Risk stratification after ST-segment elevation myocardial infarction

Sergio Buccheri, Piera Capranzano, Antonio Condorelli, Matteo Scalia, Corrado Tamburino & Davide Capodanno

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ABSTRACT

Introduction: Risk stratification according to the timing of assessment, treatment modality and outcome of interest is highly advisable in patients with ST-elevation myocardial infarction (STEMI) to identify optimal treatment strategies, proper length of hospital stay and correct timing of follow-up. Areas covered: This review is an overview summarizing the characteristics and performance of available risk-scoring systems for STEMI. In particular, we sought to highlight the characteristics of STEMI cohorts used for derivation and validation of the available algorithms and appraise their discrimination ability, calibration and global accuracy. Expert commentary: Applying the appropriate score, customized on patients’ profile and clinical characteristics at presentation or during the hospitalization, might prove useful to improve the overall quality of care provided to STEMI patients.

1. Introduction

In medicine, the word ‘risk’ typically defines the probability that something unpleasant is going to happen. Indeed, any pathological condition embraces a wide array of potential outcomes ranging from complete recovery to death, and risk scores seek to trap the stochastic and time-varying nature of these outcomes into a mathematical model [1]. As such, risk scores serve as helpful aids in daily practice and many of them are endorsed by clinical practice guidelines to tailor decisions for individual patients.

ST-elevation myocardial infarction (STEMI) is a complex clinical scenario that requires immediate diagnosis, rapid therapeutic management and early risk stratification. Recent advances in the fields of percutaneous coronary intervention (PCI) and cardiovascular pharmacotherapy, along with development of dedicated regional networks, have significantly improved the outcomes of patients with STEMI [2,3]. However, mortality after STEMI still remains significant, being reported at 6–14% in-hospital and 12% at 6-months [4]. Such rates may vary significantly across subsets of patients, underscoring the existence of sizeable STEMI populations at higher and lower risks, respectively [5]. In patients at low risk, a strategy of early discharge (i.e. at 48–72 h from hospitalization) has been shown to be safe and cost-effective, while the length of hospital stay is typically longer in patients at higher risk [6,7]. On this background, many risk scores have been built and validated in the setting of STEMI to get useful prognostic information and facilitate a better allocation of health resources [8–10].

This article aims at practically reviewing the current landscape of risk-scoring systems for STEMI. In particular, we sought to highlight the characteristics of STEMI cohorts used for derivation and validation of the available algorithms and appraise their discrimination ability, calibration and global accuracy. Scores developed in clinical settings other than STEMI (i.e. non-ST elevation acute coronary syndromes, elective PCI) are beyond the scope of this review.

1.1 Epidemiology, length of hospitalization, and mortality in ST-elevation myocardial infarction

Trends in the varying epidemiology of acute coronary syndromes (ACS) have been well documented in recent years, with decreasing proportions of newly onset STEMI diagnoses paralleled by increased rates of non-ST elevation myocardial infarction [11]. In a community-based cohort of 46,086 US patients hospitalized for STEMI, Yeh et al. described a significant decline in the rate of age- and sex-adjusted risk of experiencing STEMI, moving from 133 cases per 100,000 person-years in 1999 to 50 cases per 100,000 person-years in 2008 [12]. Consistently, another large cohort (N = 5383) US registry confirmed this trend by showing a reduction in STEMI cases from 121 to 77 per 100,000 subjects [13]. Potential explanations to the observed decrease in STEMI include the impact of primary prevention measures and the introduction of highly sensitive laboratory assays (i.e. high sensitive troponin) that likely promote more frequent diagnoses of non-ST elevation myocardial infarction at an earlier stage of the physiopathologic continuum of ACS.

The length of hospitalization after STEMI has also shown a decreasing trend in recent years. For example, data from 33,920 STEMI patients in the CathPCI registry [14] showed the mean length of stay to decrease significantly from 2005 to 2009, with the proportion of patients discharged after 2 days declining from 72% to 66%.

Despite these ameliorations, the prognosis of STEMI remains suboptimal. In a recently meta-analysis of STEMI...
trials of anticoagulation, the pooled rate of 30-day all-cause mortality was 2.8% [15]. Indeed, clinical trials may underestimate the mortality rates observed in daily practice, due to a certain degree of patient selection. In unselected patients from the Minnesota Heart Survey, for example, in-hospital mortality was sensibly higher at 5.3% [16].

In summary, the decreasing rates of STEMI diagnoses and length of hospitalization observed in the past 15 years have not been paralleled by notable improvements in survival (Figure 1) [12]. Clearly, it is important to emphasize that not all STEMI patients are equal. In fact, patients at low risk have an excellent prognosis, which sets the rationale for risk stratification in this setting [17]. Accordingly, disparate prognostic tools, developed specifically from large series of STEMI patients enrolled in clinical trials or registries have been developed to enable meaningful risk assessment both at short- and long term [8–10,17–22].

1.2. How to appraise the quality of a clinical risk score: a brief walkthrough

Derivation and validation of a clinical score imply the use of several statistical methods to ideally obtain a well-calibrated, discriminative and clinically useful score. In brief, when constructing a score, statisticians work in identifying a mathematical model that is able to describe and categorize the risk conveyed by a specific pathological condition. Since clinical risk is inherently time varying and affected by dynamic changes in clinical status as often seen in complex circumstances, this task is methodologically demanding. Disparate statistical methodologies including multivariate analyses, receiver operating curves, and Cox proportional hazard models are used for model building. Moreover, many parameters are used to assess the statistical performance of a newly developed score (number of subjects and events used for score derivation, discrimination, calibration, reclassification, overall performance) [1,23]. Among these, one of the most accepted and widely adopted tests is the c-statistic value. The c-statistic represents a simple measure of concordance that discriminates between high- and low-risk subjects with values ranging from 0.5 to 1.0 for worst and perfect discrimination, respectively.

Table 1. Statistical and clinical rules for proper application of risk scores.

<table>
<thead>
<tr>
<th>Statistical rules</th>
<th>Clinical rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate powered sample size and number of events in relationship to predictors (e.g. over-fitting avoidance)</td>
<td>Proper matching of the score to the patient clinical profile</td>
</tr>
<tr>
<td>Independence of predictors (e.g. no multi-collinearity in the model)</td>
<td>Correct timing of score evaluation (e.g. at presentation, during hospitalization, at discharge)</td>
</tr>
<tr>
<td>Good discrimination and calibration ability, acceptable overall performance of the model (e.g. Brier’s statistic)</td>
<td>Use of the proper score for the outcome of interest (e.g. mortality, re-hospitalization, MACE)</td>
</tr>
<tr>
<td>Internal and external validation</td>
<td>Adequate intensity of care and timing of follow-up intervals based on the identified patient risk profile</td>
</tr>
<tr>
<td>Comparison with already available risk scores to confirm improved predictive performance</td>
<td></td>
</tr>
</tbody>
</table>

MACE: major adverse cardiac events.

Beyond statistical performance, a risk score has to be user-friendly and properly applicable in the daily clinical setting. Clearly, the statistical excellence of a score is useless without adequate clinical applicability. Such simple rule is based on the evaluation of different aspects, including clinical presentation, patient profile, timing of risk assessment, outcome evaluated by the specific score and temporal interval between risk assessment and events prognostication. Table 1 summarizes statistical and clinical rules for correct prognostication with use of risk scores. Accordingly, risk-scoring algorithms in the current review (Table 2) will be reported highlighting both statistical aspects of each prognostic tool and their clinical counterpart.

2. Risk scores from derivation cohorts of STEMI patients mostly undergoing fibrinolysis

2.1. GUSTO nomograms

Data of STEMI survivors from the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO-I) have been used to derive two algorithms for predicting 1-year mortality after a 30-day event-free period [8]. Two simple nomograms were developed using independent predictors identified by multivariate analyses

Figure 1. Temporal trends in STEMI incidence and mortality. Adapted with permission from Yeh et al. [12].
The TIMI risk score is one of the most extensively applied score for risk stratification in STEMI. It was originally derived from 14,114 patients enrolled in the Intravenous nPA (lanoteplase) for Treatment of Infarcting Myocardium Early II (InTIME II) trial and validated in an external population of 3687 patients enrolled in the TIMI 9A and 9B trials [9]. The TIMI risk score is a bedside clinical risk stratification tool, quantifiable at hospital presentation and calculated as the sum of weighted point values assigned to independent predictors of 30-day mortality. Figure 3 summarizes clinical variables, assigned points and the risk of death for each cumulative score value in the model. The prognostic ability of the TIMI risk score has shown to be consistent at different time points (24 h, in-hospital, 6 months, and 1-year). In the validation set, a score value ≤2 identified patients at low risk of mortality. The TIMI risk score has been largely validated in the literature [24–37] and its prognostic value has been also confirmed in patients undergoing primary PCI [38].

2.3. Dynamic TIMI risk score

A recent modification of the TIMI risk score has been proposed and defined as Dynamic TIMI risk score [21]. The dynamic TIMI risk score accounts for the development of in-hospital complications with additional integer points to be added at the conventional TIMI risk score, including: recurrent myocardial infarction (1 point), stroke (5 points), major bleed (1 point), congestive heart failure/shock (3 points), arrhythmias (2 points), and renal failure (3 points). The dynamic TIMI risk score has been derived from data of patients enrolled in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)-TIMI 25 and subsequently validated in 3534 STEMI patients of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38. Similar to the conventional TIMI risk score, it is a simple and bedside scoring algorithm for long-term prognostic stratification at discharge. In the derivation cohort, a score value of 0/1 predicted a low risk (1.3%) of 1-year mortality and in the validation set a value ≤3 identified patients with 0.5–0.6% risk of 1-year mortality (Figure 4). Despite attracting for its simplicity and for the unique ability to capture the dynamic nature of risk in STEMI patients by considering in-hospital events, the score has been poorly validated by other studies in the literature. In addition, the dynamic-TIMI risk score was developed and validated only in populations of patients enrolled in clinical trials, which are typically highly selected and at lower risk. Further confirmation of the predictive ability of the Dynamic-TIMI score in unselected STEMI populations is, therefore, warranted before extending its use in daily practice.

2.4. Simple risk index

The ‘law of parsimony’ or ‘Ockham razor’ hypothesizes that a simple mathematical model could be able to describe and represent even complex scenarios. This principle gives priority to simplicity and when a complex scenario could be explained by two or more models, the simpler should be preferred

(Figure 2). The first nomogram is based on clinical parameters (age, prior myocardial infarction, in-hospital onset of congestive heart failure, or pulmonary edema) while the second nomogram integrates both clinical and angiographic measures (i.e. ejection fraction by ventriculography). C-indexes of 0.80 and 0.81 for the estimation of 1-year mortality were measured in the multivariate models with and without angiographic data, respectively, underscoring good discrimination. The simplified nomograms had c-statistic values of 0.75 and 0.79 for models with and without angiographic data, respectively. However, such models had poor validation in subsequent studies and fit poorly with current practices characterized by larger use of primary PCI. Moreover, these models can be applied to 30-day survivors only and, therefore, may not serve as useful tools to stratify the risk of in-hospital and 30-day mortality after STEMI.

### Table 2. Algorithms for prognostic stratification in STEMI patients.

<table>
<thead>
<tr>
<th>Score</th>
<th>Population for derivation</th>
<th>Revascularization modality</th>
<th>Predicted event</th>
<th>c-Statistic$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GUSTO-I score</td>
<td>RCT</td>
<td>Fibrinolysis</td>
<td>1-Year mortality from 30 day survivors</td>
<td>0.75 and 0.79$^b$</td>
</tr>
<tr>
<td>TIMI risk score</td>
<td>RCT</td>
<td>Fibrinolysis</td>
<td>30-Day mortality</td>
<td>0.78</td>
</tr>
<tr>
<td>Dynamic TIMI risk score</td>
<td>RCT</td>
<td>Fibrinolysis</td>
<td>1-Year mortality</td>
<td>0.76</td>
</tr>
<tr>
<td>Simple risk index</td>
<td>RCT</td>
<td>Fibrinolysis</td>
<td>Early events (24 h) and 30-day mortality</td>
<td>0.81 and 0.78 for each predicted event, respectively</td>
</tr>
<tr>
<td>GRACE risk score$^c$</td>
<td>Registry</td>
<td>45% PCI treated$^d$</td>
<td>6-Month mortality</td>
<td>0.71$^e$</td>
</tr>
<tr>
<td>CADILLAC risk score</td>
<td>RCT</td>
<td>Primary angioplasty</td>
<td>30-Day and 1-year mortality</td>
<td>0.83 and 0.79</td>
</tr>
<tr>
<td>PAMI risk score</td>
<td>RCT</td>
<td>Primary angioplasty</td>
<td>6-Month mortality</td>
<td>0.78</td>
</tr>
<tr>
<td>APEX-AMI risk score</td>
<td>RCT</td>
<td>Primary angioplasty</td>
<td>90-Day mortality</td>
<td>0.81</td>
</tr>
<tr>
<td>Zwolle risk score</td>
<td>Registry</td>
<td>Primary angioplasty</td>
<td>30-day mortality In-hospital mortality</td>
<td>0.91</td>
</tr>
<tr>
<td>ACTION-GWTG risk score</td>
<td>Registry</td>
<td>Primary angioplasty</td>
<td>(88.4% in STEMI patients)</td>
<td>0.88</td>
</tr>
<tr>
<td>Mi-SYNTAX score</td>
<td>RCT</td>
<td>Primary angioplasty</td>
<td>1-Year MACE</td>
<td>0.69 (combined Mi-SYNTAX and TIMI risk score)</td>
</tr>
<tr>
<td>PAMI-SYNTAX score</td>
<td>RCT</td>
<td>Primary angioplasty</td>
<td>1-Year mortality</td>
<td>0.73</td>
</tr>
<tr>
<td>Residual SYNTAX score</td>
<td>Registry</td>
<td>Primary angioplasty</td>
<td>1-Year mortality</td>
<td>NA</td>
</tr>
</tbody>
</table>

$^a$: Derivation cohort.

$^b$: Nomograms with and without angiographic data.

$^c$: Score derived from all ACS spectrum.

$^d$: Value in STEMI only patients.

$^e$: Score only and, therefore, may not serve as useful tools to stratify the risk of in-hospital and 30-day mortality after STEMI.
(‘pluralitas non est ponenda sine necessitate’). Accordingly, in the same derivation and validation cohorts of the TIMI risk score, a simple risk index (SRI) including three clinical variables (age, heart rate [HR] and systolic blood pressure) was developed for risk assessment of in-hospital and 30-day mortality [17]. The SRI was also able to predict early events, including mortality within 24 h. The score could be calculated in the pre-hospital setting or in the emergency department. Clinical variables are combined using the following formula: (HR × \( \frac{\text{age}}{10} \))^2 / systolic blood pressure. The SRI was validated in a large population of unselected STEMI patients included in the National Registry of Myocardial Infarction-3 and -4 in the United States [39]. A score value <10 identified patients with a risk of in-hospital mortality below 1% and mortality was slightly higher in patients without immediate revascularization therapy (1.9%). Bradshaw et al. [40] further confirmed the

<table>
<thead>
<tr>
<th>Clinical nomogram</th>
<th>Clinical and angiographic nomogram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameters</strong></td>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>Age, years</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>90</td>
<td>73</td>
</tr>
<tr>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>Prior MI</td>
<td>No</td>
</tr>
<tr>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>In-hospital CHF/PE</td>
<td>No</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>≥ 120</td>
</tr>
<tr>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>30</td>
<td>97</td>
</tr>
<tr>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>50</td>
<td>95</td>
</tr>
<tr>
<td>60</td>
<td>94</td>
</tr>
<tr>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Prior MI</td>
<td>No</td>
</tr>
<tr>
<td>In-hospital CHF/PE</td>
<td>No</td>
</tr>
</tbody>
</table>

**Figure 2. GUSTO nomograms.**

**TIMI Risk Score for STEMI**

<table>
<thead>
<tr>
<th>Historical</th>
<th>Risk score</th>
<th>Odds of death by 30 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65-74</td>
<td>2 points</td>
<td>0</td>
</tr>
<tr>
<td>≥ 75</td>
<td>3 points</td>
<td>1</td>
</tr>
<tr>
<td>DM/HTN or angina</td>
<td>1 point</td>
<td>2</td>
</tr>
<tr>
<td>Exam</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>SBP &lt; 100</td>
<td>3 points</td>
<td>4</td>
</tr>
<tr>
<td>HR &gt; 100</td>
<td>2 points</td>
<td>5</td>
</tr>
<tr>
<td>Killip class II-IV</td>
<td>2 points</td>
<td>6</td>
</tr>
<tr>
<td>Weight &lt;67 Kg</td>
<td>1 point</td>
<td>7</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Anterior STE or LBBB</td>
<td>1 point</td>
<td>&gt; 8</td>
</tr>
</tbody>
</table>

**Figure 3. TIMI risk score.**
good discriminatory ability of the SRI (c-statistic 0.82) in the large STEMI cohort of the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study. However, the score poorly performed in elderly patients (older than 65 years) as shown in a large community-based population of 55,078 patients from the Cooperative Cardiovascular Project in the United States [41] and, therefore, should be cautiously applied in this group of subjects.

2.5. GRACE risk score

The Global Registry of Acute Coronary Events (GRACE) score was derived from a large multinational registry of patients experiencing all the spectrum of ACS and was originally designed to predict in-hospital and 6-months mortality through a multivariable stepwise regression model. Less than half of STEMI patients in the registry (45%) received revascularization with a percutaneous approach. The score evaluates the following variables: age, HR, systolic blood pressure (SBP), creatinine level, Killip class, cardiac arrest at admission, ST-segment deviation and elevated troponin level or necrosis cardiac biomarkers, and should be calculated at hospital presentation. The GRACE score is recommended by actual guidelines for the selection of NSTEMI patients that could benefit from an early invasive strategy [42]. Several studies confirmed the prognostic ability of the GRACE score even in the STEMI setting [24,25]. A meta-analysis of studies exploring the predictive ability of the GRACE score in STEMI patients identified a pooled c-statistic 0.82 and 0.81 for short- and long-term adverse events prediction, respectively [43]. The predictive ability of the model for long-term adverse events has been recently confirmed [44,45] with a good performance up to 5 years in patients treated invasively [32]. However, one previous report [33] showed poor performance of the GRACE score in STEMI patients with a c-statistic of only 0.47 (patients with cardiogenic shock were excluded and this could have affected the results). A user-friendly and simple online calculator of the score is available at: http://www.gracescore.org/WebSite/WebVersion.aspx.

3. Risk scores from derivation cohorts of STEMI patients undergoing percutaneous coronary intervention

Recently published guidelines recommend timely reperfusion by primary angioplasty as the preferred revascularization modality in patients with STEMI. Consequently, the proportion of patients receiving such therapeutic treatment significantly increased in recent years [46]. This prompted the development of specific risk stratification tools (CADILLAC, PAMI, Zwolle, and MI synergy between percutaneous coronary intervention with taxis and cardiac surgery (SYNTAX) score) derived and validated in patients achieving revascularization by primary PCI [10,18,20,22].

3.1. CADILLAC risk score

The CADILLAC risk score was derived from 2082 patients enrolled in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial [47] identifying independent predictors of 1-year mortality. The score evaluates both clinical, angiographic and laboratory parameters (see Table 3) and was validated in a large group of 900 patients enrolled in the Stent-Primary Angioplasty in Myocardial Infarction trial [48]. The CADILLAC risk score had good prediction ability for the estimation of 1-year mortality in both the derivation and validation cohort (c-statistic of 0.79 and 0.78, respectively). The performance of the score was also confirmed for the prediction of 30-day mortality (c-statistic of 0.83 and 0.81 for the derivation and validation cohort, respectively). Patients with a score of 0–2 were at low mortality risk (<1%). As a limitation, the score was entirely derived and validated in patients enrolled in clinical trials that, as previously seen, are generally at lower risk of mortality. Indeed, in the CADILLAC trial, patients with failed thrombolytic therapy, need for multi-vessel PCI, known renal or hepatic dysfunction, bleeding diathesis and a previous (two years) cerebrovascular accident were excluded. Moreover, STEMI patients with cardiogenic shock were not included and therefore the score must not be applied for prognostic stratification in this group of patients. Finally, coronary stenting in the
CADILLAC trial was performed with the use of bare metal stents (Guidant MultiLink stent) while, in current clinical practice, a larger use of drug-eluting stents (DES) is adopted. DES use in STEMI patients is associated with a reduction in the rate of target vessel revascularization (i.e., everolimus eluting stents) and also characterized by a substantial reduction in the rate of stent thrombosis as compared to bare metal stents [49]. Moreover, use of newer devices (e.g., biolimus eluting stents with biodegradable polymers) has been shown to reduce rate of cardiac death, as compared to first generation DES in STEMI patients [50]. Therefore, the CADILLAC algorithm could overestimate cardiac mortality in current clinical practice and the predictive accuracy of the model should be confirmed in STEMI patients treated with newer devices.

### 3.2. PAMI risk score

The PAMI risk score was developed from a pooled analysis of patients-level data obtained from different PAMI trials (PAMI 1 and 2, AIR PAMI, and STENT PAMI trials) and was designed for the prediction of 6-month mortality. The risk score is quantifiable as the simple sum of integer points, calculated as follows: age ≥75 years (7 points), age 65–74 years (3 points), Killip class >1 (2 points), heart rate >100 (2 points), anterior myocardial infarction and left bundle branch block (2 points). The model had good discrimination ability (c-statistic 0.78) for the prediction of 6-months mortality. The score is not valid in patients with cardiogenic shock, stroke in the previous month and end-stage renal failure because patients in these groups were not included in PAMI trials. The same limitations of the CADILLAC score, concerning the typology of stent (i.e., Palmaz–Schatz stent) used must be considered.

### 3.3. APEX-AMI risk score

Data from 5745 STEMI patients enrolled in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial were used to identify independent predictors of 90-day mortality through Cox proportional hazards model [51]. Patients were enrolled in the study if primary PCI was planned and if high-risk electrocardiographic features (at least 2-mm ST elevation in two anterior lateral leads or at least 2-mm ST elevation in two inferior leads coupled with ST depression in two contiguous anterior leads for a total of 8 mm or more or a new left bundle branch block with at least 1-mm concordant ST elevation) were present. Variables identified as independent predictors of mortality included both clinical and electrocardiographic parameters (increasing age, low systolic blood pressure, advanced Killip classes, heart rate >70 bpm, anterior STEMI, sum of total ST-segment deviations). A simple nomogram useful for score calculation has been provided (Figure 5). The model had good performance (c-statistic of 0.82) and was internally validated through bootstrap sample analysis (c-statistic 0.81). A score value below 80 points identified STEMI patients with low risk of mortality (below 5%).

In the same group of patients, the authors also found that among previous identified predictors of mortality in the APEX-AMI score, the relative importance of heart rate, Killip class and creatinine declined progressively over time whereas markers of coronary reperfusion and in-hospital events (shock, congestive heart failure) became increasingly influential. They also identified a changing pattern of risk categorization during the hospitalization with the proportion of low-risk patients (<1.1% 90-day mortality) increasing from 20% to 49% during in-hospital stay. These findings highlight the dynamic nature of risk in STEMI patients and underline the need for correct timing and appropriate methodology of risk categorization in this group of patients.

As a major limitation, the score has been poorly investigated in the literature and external validation is missing. However, broader inclusion criteria in the APEX-AMI trial confer a high clinical validity to the score.

### 3.4. Zwolle risk score

The Zwolle risk score is a risk-scoring tool developed in a large group of unselected STEMI patients treated by primary angioplasty [10]. The model is able to identify patients at low-risk of 30-day adverse clinical events and is appropriate for the identification of patients that could be discharged after 48–72 h of in-hospital stay. Patients with a score value ≤3 had indeed a low risk of early adverse events (0.1% mortality at 2 days and 0.2% between 2 and 10 days) and the predictive ability of the model was also stable at 30-days and at 1-year with excellent survival in this group of patients. In a cost-effectiveness analysis, the authors showed that avoiding an early discharge strategy in patients with a score value ≤3 would save 1 life per 1097 low-risk patients at an additional cost of €194,933.33. The value of Zwolle risk score for the selection of low-risk STEMI patients that could be early discharged has been confirmed in three recently reported randomized trials [7,52,53].

### 3.5. Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get With the Guidelines (GWTG) model

Based on the large ACTION Registry–GWTG database (243,440 patients from 655 hospitals), the ACTION-GWTG model was
recently developed to predict in-hospital mortality in patients with AMI (both STEMI and NSTEMI) admitted between January 2012 and December 2013 [54]. The score was obtained according to a parsimonious approach based on a multivariate hierarchical logistic regression model. After selection, nine variables were independently associated with in-hospital mortality, including age, heart rate and systolic blood pressure at presentation, diagnosis of STEMI, presentation after cardiac arrest, in cardiogenic shock or heart failure, creatinine clearance, and troponin ratio. The overall model predictive ability was excellent (c-statistic of 0.88 both in the derivation and validation cohort). In the subgroup of patients with STEMI, the performance of the model was unchanged (c-statistic of 0.895). Of note, a large proportion of STEMI patients in this study were managed invasively (primary PCI in 88.4% of patients). The multivariate model was then used to derive a clinically useful integer score and in-hospital mortality ranged from 0.4% for patients with a score value below 30% to 49.5% in patients with a score >59. The ACTION–GWTG model has different strengths including the large number of unselected patients used for the derivation and validation of the score. Moreover, the risk model has been derived in a contemporary series of patients treated according to current guidelines and technologies. However, the score should be used for the prediction of in-hospital (very early) death risk and currently lacks of external validation.

4. Risk scores integrating angiographic stratification by the SYNTAX score or related iterations

The SYNTAX score is a largely adopted angiographic tool that evaluates and quantifies the complexity and extension of coronary artery disease. Firstly introduced within the landmark SYNTAX trial, it is routinely used in clinical practice to guide the decision-making process between coronary artery bypass surgery (CABG) and PCI. The SYNTAX score (SX score) was originally adopted and validated in stable coronary artery disease (CAD) and patients with STEMI were not included in the SYNTAX trial [55]. However, validation of the SX score in STEMI patients represented an appealing concept since quantification of CAD complexity could better reflect the amount of jeopardized myocardium after an acute ischemic insult that could potentially impact on prognosis.

4.1. MI SYNTAX score

Magro et al. sought to explore the prognostic ability of the SX score in STEMI patients undergoing primary PCI (MI SYNTAX score) [22]. They found that calculation of the SX score after initial angiography (SX score I) generated an higher SX score, due to the higher SX value assigned to an occluded artery, as compared to SX score assessment after wiring (SX score II) but the predictive value of the two different calculation modalities was similar. Indeed, the authors found that the incidence of major adverse cardiac events (MACE), defined as the composite endpoint of repeat MI, target vessel revascularization and mortality, was more frequently seen in patients in the highest SX score I and II tertiles. The MI Syntax score was further validated in 1132 STEMI patients enrolled in the COMFORTABLE AMI trial. Patients in the highest SX score tertile (SX score ≥19) had a significantly increased incidence of patient- (death, myocardial infarction, any revascularization) and device-oriented (cardiac death, target-vessel MI, target lesion revascularization) adverse events. Moreover, addition of the MI Syntax score significantly improved the c-statistic of the TIMI risk score for the prediction of patient- and device-oriented MACEs (from 0.63 to 0.69 and from 0.65 to 0.70, respectively).
The predictive ability of the SX score has been successively refined with the integration of clinical variables into the anatomical score (i.e. global risk stratification, SYNTAX Score II) [56,57]. Usefulness of these combined clinical–angiographic scores has not been widely explored in STEMI patients. Recently, Cetinkal et al. [58] showed that the clinical SX (cSX) score, calculated by multiplying the anatomically derived SYNTAX score (Sx) by the modified age, creatinine, and ejection fraction score, was useful to stratify prognosis in STEMI patients. The authors found that a cSX score >26 was an independent predictor for all-cause mortality, myocardial infarction, and cerebrovascular adverse events. The score had good discrimination with a c-statistic of 0.66 (better than SX score alone).

4.2. PAMI and SYNTAX score

Garg et al. recently proposed an integration of the PAMI risk score with the SX score into the PAMI-SX score to improve the prognostic ability of both clinical and angiographic risk scores [59]. The authors explored the predictive ability for 1-year clinical adverse outcomes including all-cause death, MACEs (composite of death, re-infarction and target vessel revascularization) and stent thrombosis. As expected, patients in the highest SX score tertile (SX score > 16) had a higher incidence of adverse clinical outcomes. The combination of the SX and PAMI scores yielded to a net reclassification improvement of 15.7% and 4.6% for mortality and MACEs, respectively. Interestingly, the authors looked at the optimal methodology to evaluate the SX score in STEMI patients. Due to improved predictive ability, the authors found that the preferred strategy is to calculate SX score before any intervention (e.g. rating an infarct related artery as occluded) and not immediately before stenting. The PAMI-SX score was retrospectively analyzed, a validation cohort was not included in the study design and further validation data in the literature are awaited.

4.3. Residual SX score

Invasive management of STEMI patients with multivessel disease is a controversial and debated topic in the literature [60]. Whether benefits of timely performed primary PCI of the culprit artery are unquestionable, timing and modality of revascularization for bystander lesions still remains unclear. However, a larger extent of CAD represents a marker of increased risk in STEMI patients. Along this line, the prognostic impact of residual CAD as assessed by residual SX (rSX) Score, after a simultaneous or staged PCI for non-culprit lesions, has been recently identified. Loutfi et al. [61] found that a rSX score >8 was an independent predictor of major cardiac and cerebrovascular adverse events at one year in STEMI patients. Similarly, Khan et al. also found that a rSX score ≥8 was an independent predictor of in-hospital death, congestive heart failure, recurrent MI and bleeding.

5. Laboratory refinement in predictive ability

Different laboratory markers have been related to the extent of myocardial injury after STEMI (i.e. natriuretic peptides and troponins) [62,63]. The evaluation of laboratory parameters may be useful and of incremental value for the prognostic stratification of STEMI patients [64,65].

Natriuretic peptides (NPs) have been largely adopted for the diagnosis, therapeutic management and prognostic stratification of patients with heart failure. However, NPs release from myocardial cells is also triggered by myocardial ischemia and infarction [63]. Increased NPs blood levels in patients with STEMI have been found to be strongly and independently associated with mortality [66]. The evaluation of the N-terminal pro-brain NP (NT Pro-BNP) has proven to improve the overall performance of different risk scoring systems in STEMI patients. Schellings et al. [67] showed that the predictive ability of the Zwolle risk score was significantly improved by the simultaneous evaluation of NT pro-BNP values. A Zwolle score ≤2 combined with NT pro-BNP values <200 pg/ml had indeed an excellent discrimination (area under the curve for 30-day mortality of 0.94) for the selection of a low-risk population (1.3% incidence of MACEs at follow-up). The evaluation of B-type natriuretic peptide on admission also improved the discriminative power of the TIMI risk score by adding significant prognostic information (AUC from 0.852 to 0.918); A TIMI risk score <4 and BNP levels <331 pg/ml identified indeed a low risk cohort with 0% mortality at follow-up [64]. Finally, Parenica et al. [68] recently confirmed that NP assessment added incremental prognostic information to clinical GRACE score for combined risk estimation of one-year mortality and hospitalization for acute heart failure.

Additional laboratory parameters, including creatinine clearance and hemoglobin concentration evaluated at presentation, have been related to adverse prognosis in STEMI patients [65]. Indeed, hemoglobin levels <15.0 g/dl and creatinine clearance <100 ml/min were significantly and independently related to increased mortality at follow-up. Combination of the two laboratory parameters into a Laboratory Index (LI) significantly improved the predictive ability of the TIMI risk score (c-statistic from 0.755 to 0.789, p < 0.001) when a simultaneous evaluation was performed. In addition, increasing levels of the platelet to lymphocyte ratio were identified as a predictors of in-hospital and long-term MACE in a large color of STEMI patients treated by primary PCI [69].

Finally, two multiple biomarker risk-scoring algorithms have been developed in STEMI patients. The first score integrates glucose blood levels, estimated glomerular filtration rate and N-terminal pro-brain natriuretic peptide levels (see Table 4). A score value ≤4 identified a low risk population with a mortality rate at long-term follow-up of 5.8% [70]. The second score [71] was derived using blood sample assays of 1258 patients included in the clopidogrel as adjunctive reperfusion therapy-thrombolysis in myocardial infarction 28 (CLARITY-TIMI 28) trial. The predicted event of interest by the model is the combined endpoint of cardiovascular mortality and heart failure at 30-days. After selection, three biomarkers were identified as independent predictors of the composite endpoint, including: suppressor of tumorigenicity 2 (OR adjusted, 2.87; 1.61–5.12), troponin T (OR adjusted 2.34; 1.09–5.01 and 4.13, 1.85–9.20, for intermediate and high levels, respectively) and myeloperoxidase (OR adjusted 2.49; 1.04–5.96). When assessed simultaneously, the multmarker...
risk score significantly improved the c-statistic of the TIMI STEMI risk score (area under the curve from 0.75 [95% CI, 0.69–0.81] to 0.82 [0.78–0.87]; p = 0.001).

6. Expert commentary

In recent years, progresses in the pharmacological and invasive management of STEMI patients conveyed an increased survival with parallel reduction of morbidity following the acute event. However, a sizeable proportion of patients still remain at substantial risk of experiencing adverse events during follow-up. The identification and quantification of a patient’s risk profile is therefore of paramount importance to guide medical management such as the duration and intensity of in-hospital care together with proper optimization of medical therapy during follow-up. Risk scores may provide daily aids in clinical practice to achieve the goal of proper risk estimation in STEMI patients. However, a granulation of risk scoring algorithms has been observed in medical literature. Indeed, several risk scores have been developed and validated according to treatment strategies, timing of presentation and outcome of interest. The current review systematically reported and critically assessed strengths and limitations of current landscape of risk stratification in STEMI patients. Risk stratification according to timing of assessment, treatment modality and outcome of interest is highly advisable in this group of patients to identify optimal treatment strategies, proper length of hospital stay and correct timing of follow-up. Evaluation of laboratory biomarkers could be of added value and should be recommended to improve the predictive ability of available risk scores. In our opinion, applying the appropriate score, customized on patients’ profile and clinical characteristics at presentation or during the hospitalization, might prove useful to inform and support medical decision-making whilst improving the overall quality of care provided to STEMI patients. As reported earlier, timely application of a properly identified risk score is a crucial step to preserve and strengthen the reliability and clinical validity of risk stratification tools in daily practice. Accordingly, Figure 6 shows a suggested flowchart for the selection of the most appropriate score in a prototypical STEMI patient based on both the timing of assessment and the received treatment. Due to the extensive validation obtained in the literature, the TIMI risk score and/or the GRACE risk score should be used for risk estimation at clinical presentation. The use of these scores is endorsed by the international guidelines for early risk stratification in STEMI patients. The TIMI risk score is relatively simple to recall and this could favor the bedside application of the score whilst the GRACE score requires an online/application-based calculator. Currently, a growing use of handheld personal computers in daily clinical practice may overcome such computational limitations. In addition to the GRACE and TIMI risk scores, the SRI at presentation is a simple and powerful tool to meaningfully quantify the hemodynamic status and the global clinical risk profile of STEMI patients. However, the use of SRI should be avoided in older patients (>65 years). In keeping with the time changing nature of risk in STEMI, we carefully recommend a detailed re-evaluation of patients’ risk during the hospitalization course. In this context, it is very important to select the proper risk stratification tools based on the received treatment. The ACTION-GWGT model looks as a promising tool for the estimation of in-hospital mortality being based on the largest and most contemporary series of STEMI patients and due to the strong statistical framework used for derivation of the score. Finally, we consider the Zwolle risk score before discharge as a reliable tool that should be used for prognostication and the identification of proper timing for a safe discharge strategy. Indeed, small-sized randomized clinical trials have recently provided confirmatory data on the clinical reliability of the Zwolle risk score in STEMI patients.

7. Five-year view

Further validation of the statistical and clinical performance for available risk scores has to be confirmed in the next 5-year. A wider reporting of the prognostic predictive ability is warranted to move risk-based medical care from the academic scenario to the daily clinical context. Moreover, improvement and cost-effectiveness of medical management strategies in STEMI patients according to patients’ risk profile should be further investigated.

Key issues

- ST-elevation myocardial infarction (STEMI) is a complex clinical scenario that requires immediate diagnosis, rapid therapeutic management and early risk stratification.
- Risk scores serve as helpful aids in daily practice and many of them are endorsed by clinical practice guidelines to tailor decisions for individual patients.
- Many risk scores have been built and validated in the setting of STEMI to get useful prognostic information and facilitate a better allocation of health resources.
- Different aspects should be considered for the selection of proper risk score, including: clinical presentation, patient profile, timing of risk assessment, outcome evaluated by the specific score and temporal interval between risk assessment and events prognostication.
- Improvement and cost-effectiveness of medical management strategies according to patients’ risk profile should be further investigated in next years.

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Figure 6. Picture showing a classification system for STEMI risk scores based on timing of assessment and therapeutic strategies. Scores in bold format are suitable for routine clinical use.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (†) to readers.


• A landmark paper reporting an important prognostic stratification tool in STEMI patients.


• An important analysis of mortality trends after myocardial infarction.

A risk model from a large and contemporary series of patients with acute myocardial infarction.


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