Improving risk stratification after acute myocardial infarction : focus on emerging applications of echocardiography

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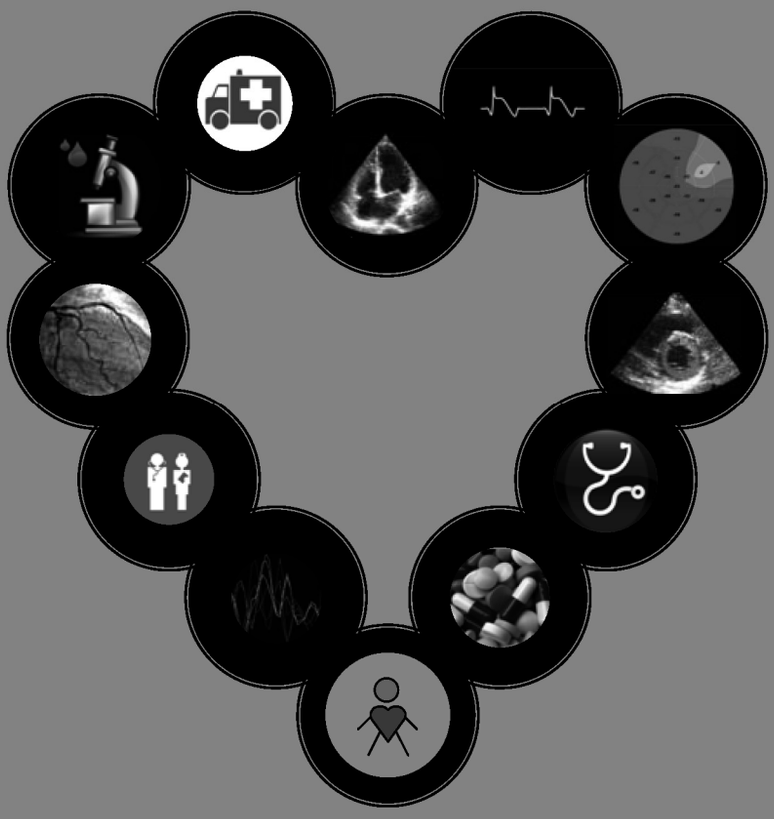

Chapter 6

Cardiovascular Mortality and Heart Failure Risk Score for Patients after ST-Segment Elevation Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention (Data from the Leiden MISSION! Infarct Registry)

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Abstract

Objectives

Risk scores developed for the prediction of an adverse outcome in patients after ST-segment elevation myocardial infarction (STEMI) have mostly addressed patients treated with thrombolysis and evaluated solely all-cause mortality as primary end point. Primary percutaneous coronary interventions (PCI) in STEMI patients have improved the outcome significantly and may have changed the relative contribution of different risk factors.

Methods and results

The patient population comprised 1484 consecutive patients admitted with STEMI treated with primary PCI. Clinical, angiographic and echocardiographic data that were obtained during the hospitalization were used to derive a risk score for the prediction of short-term (30-days) and long-term (1-and 4-years) cardiovascular mortality and hospitalization for heart failure. During a median follow-up duration of 30 months, 87 (6%) patients died from cardiovascular mortality or were hospitalized for heart failure. Multivariate Cox regression analyses identified age ≥70 years, Killip class ≥2, diabetes, left anterior descending coronary artery as culprit vessel, three vessel disease, peak cardiac troponin T level ≥3.5μg/l, left ventricular ejection fraction ≤40% and heart rate at discharge ≥70bpm as relevant factors for the construction of the risk score. The discriminatory power of the model as assessed with the areas under the receiver operating characteristic curves was good (0.84, 0.83, 0.81 at 30-days, 1-and 4-years, respectively) and patients could be allocated to low, intermediate, or high risk categories with event rates of 1%, 6% and 24%, respectively.

Conclusions

In conclusion, the current risk model demonstrates for the first time that eight parameters which are readily available during the hospitalization of STEMI patients treated with primary PCI can accurately stratify patients at long-term follow-up (up to 4 years after the index infarction) into low, intermediate and high risk categories.

Introduction

Several risk scores have been proposed for predicting long-term survival after myocardial infarction.[1 2] However, most of them have been developed from patient-cohorts treated with thrombolysis.[1-4] In the Western countries, patients with ST-segment elevation acute myocardial infarction (STEMI) preferably should be treated with primary percutaneous coronary intervention (PCI). Primary PCI in STEMI patients results in limited infarct size and preserved left ventricular systolic function.[5 6] As previously shown, infarct size and left ventricular ejection fraction are powerful determinants of long-term survival in these populations and form part of established risk scores.[7 8] However, the wide use of primary PCI may have changed the relative contribution of these parameters to the prediction of long-term outcome. Data concerning which risk factors are most important in this contemporary population of patients for the prediction of cardiovascular mortality and heart failure hospitalization during long-term follow-up are currently not available.[9 10] In addition, risk models focusing on cardiovascular mortality and development of heart failure have not been explored, which may be more relevant end points in this population rather than all-cause mortality. Therefore, the aim of the current evaluation was to derive a risk score for the prediction of short-term and long-term cardiovascular mortality and hospitalization of heart failure in STEMI patients treated with primary PCI using clinical, angiographic and echocardiographic parameters that are available during the hospitalization for the index infarction.

Methods

Since February 2004, clinical, angiographic and echocardiographic data from consecutive patients who were admitted with a STEMI in the Leiden University Medical Center were prospectively collected in the departmental cardiology information system (EPD-Vision®) and retrospectively analyzed. All patients underwent primary PCI and were treated according to the institutional protocol for patients admitted with STEMI (MISSION!).[11] This protocol is based upon the most recent American College of Cardiology/American Heart Association/ European Society of Cardiology guidelines and includes a prehospital, inhospital and outpatient clinical framework designed to optimize the care for these patients.[6 12-14] Evidence based medical therapy is initiated early during hospitalization.[15] In

addition, left ventricular ejection fraction is assessed with 2-dimensional echocardiography within 48 hours of admission to refine risk stratification and clinical management of the patients.[16]
For the present evaluation, clinical, angiographic and echocardiographic data from consecutive patients admitted with STEMI and who were not in cardiogenic shock at admission were analyzed. Among various clinical, angiographic and echocardiographic variables that were routinely collected, a practical risk score was created to accurately predict cardiovascular mortality and hospitalization for heart failure at short-term (30 days) and long-term follow-up (1 and 4 years) in this contemporary population of STEMI patients.

Coronary angiography was performed in all patients in the setting of primary PCI. During angiography, the coronary artery in which the culprit lesion was located, the number of diseased vessels (defined as ≥50% diameter stenosis), the time of first balloon dilatation and the final Thrombolysis in Myocardial Infarction (TIMI) flow grade were noted. Thereafter, patients were transferred to the coronary care unit and 2-dimensional echocardiography was performed within 48 hours of admission.[11] Left ventricular ejection fraction was calculated from the end-systolic and end-diastolic volumes measured at the apical 4- and 2-chamber views with the biplane Simpson's method.[16 17] All measurements were performed by two experienced observers. Inter- and intra-variability for echocardiographic measurements were good as previously published.[18]

All patients were scheduled for visits at the out-patient clinic at 1, 3, 6 and 12 months according to protocol. Data on the occurrence of adverse events after discharge were collected by reviewing medical records, retrieval of survival status through the municipal civil registries and telephone interviews. The primary end point was defined as a composite of cardiovascular mortality and hospitalization for heart failure. All medical records were reviewed independently by two observers, and the primary cause of death was recorded. All deaths were classified as cardiac unless unequivocally proven non-cardiac. Hospitalization for heart failure was defined as hospitalization for either new-onset or worsening of heart failure. In addition, both cardiovascular mortality and hospitalization for heart failure were assessed as individual end points. Patients without data on the last 6 months were

considered as lost to clinical follow-up. Data of these patients were included up to the last date of follow-up.

Continuous data are presented as mean ± standard deviation or median with 25th and 75th percentiles where appropriate. Categorical data are presented as frequencies and percentages. Differences in baseline characteristics between patients who reached the composite end point versus patients who remained event free were evaluated using the unpaired Student's *t*-test and chi-square test. Continuous variables which were not normally distributed were compared using Wilcoxon Rank-Sum test.

Event rates for cardiovascular mortality and hospitalization for heart failure were analyzed by the method of Kaplan-Meier. Differences in event rates were assessed using the log-rank test. In the presence of missing data, the single imputation procedure was applied.[19] In studies with a small number of missing variables (<10% for any parameter), single imputation has been shown to perform equally well as multiple imputation techniques.[20] To obtain a risk score, composed of robust, reproducible and non-clinician driven parameters, the use of medication was not used in the analysis. All variables were entered as categorical variables according to previously defined cut-off values in the literature (Table 1). Age was categorized in ≥70 years or <70 years;[21] three vessel disease was defined as ≥50% stenosis in 3 major epicardial branches;[10] symptoms to balloon time was categorized in ≥4 hours and <4 hours;[22] peak cardiac troponin T level was categorized in ≥3.5 µg/l or <3.5 µg/l;[23] glucose level was categorized in ≥8 mmol/l or <8 mmol/l;[24] renal clearance was estimated with the formula of Cockcroft-Gault and categorized in abnormal (≤60 ml/min) or normal (>60 ml/min);[25] left ventricular ejection fraction was categorized as ≤40% and >40%;[10] heart rate was categorized in ≥70 bpm or <70 bpm;[26-28] and systolic blood pressure was categorized in ≤100 mmHg or >100 mmHg.[22]

Thereafter, univariate Cox regression analysis was performed with the composite end point of cardiovascular mortality and hospitalization for heart failure. All parameters with a P-value less than 0.10 were further evaluated in a multivariate Cox regression model. Using backwards stepwise elimination, the least significant parameter was discarded from the model until all parameters reached a P-value of less than 0.25. Subsequently, each

remaining significant variable in the model was assigned a weighted score proportional to the regression coefficient. For this purpose, the base regression coefficient was assigned the value of one point and all variables were given the associating score, according to their multiplication of this base regression coefficient and rounding it of to the nearest whole number. More in detail, 0.46 was used as the base regression coefficient and was assigned the value of one point. The ability of the risk score to discriminate between patients who did and patients who did not reach the composite end point was estimated by the area under the curve of the receiver operator characteristic curve at short-term (30 days) and long-term follow-up (1 and 4 years). The developed risk score based on the whole study cohort was further evaluated by drawing 1000 bootstrap samples, with replacement, to estimate the extent to which the predictive accuracy of the model was overoptimistic. The mean C-index and corresponding standard error (SEM) was reported.[29] In addition, the discriminative capacity of the derived risk score was evaluated for the individual end points cardiovascular mortality and hospitalization for heart failure at 30 days, 1 year and 4 years. Finally, after determination of the individual risk score per patient, cut-off values were determined to divide the population in a low, intermediate and high risk population. These cut-off values were chosen to optimize the discriminative effect of the model without making the different groups too small.[30] A P-value <0.05 was considered significant and analyses were performed with SPSS, version 16.0 (Chicago, IL, USA).

Results

A total of 1523 consecutive patients admitted with STEMI treated with primary PCI were evaluated in the current study. During hospitalization for the index infarction, 39 patients (2%) died and were excluded from further analysis. The final study population therefore comprised 1484 patients. Table 1 shows the characteristics of all included patients. The mean age of the patients was 61 ± 12 years and 76% of the patients were men. Four percent of the patients presented with a Killip class ≥2 and 12% of the patients had diabetes. The left anterior descending coronary artery was the culprit vessel in 46% of the patients and peak creatine phosphokinase level and peak cardiac troponin T level were 1488 (647 – 2921) U/l and 3.8 (1.4, 7.7) µg/l, respectively. Baseline echocardiography performed within 48 hours of admission revealed a mean left ventricular ejection fraction of 47 ± 9%.

Table 1. Baseline characteristics

	All Patients (N =1484)	*Endpoint (N = 87)*	*Event-free (N = 1397)*	*P*
Age (years)	61 ± 12	65 ± 14	61 ± 12	0.002
Age ≥70 years	366 (25%)	38 (44%)	328 (24%)	<0.001
Women	356 (24%)	20 (23%)	336 (24%)	0.82
Killip class 1/2/3	1430/40/14	73/8/6	1357/32/8	<0.001
Killip class ≥2	54 (4%)	14 (16%)	40 (3%)	<0.001
Current smoker	702 (47%)	43 (49%)	659 (47%)	0.68
Diabetes mellitus	175 (12%)	26 (30%)	149 (11%)	<0.001
Family history of CAD	613 (41%)	32 (37%)	581 (42%)	0.38
Hypercholesterolemia*	290 (20%)	13 (15%)	277 (20%)	0.27
Hypertension†	517 (35%)	30 (35%)	487 (35%)	0.94
Prior myocardial infarction	129 (9%)	10 (12%)	119 (9%)	0.34
LAD as culprit artery	679 (46%)	55 (63%)	624 (45%)	0.001
Number of diseased vessels	698/504/282	30/27/30	668/477/252	0.001
Three vessel disease	282 (19%)	30 (35%)	252 (18%)	<0.001
Symptoms to balloon time (min)	174 (128, 255)	178 (144, 291)	174 (126, 254)	0.05
Symptoms to balloon time ≥240 min	423 (29%)	26 (30%)	397 (28%)	0.77
Final TIMI flow 0/1/2/3	7/22/79/1376	0/1/5/81	7/21/74/1295	0.91
TIMI ≤2	108 (7%)	6 (7%)	102 (7%)	0.89
Peak creatine phosphokinase (U/l)	1488 (647, 2921)	3430 (1689, 5530)	1417 (619, 2676)	<0.001
Peak cardiac troponin T (µg/l)	3.8 (1.4, 7.7)	9.2 (3.8, 14.5)	3.6 (1.4, 7.3)	<0.001
Peak cardiac troponin T ≥3.5 µg/l	772 (52%)	67 (77%)	705 (51%)	<0.001
Glucose (mmol/l)	8.5 ± 3.0	9.8 ± 4.2	8.4 ± 2.9	0.003
Glucose ≥8 mmol/l	705 (48%)	51 (59%)	654 (47%)	0.03
eGFR (ml/min/1,73m^2)	98 ± 33	89 ± 39	99 ± 33	0.008
eGFR ≤60 ml/min/1,73m^2	172 (12%)	67 (77%)	20 (23%)	0.001
LV ejection fraction (%)	47 ± 9	41 ± 10	48 ± 9	<0.001
LV ejection fraction ≤40%	315 (21%)	38 (44%)	277 (20%)	<0.001
Heart rate at discharge(bpm)	70 ± 12	77 ± 16	70 ± 12	<0.001
Heart rate ≥70 bpm	730 (49%)	57 (66%)	673 (48%)	0.002
Systolic blood pressure at discharge (mmHg)	115 ± 16	111 ± 17	115 ± 16	0.02
Systolic blood pressure ≤100 mmHg	270 (18%)	23 (26%)	247 (18%)	0.04
Diastolic blood pressure at discharge	70 ± 22	67 ± 12	70 ± 23	0.20

Table 1. Baseline characteristics (continued)

	All Patients (N =1484)	*Endpoint (N = 87)*	*Event-free (N = 1397)*	*P*
Medication at discharge				
ACE inhibitors / ARBs	1434 (98%)	86 (100%)	1397 (100%)	1.00
Antiplatelets	1484 (100%)	82 (95%)	1365 (98%)	0.17
Beta-blockers	1390 (95%)	83 (97%)	1386 (99%)	0.01
Statins	1456 (99%)	76 (88%)	1327 (95%)	0.008

* Total cholesterol ≥190 mg/dl or previous pharmacological treatment.

† Blood pressure ≥140/90 mmHg or previous pharmacological treatment.

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; eGFR: glomerular filtration rate estimated with the Cockcroft-Gault formula; LAD: left anterior descending coronary artery; TIMI: Thrombolysis In Myocardial Infarction.

At discharge, mean heart rate was 70 ± 12 bpm. In addition, the use of evidence-based medical therapy at discharge was high, 98% of the patients were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 95% of the patients with beta-blockers and 99% of the patients with statins.

Clinical follow-up was completed in 1389 patients (94%) and the median follow-up duration was 30 (13, 48) months. During this period, 87 patients (6%) reached the composite end point. More in detail, 52 patients (4%) died from cardiovascular mortality and 46 patients (3%) were hospitalized for new-onset or worsening of heart failure. Of note, a total of 78 patients (5%) died during the follow-up period and only 67% of the deaths were defined with a cardiovascular cause. In the current population, the non-cardiovascular deaths were mostly due to malignancy.

Univariate and subsequent multivariate Cox regression analyses identified 8 variables for the construction of the risk score: age ≥70 years, Killip class ≥2, diabetes, left anterior descending coronary artery as culprit vessel, three vessel disease, peak cardiac troponin T level ≥3.5 μg/l, left ventricular ejection fraction ≤40% and heart rate at discharge ≥70 bpm (Table 2). The regression coefficient of heart rate at discharge of 0.46 was used as the base regression coefficient. For each variable, a weighted risk score was assigned based on the corresponding regression coefficient (Table 2).

Table 2. Multivariable Cox regression model and corresponding risk score

	Regression coefficient	*Hazard Ratio (95% CI)*	*P*	*Score*
Age ≥70 years	0.69	2.00 (1.29 – 3.09)	0.002	1
Killip class ≥2	1.29	3.65 (2.02 – 6.58)	<0.001	3
Diabetes mellitus	0.90	2.45 (1.52 – 3.96)	<0.001	2
LAD as culprit artery	0.49	1.64 (1.04 – 2.56)	0.03	1
Three vessel disease	0.62	1.86 (1.16 – 2.98)	0.01	1
Peak cardiac troponin T level ≥3.5 µg/l	0.86	2.37 (1.42 – 3.94)	0.001	2
Left ventricular ejection fraction ≤40%	0.66	1.93 (1.25 – 2.99)	0.003	1
Heart rate at discharge ≥70 bpm	0.46	1.59 (1.01 – 2.50)	0.04	1

LAD: left anterior descending coronary artery.

Thereafter, a risk score was calculated for each patient by adding up the points for each risk factor present. The areas under the receiver operator characteristic curve for the risk score and the composite end point at 30 days, 1 year and 4 years were 0.77, 0.81 and 0.79, respectively, indicating good discriminatory power of the model. The mean C-indexes of the risk score as obtained in the 1000 bootstrap samples were fairly similar, 0.78 (SEM 0.04), 0.82 (SEM 0.03) and 0.79 (SEM 0.79) for the composite end point at 30 days, 1 year and 4 years, respectively.

For the individual end points, the area under the receiver operating characteristic curves were 0.84, 0.83 and 0.81 for cardiovascular mortality and 0.73, 0.80 and 0.78 for hospitalization for heart failure at 30 days, 1 year and 4 years, respectively.

Figure 1 shows the observed event rates of the composite end point and cardiovascular mortality and hospitalization for heart failure individually according to the scoring system. For simplicity, patients were divided in 3 risk categories based on the derived risk score: 1. low risk (0 – 2 points); 2. intermediate risk (3 – 5 points) and 3. high risk (≥6 points). In the low risk group consisting of 644 patients (43% of the total patient population), 9 patients (1%) died from cardiovascular mortality or were hospitalized for heart failure during 1591 patient-years, corresponding to an event rate of 0.6 per 100 patient-years (Table 3).

Table 3. Event rates according to risk score

Risk	*Risk score*	*Patients*	*Patient years*	*Number or events and corresponding event rate per 100 patient-years*					
				Composite		*CV death*		*Heart failure*	
				Events	*Event rate*	*Events*	*Event rate*	*Events*	*Event rate*
Low	0 – 2	644	1591	9	0.6	5	0.3	4	0.3
Intermediate	3 – 5	689	1976	42	2.1	24	1.2	23	1.2
High	6 – 12	151	357	36	10.1	23	6.4	19	5.3
Total		1484	3924	87	2.2	52	1.3	46	1.2

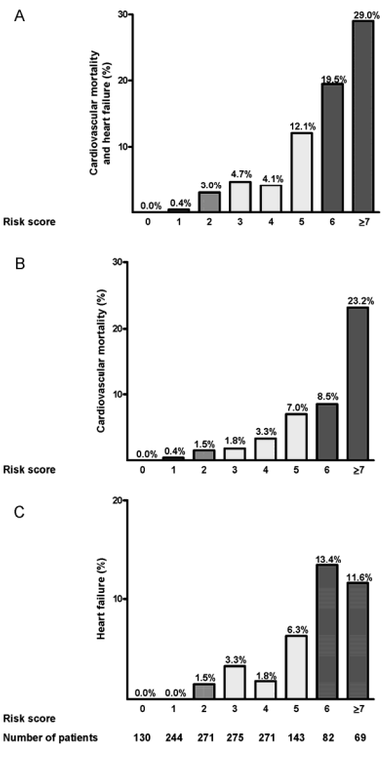

Figure 1.

Number of patients in each category with the corresponding event rates for the combined end point (A), cardiovascular mortality (B) and hospitalization

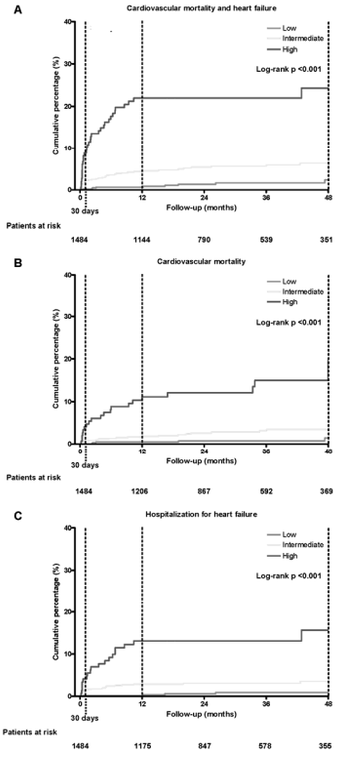

Figure 2.

Kaplan-Meier curves for the cumulative incidence of the combined end point (A), cardiovascular mortality (B) and hospitalization for heart failure (C) in patients with low, intermediate and high risk.

In the 689 patients (46%) with an intermediate risk, 42 patients (6%) reached the composite end point during 1976 patient-years. Therefore, the calculated event rate was 2.1 per 100 patient-years. The high risk group included 151 patients (10% of the total population) and in this group 36 patients (24%) died from cardiovascular mortality or were hospitalized for heart failure and the corresponding event rate was 10.1 per 100 patient-years.

More in detail, the Kaplan-Meier curves stratified according to the risk score demonstrate cumulative event rates of 0.2%, 0.6% and 2.4% for the composite end point in the low-risk group at 30 days, 1 year and 4 years, respectively. In the intermediate group, the cumulative event rates were 2.1% at 30 days, 4.4% at 1 year and 6.3% at 4 years for the composite end point. Finally, the high risk group demonstrated event rates of 8.8%, 21.9% and 24.3% for the composite end point at 30 days, 1 year and 4 years, respectively (Figure 2).

Discussion

The current evaluation proposes a novel risk score including clinical, laboratory, angiographic and echocardiographic parameters routinely used in clinical practice to provide a good estimation of the individual patient's risk for adverse outcome. With this risk score, contemporary patients with STEMI treated with primary PCI can be allocated to low (1%), intermediate (6%), or high (24%) risk categories for the occurrence of cardiovascular mortality and heart failure during short- term (30 days) and long-term (1 year and 4 years) follow-up. Currently, early primary PCI is the preferred treatment for patients presenting with STEMI.

Moreover, these favorable results were sustained during long-term follow-up, and primary PCI was still superior to any type of thrombolytic therapy, even when reperfusion was delayed because of transferring to another center.[5]

However, despite aggressive therapy with primary PCI, mortality rates after STEMI are still substantial. Previous studies have reported cumulative event rates ranging from 5% at 90 days to 6% at 1 year and 14% at 3 years for all-cause mortality.[21 24 28] In addition, due to improved survival of STEMI patients and the aging population, the number of patients with ischemic heart failure in the Western countries is growing and determines a significant socioeconomic burden.[31] Therefore, risk stratification of this population is important with special focus on cardiovascular mortality and heart failure.

Several risk scores have been developed for patients presenting with STEMI from thrombolysis trials.[1-3 22] In these early trials, angiography was not routinely performed and therefore the models often did not incorporate variables such as the culprit vessel and multivessel disease, which have been shown to be important predictors of outcome in patients treated with primary PCI.[32 33] In addition, parameters reflecting final infarct size (left ventricular ejection fraction and peak cardiac enzymes) are lacking in the traditional risk scores developed by the GUSTO-I, GISSI, TIMI and GRACE investigators.[1-3 22] Recently, a few studies have focused on developing risk scores for STEMI patients treated with primary PCI.[9 10 28 34] De Luca et al. proposed a score to predict all-cause mortality at 30 days.[34] Age, anterior infarction, Killip class, time to treatment, procedural success and multivessel disease were independent predictors of all-cause mortality.[34] Similar results were observed in subsequent trials with longer follow-up up to 1 year yielding useful risk scores to predict all-cause mortality such as the PAMI and CADILLAC risk scores.[9 10 28] The present evaluation provides further evidence by focusing on longer follow-up until 4 years. To the best of our knowledge, only the GRACE and the KAMIR risk scores have been recently evaluated to predict mortality during 4 years follow-up.[35 36] However, these cohorts included heterogeneous populations with STEMI and non-STEMI patients and patients were not treated with primary PCI. In addition, the present study extends the current knowledge by evaluating cardiovascular mortality and heart failure as end points rather than all-cause mortality. The increased prevalence of deaths due to malignancy makes the use of cardiovascular mortality a more useful end point rather than all-cause mortality. On the other hand, improved survival of STEMI patients in combination with the aging population has resulted in a growing number of patients with chronic heart disease and therefore secondary prevention of the development of heart failure will play a key role in the management of STEMI patients in the future.

Interestingly, many of the predictors included in the novel risk scores are the same predictors identified by the risk scores developed in the thrombolytic era. The prognostic value of traditional predictors including age, Killip class, diabetes and heart rate was again confirmed. In addition, parameters reflecting the final infarct size appeared to be powerful determinants of the composite end point. These findings are in line with the study performed by Halkin et al.[10] The authors recently demonstrated that left ventricular ejection fraction was the most important predictor for long-term mortality after primary PCI.

However, this is the first study to identify infarct size assessed with peak cardiac troponin T level as one of the most powerful determinants of short-term and long-term cardiovascular mortality and heart failure as part of a risk score. The present risk score confirms that several well-known risk factors remain of importance in the contemporary population of STEMI patients to predict cardiovascular mortality and heart failure. In addition, the current analysis emphasizes the importance of assessing infarct size with left ventricular ejection fraction and peak cardiac enzymes to differentiate between patients at low and high risk for adverse outcome.

The risk score presented in the current study does not take medical therapy into consideration as the aim of the evaluation was to construct a robust and non-clinician driven risk model.[10] However, all patients were treated according to the institutional protocol which includes the initiation of evidence-based medical therapy during hospitalization and accordingly the use of ACE-inhibitors, beta-blockers and statins was high in this population of patients.[11]

Furthermore, patients who presented with cardiogenic shock were not included in the current study since it is already well known that patients with congestive heart failure have a worse prognosis.[37] Finally, the results of the present evaluation need to be confirmed and validated in prospective large series of STEMI patients treated with primary PCI.

Conclusions

The current risk model demonstrates for the first time that eight parameters which are readily available during the hospitalization of STEMI patients treated with primary PCI can accurately stratify patients at long-term follow-up (up to 4 years after the index infarction) into low, intermediate and high risk categories.

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