rates (from PCI up to the end of follow-up) in the low-, intermediate- and high-risk groups were 4.8%, 16.1%, and 43.9%, respectively. The differences were observed at a follow-up up to 30 days (log- rank p<0.001) as well as after 30 days (log-rank p<0.001) (Figure 1). As shown in Table 2, the prognostic value of our multimarker risk score was independent of established predictors of mortality for both time intervals.

We assessed the discriminative value of the score as a continuous variable in logistic regression. The C-statistic for 4-year mortality was 0.80. The C-statistics for 30-day follow-up was 0.84, and 0.78 for 30-days up to the end of follow-up.

Discussion

This study describes the short-term and long-term mortality in a STEMI patient population undergoing primary PCI. Using a simple risk score based on admission levels of glucose, NT-proBNP, and eGFR we identified low-, intermediate-, and high-risk patients for short-term and long-term mortality.

Figure 1 | 30-day landmark Kaplan-Meier mortality per risk subgroup using the multimarker risk score. P-value by the log-rank test



No. at risk						
Low	1531	1517	1394	1070	470	34
Int	403	388	341	247	81	11
High	421	361	306	217	74	8

Multimarker risk score

The benefit of this multimarker risk score is its simplicity, providing fast and important prognostic information. Several risk scores have been developed for STEMI patients, however most risk scores require many variables,[1,2] making them more difficult to use in clinical practice. Our multimarker risk score is based on glucose, NT-proBNP, and eGFR using different weighting factors and can be calculated after analysis of the biomarkers obtained at admission. Using only three biomarkers that are frequently available makes it easy to apply this multimarker risk score in clinical practice. Rapid use of the risk score can be improved by implementing biomarker kits on the coronary care unit or catheterization laboratory.

A multimarker risk score was applied to the combined AMC and UMCG cohort and resulted in the identification of patients at high risk for short- and long-term mortality. Although the incidence of patients with high-risk was relatively low with 19% of patients in the combined cohort, the mortality at long-term follow-up in this subgroup was as high

as 43.9%. No information was available on cause of death or other cardiac adverse events. Still, this high-risk subgroup may benefit from additional treatment strategies. Therefore, early prognostication might improve the out- come in this high-risk subgroup. Another important observation is the high proportion of low-risk patients with 65% of patients in the combined cohort, with indeed a low mortality of 5%. Although not evaluated in this study, reduced hospital stay might be considered for these low- risk patients, which will decrease the overall healthcare costs of STEMI-patients. We have previously described that the multimarker risk score is associated with angiographic, electrocardiographic and cardiac magnetic resonance mechanistic markers of outcomes.[7] These data support the ability of the multimarker risk score to identify patients at high-risk of sub-optimal reperfusion and cardiac magnetic resonance outcomes, providing possible targets for future therapeutic research.

The landmark analysis showed that the risk score had prognostic value regarding short- and long-term mortality with high C-statistics. This prognostic value at short- and as well at long-term follow-up might be explained by different pathophysiological mechanisms represented by serum glucose (accelerated atherosclerosis), NT-proBNP (hemodynamic stress), and eGFR levels (vascular damage) contributing to both acute and chronic morbidity.[8] For example, we hypothesize that in the acute phase NT-proBNP and glucose identify patients with larger myocardial infarctions, while at long-term follow-up patients with possible diabetes mellitus or impaired left ventricular function are identified. Estimated GFR identifies patients with a high prevalence of co-morbidities, potentially explaining both short- and long-term mortality.

Limitations

The main limitation of the current analysis is that data on the cause of death was not available. We therefore reported all-cause mortality. Second, we did not have a repeated measure of the biomarkers at 30-days. Third, 4-year follow-up was not completely available for all patients.

Conclusion

A multimarker risk score, based on admission levels of glucose, NT-proBNP, and eGFR identifies low-, intermediate-, and high-risk STEMI patients for short-term and long-term mortality.

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