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A new score based on the PEGASUS-TIMI 54 criteria for risk stratification of patients with acute myocardial infarction☆

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ABSTRACT

Background: Acute myocardial infarction (AMI) patients are at increased risk of death and recurrent ischemic events. We aimed to elaborate a risk score, based on the PEGASUS-TIMI 54 criteria, to predict mortality and non-fatal AMI in AMI patients.
Methods: We retrospectively analyzed two prospectively collected AMI cohorts. We calculated a cut-off for the developed score and investigated its 1-year prognostic power in the derivation cohort ($n = 1257$). We externally validated our score in 913 AMI patients with a longer follow-up.
Results: In the derivation cohort, the area under the curve of the score for the primary endpoint (1-year death and non-fatal AMI) was 0.70 (95% CI 0.65–0.76; $P < 0.0001$) and a cut-off of 6 was identified. The primary endpoint incidence in patients with a score above and below the cut-off was 12% and 3% ($P < 0.001$) in the derivation cohort and 16% and 6% in the validation cohort ($P < 0.001$). At multivariate analysis, the HR for the primary endpoint associated with a score ≥ 6 was 4.45 ($P < 0.0001$) in the derivation cohort and 2.86 ($P < 0.0001$) in the validation cohort. One-year major bleeding rate was low (<0.2% overall) and similar between risk groups. The prognostic performance of the score cut-off persisted beyond the first year after AMI in the validation cohort, maintaining a similar risk for death and non-fatal AMI (HR 3) at every following year.
Conclusions: Our score, based on the PEGASUS-TIMI 54 criteria, may identify AMI patients at high risk of recurrent ischemic events, who might benefit from thorough preventive strategies.

1. Introduction

Patients with acute myocardial infarction (AMI) are at increased risk of death and recurrent ischemic events after hospital discharge, despite current optimal medical therapy [1,2]. The probability of recurrent ischemic events is higher in the first year after AMI, and it continues in the subsequent years, in parallel with the number of cardiovascular risk factors [1–4]. Therefore, current practice guidelines strongly encourage the early assessment of ischemic risk in post-AMI patients, in order to identify those who may benefit from a prolonged dual antiplatelet therapy [5]. To this end, several scoring systems have been proposed [6–13]. However, most scores were developed for patients undergoing percutaneous coronary intervention (PCI), including mostly elective procedures [7,8]. Moreover, nearly all failed to be implemented in everyday clinical practice, probably because of the perceived complexity due to the large number of incorporated variables [6–13].

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial was the first study that prospectively focused on patients with prior (1 to 3 years) AMI and at least one additional risk factor [14]. This trial demonstrated that the addition of the $P2Y_{12}$ ticagrelor to low-dose aspirin reduces long-term ischemic risk in these patients. The reduction in ischemic risk was associated with an increase in major bleeding; therefore, the identification of AMI patients who may derive the greatest benefit from a long-term dual antiplatelet therapy still remains an open issue. Noteworthy, the prevalence of AMI patients meeting the PEGASUS-TIMI 54 criteria is very high in clinical practice, reaching almost 80% [15]. Thus, we hypothesize that using these criteria in a more comprehensive risk score, rather than considering them as

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single and/or binary variables, may help physicians to better discriminate AMI patients with a worse prognosis. Moreover, the PEGASUS-TIMI 54 criteria can be easily collected during the index hospitalization, possibly allowing timely patients' risk stratification and optimization of long-term secondary prevention strategies at an earlier stage of time than the one explored in the trial [14].

The aim of the present study was to assess whether a new risk score derived from the PEGASUS-TIMI 54 criteria may be able to predict 1-year mortality and re-hospitalization for non-fatal AMI in a real-world population of consecutive AMI patients. The score was externally validated with a longer follow-up in a similar set of AMI patients admitted to another hospital.

2. Methods

2.1. Study population

This retrospective analysis was based on two prospectively enrolled cohorts of consecutive AMI patients who were admitted to the Centro Cardiologico Monzino, Milan, Italy between June 1st, 2010 and June 30th, 2015, and the Spedali Civili Hospital, University of Brescia, Italy between June 4th, 2010 and June 30th, 2015. The former group was the derivation cohort for the development of the risk score, while the latter group was used as a validation set. We excluded patients who died during the index hospitalization, those with a life expectancy < 1 year, and those lost to follow-up. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The Ethical Committees (R523/CCM 541) approved the study, and all patients gave written informed consent.

2.2. Study protocol

All AMI patients were treated during hospital stay and after discharge according to the current standards of care recommended by published guidelines. Demographical, clinical, biochemical, echocardiography, and angiography data were obtained in the two cohorts, along with drug therapy at hospital discharge. The presence of the PEGASUS-TIMI 54 criteria (at least 50 years of age, and one of the following additional high-risk features: age ≥ 65 years, diabetes mellitus requiring medication, prior AMI, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance < 60 ml/min) was assessed during hospital stay in all patients [14]. Moreover, the Thrombolysis in Myocardial Infarction (TIMI) for non-ST-elevation myocardial infarction patients [16] and for ST-elevation myocardial patients [17], the Global Registry of Acute Coronary Events (GRACE) [18], and the DAPT scores [8] were computed in all patients of the derivation cohort, in order to compare their predictive accuracy for the primary endpoint with that of our score.

After hospital discharge, all patients were followed-up for at least one year. Follow-up data were obtained mainly through regularly scheduled outpatient visits and, in a minority of cases, through telephone interviews performed by dedicated medical personnel.

The primary endpoint of the study was the composite of mortality and re-hospitalization for non-fatal AMI at 1-year follow-up. A risk score for this endpoint, based on the PEGASUS-TIMI 54 criteria, was developed in the derivation cohort and then tested in the validation cohort, both at one year and at a longer follow-up. One-year mortality and re-hospitalization for non-fatal AMI, considered separately, and major bleeding, defined as fatal bleeding, the need for blood transfusion, or hemorrhagic stroke, were considered as secondary endpoints.

2.3. Statistical analysis

A sample size of 1.100 patients was calculated for the derivation cohort under the following assumptions: 6% mortality and re-hospitalization for AMI at one year [19] with 3% and 9% incidence (Hazard ratio [HR] = 3) in patients with risk scores below and above the identified cut-off value, respectively. The sample size allowed a 90% statistical power in assessing a significant difference (alpha error of 0.05) in the primary endpoint between the two groups. Based on the derivation cohort data (6% overall incidence of the primary endpoint, with an observed 3% and 12% incidence in patients with scores below and above the cut-off value, respectively), a sample size of 900 patients for the validation cohort allowed a 95% statistical power in assessing significantly different (alpha error of 0.05) primary endpoint between the two groups.

Continuous variables are presented as mean ± standard deviation. Non-normally distributed variables are presented as median and interquartile ranges, and categorical variables as absolute numbers and percentages. Comparisons between groups were performed using unpaired *t*-test for normally distributed variables and Wilcoxon Rank-Sum test for non-normally distributed variables. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate.

We evaluated in the derivation cohort HR with 95% confidence intervals (CI) of each PEGASUS-TIMI 54 criterion for the primary endpoint, using Cox regression analysis. For each item, HR was converted to the nearest integer number; the sum of the integers gave a risk score value. Receiver Operating Characteristic (ROC) curve was used to measure the ability of the risk score to predict the primary endpoint and to compare the area under the curve (AUC) of our score with the AUC associated with the presence of at least one PEGASUS-TIMI 54 criterion. Comparisons were performed as recommended by DeLong et al. [20]. Moreover, we calculated a cut-off value for our risk score that was able to maximize the sum of sensitivity and specificity (Jouden method).

The score was then evaluated in the validation cohort. The rate of the primary endpoint in patients with a risk score below and above the cut-off value was compared within each cohort. The association between the risk score above the cut-off value and the primary and secondary endpoints was assessed in both cohorts by Cox regression analysis. Moreover, the HRs for mortality and non-fatal AMI associated with a score above the cut-off value were investigated in the validation cohort every year after the first year of follow-up, up to 7 years. The consistency of the primary endpoint risk associated with a score above the cut-off value was explored in 8 pre-specified subgroups by pooling together the two cohorts.

Kaplan-Meier analysis was employed to generate time-to-event curves for primary and secondary endpoints stratified according to the risk score cut-off value. Log-rank test was used to compare strata. Landmark analysis was performed after 1-year to explore the possible different impact of our score on early and late outcomes. Finally, net reclassification improvement (NRI) was used to compare the prognostic value of our score with those of the DAPT, TIMI, and GRACE scores.

All tests were two-sided, and a *P* value of <0.05 was required for statistical significance. Statistical analysis was performed using the SAS software package (Version 9.4 SAS Institute Inc., Cary, NC). Reclassification statistics were assessed with the SAS macros published by Cook and Ridker [21].

3. Results

The derivation cohort included 1257 consecutive AMI patients (553 ST-segment elevation AMI and 704 non-ST-segment elevation AMI; mean age 67 ± 12 years, 923 men) (Supplemental Fig. 1). Out of them, 941 (75%) had at least 1 PEGASUS-TIMI 54 criterion. All PEGASUS-TIMI 54 criteria independently predicted the primary endpoint. By converting HR of each of these variables to its closest integer, we obtained a maximum risk score of 13 (Table 1). The AUC of the score for prediction of the primary endpoint in the derivation cohort was 0.70 (95% CI 0.65–0.76; $P < 0.0001$). The AUC value was significantly higher than that associated with at least one PEGASUS-TIMI 54 criterion (AUC 0.58 [95% CI 0.54–0.61; $P = 0.02$]; $P < 0.001$ for comparison) and than those associated with the most widely used risk scores (Supplemental Table 1). In particular, at reclassification analysis, our score allowed a proper reclassification of 30–40% of patients when compared to the other risk scores.

The cut-off value of our score maximizing sensitivity and specificity for primary endpoint prediction was 6 (sensitivity 67%, specificity 70%), with 404 (32%) and 853 (68%) patients above and below this threshold, respectively. The primary endpoint incidence in patients with a score above and below the cut-off was 12% and 3%, respectively ($P < 0.001$).

The clinical characteristics and 1-year outcomes of patients stratified according to the risk score cut-off are shown in Supplemental Table 2. Patients with a risk score above the cut-off had significantly worse 1-year event-free survival curves than those with a score < 6. This was observed when the primary endpoint (Fig. 1, Panel A) or its single components were considered (Supplemental Fig. 2). The incidence of major bleeding was low and not significantly different between patients with a score ≥ 6 or < 6 (0.5% vs. 0%; $P = 0.11$).

The validation cohort included 913 consecutive AMI patients (269 ST-segment elevation AMI and 644 non-ST-segment elevation AMI; mean age 67 ± 11 years, 708 men) (Supplemental Fig. 3). The baseline

Table 1
Hazard Ratio and 95% Confidence Intervals for each PEGASUS-TIMI 54 criterion in the derivation cohort.

	HR	95% CI	*P* value	Weighted score
Age > 65 years	2.04	1.24–3.36	0.005	2
eGFR<60 ml/min/1.73m^2	2.49	1.55–4.00	0.0002	2
Prior AMI	4.21	2.66–6.65	<0.0001	4
Multi-vessel CAD	3.34	1.98–5.62	<0.0001	3
Diabetes mellitus	1.78	1.09–2.89	0.02	2
Maximum score				13

AMI = acute myocardial infarction; CAD = coronary artery disease; CI = confidence intervals; eGFR = estimated glomerular filtration rate; HR = hazard ratio.

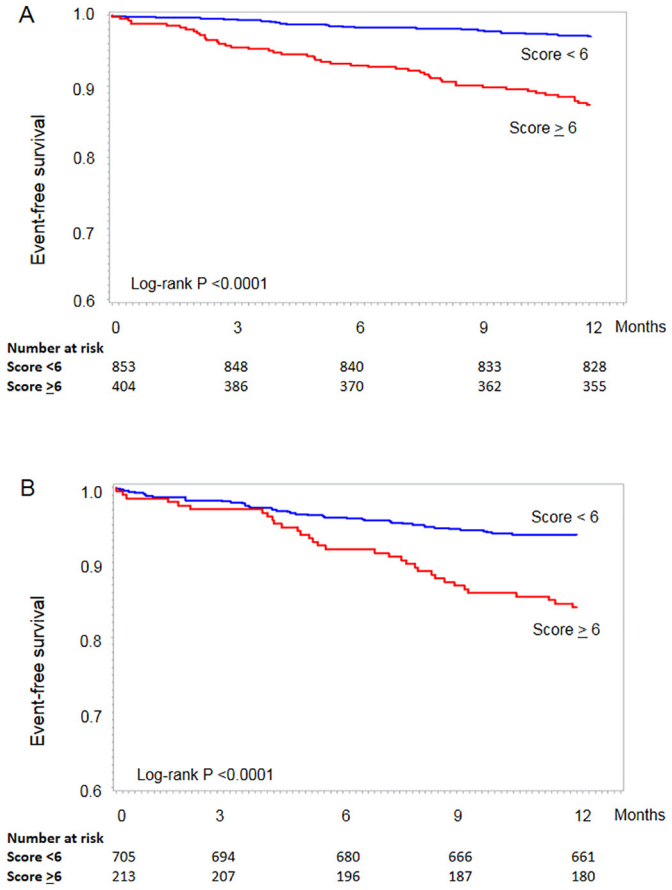

Fig. 1. Kaplan-Meier curve analysis stratified according to the risk score cut-off value (above and below 6) for the primary endpoint (1-year mortality and non-fatal acute myocardial infarction) in the derivation (*Panel A*) and validation (*Panel B*) cohorts.

clinical characteristics and 1-year outcomes of patients with or without a risk score ≥ 6 in the validation subset are shown in Supplemental Table 3. The distribution of the PEGASUS-TIMI 54 criteria, as well as their corresponding primary endpoint rates, were parallel in the derivation and validation cohorts (Supplemental Fig. 4). The AUC of the score for the prediction of the primary endpoint in the validation cohort was 0.68 (95% CI 0.64–0.75, $P < 0.001$; $P = 0.47$ for comparison with the derivation cohort). The Kaplan-Meier curves for the primary endpoint in the validation cohort patients with a risk score >6 and <6 are shown in Fig. 1 (Panel B), while those of its components considered separately are presented in Supplemental Fig. 5.

Fig. 2 reports HR for the primary endpoint, 1-year mortality, and 1-year non-fatal AMI associated with a risk score ≥ 6 in the derivation and validation cohorts. When the two cohorts were combined, a score ≥ 6 showed a significantly increased risk for the primary endpoint in major subgroups (Supplemental Fig. 6).

As observed in the derivation cohort, the 1-year major bleeding rate in the validation set was low and similar between patients with a risk score ≥ 6 or <6 (0% vs. 0.4%; $P = 0.12$).

When the prognostic prediction of our cut-off value was assessed in the validation cohort at a longer follow-up (median 1496 [970–2026] days), a similar power was observed (Fig. 3).

4. Discussion

This study showed that the risk of death and recurrent non-fatal AMI is high in the first year after AMI, and that it persists in the following years. We demonstrated that such a persistent ischemic risk can be early predicted by a simple score based on the PEGASUS-TIMI 54 criteria.

The recurrence of ischemic events after AMI has diminished over the last years due to improvements in drug therapy and interventional techniques [22,23]. Nevertheless, patients who have had AMI still are at increased risk of recurring cardiovascular events in the following years, as clearly reported in recent registries and subgroup analyses of prior trials [1–4]. Notably, AMI and death are the most frequent recurrent events [1,2]. Thus, there is an impelling clinical need for the early identification of AMI patients at high risk of future cardiovascular events, who may benefit from the optimization of long-term secondary prevention strategies, including prolonged dual antiplatelet therapy.

The PEGASUS-TIMI 54 trial was the first study that prospectively enrolled patients with a prior AMI and at least one additional risk factor [14]. The trial demonstrated that adding ticagrelor to low-dose aspirin reduces long-term ischemic risk at the expense of an increase in major bleeding. However, when the PEGASUS-TIMI 54 inclusion criteria are strictly applied to everyday clinical practice, most AMI patients result to be at high ischemic risk [15,24]. It follows that a further risk stratification should be made in order to identify the AMI patients, among those satisfying the PEGASUS-TIMI 54 criteria, who are at heightened risk of future adverse events. Importantly, this stratification can be carried

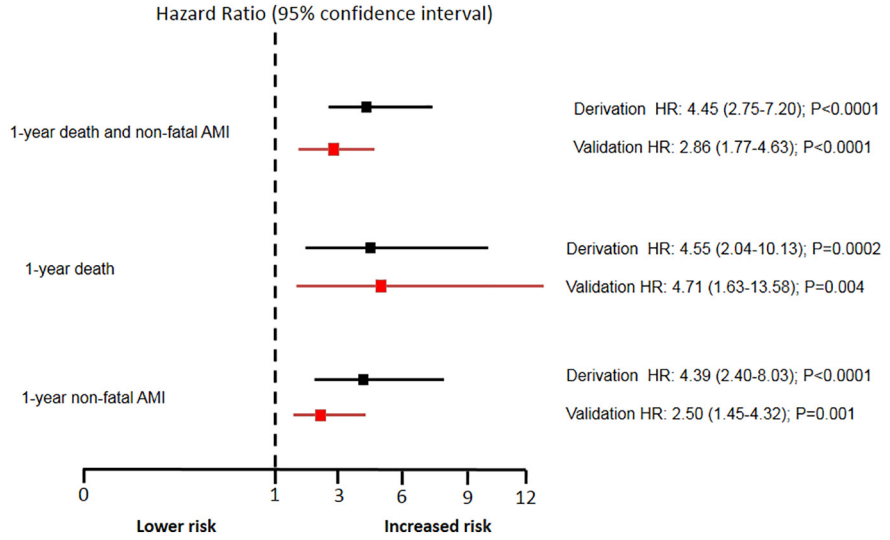

Fig. 2. Primary endpoint, 1-year mortality, and 1-year non-fatal acute myocardial infarction hazard ratios (HR) and 95% confidence intervals (CI) associated with a risk score ≥ 6 in the derivation and validation cohorts.

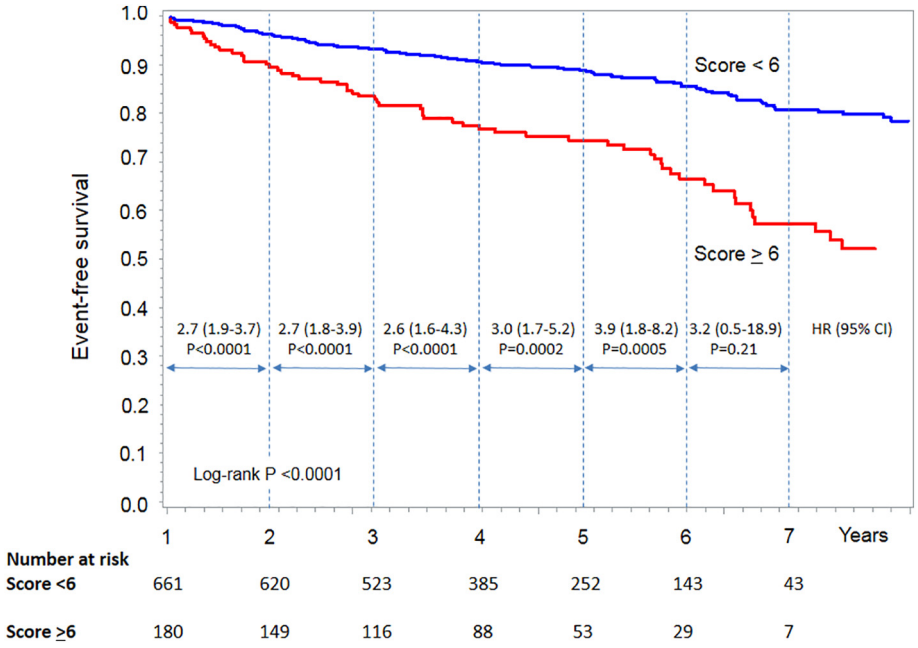

Fig. 3. One-year landmark curve analysis stratified according to the risk score cut-off value (above and below 6) for long-term mortality and recurrent non-fatal acute myocardial infarction in the validation cohort. The values shown inside the figure refer to hazard ratios (HR) and 95% confidence intervals (CI) associated with a risk score ≥ 6 at every following year.

out earlier than in the PEGASUS-TIMI 54 trial, in order to also include the ischemic risk during the first years after the index event. Therefore, we developed and validated a clinical score, based on the PEGASUS-TIMI 54 criteria, for the prediction of 1-year death and non-fatal AMI in patients admitted with AMI.

Our novel score showed reasonable discrimination in two independent cohorts - the derivation and the validation cohorts. Moreover, it showed a better predictive accuracy than the presence of at least one PEGASUS-TIMI 54 criterion and the TIMI, GRACE, and DAPT scores. Patients in the two cohorts with a clinical predictive score ≥ 6 had an absolute increase in 1-year death and non-fatal AMI risk that was 3–4 times higher than that of patients with a score below this threshold. Our findings were not unexpected, as they confirm the relevance of well-known risk factors associated with recurrent ischemic events [1–5], further emphasizing their independent and synergistic prognostic value.

Ischemic events in our validation cohort went on occurring for several years after the qualifying AMI, without any signal of risk reduction. Again, this was particularly true in high-risk patients, as those identified by our score cut-off, out of whom almost 50% experienced death or recurrent non-fatal AMI at a median 4-year follow-up. The prognostic performance of our score cut-off persisted also beyond the first year after the index event, maintaining a similar risk every following year. This implies that our score can be useful to early stratify the long-term risk of AMI patients. Notably, a risk score ≥ 6 allowed to properly reclassify almost 20% of patients, when compared to a DAPT score ≥ 2, both in the first year and at a longer follow-up. In agreement with our findings, among 1592 consecutive patients with acute coronary syndromes treated with PCI and enrolled in the Responsiveness to Clopidogrel and Stent Thrombosis 2-ACS (RECLOSE 2-ACS) study [15], the odds ratios associated to each PEGASUS-TIMI 54 criterion for adverse clinical events occurring 1 to 4 years after the index event were similar and around 2. Moreover, the risk progressively rose with the increase of risk factors, with each additional variable being associated with a 66% relative risk increase at long-term follow-up.

Recently, the Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients (PARIS) registry [7], the DAPT study [8], and the China Patient-Centered Evaluative Assessment of Cardiac Events Prospective Study of AMI (China PEACE Prospective AMI study) [13] came up with three scores for predicting ischemic risk in patients undergoing PCI, mostly elective procedures [7,8], or in patients with AMI, mostly conservatively managed [13]. However, differently from the aforementioned studies, we evaluated AMI patients only, with the great majority of them undergoing coronary revascularization. Moreover, our patients were enrolled without exclusion criteria; thus, they were representative of a real-world population. Additionally, in our study, the predominant antiplatelet agents were aspirin plus prasugrel or ticagrelor, which represent the current standard of AMI care. Furthermore, unlike these scores, which are complex and include several variables, ours is based on 5 simple items, and it may be more easily applicable on a regular basis in clinical practice [7,8,11–13].

We found no significant difference in major bleeding rates between risk groups during the first year after AMI, when most patients receive dual antiplatelet therapy. Of note, our major bleeding rate was very low (0.2% and 0.1% in the derivation and validation cohorts, respectively). This may be due, at least in part, to the fact that we considered fatal and life-threatening events only, i.e. bleeding requiring transfusion and hemorrhagic stroke. The incidence of major bleeding events in our study is similar to that reported by large trials and registries in patients with AMI undergoing PCI and treated with dual antiplatelet therapy. Indeed, these studies reported a rate of fatal bleeding within the first year after AMI always below 1% [22,23]. The very low rate of major bleeding in our patients highlights that ischemic hazard outweighs bleeding risk in the first year after AMI (Supplemental Fig. 7).

Our findings may have some relevant clinical implications. Our risk score may be applied during hospital stay to early select AMI patients who can derive the greatest benefit from a closer clinical follow-up, a more intensive therapy, and a more rigorous risk factor control. Early decision-making is especially desirable for the prevention of further ischemic events, considering that the first years after AMI are those at highest risk of recurrence [1–4,14]. In particular, although several randomized trials and meta-analyses comparing different dual antiplatelet therapy durations have been performed, the optimal duration for a given AMI patient still has to be determined in everyday clinical practice [5,25–28]. Thus, if confirmed, our findings have potential implications for customizing the duration of dual antiplatelet therapy. Indeed, future studies and/or retrospective analyses of randomized trials should investigate the clinical benefit of a prolonged dual antiplatelet therapy in patients with a score above the cut-off identified by our study. Finally, the

ability of our score to identify AMI patients who are at high risk of future events may be useful for testing novel pharmacological and non-pharmacological preventive therapies.

4.1. Study limitations

Some limitations should be considered in interpreting our data. First, this study is a retrospective analysis of a prospective registry based on two cohorts in one country. Although the simplicity of the current score represents a strong advantage, further validation studies in AMI populations from different countries and undergoing different therapeutic strategies are necessary to confirm the reproducibility of our findings. Indeed, as an example, the DAPT score recently proved to have poor discrimination for ischemic risk when applied to a large population of Swedish patients [29], suggesting that risk scores might not be generalizable to all real-world populations. Second, we acknowledge that event discrimination in our score was moderate. However, it should be noted that the $CHAD_2DS_2$-VASc score has a pooled c-statics of approximately 0.68 for predicting ischemic stroke risk in non-anticoagulated patients. Nevertheless, it has a widespread use because of its user-friendliness and the simplicity of translating the results into patient management [28]. Third, our model may lack some predictors of ischemic events. However, the results of this study suggest that our score may be a simple bedside risk assessment tool easily employable in daily clinical practice, particularly when compared to previous scoring systems proposed in AMI [11,13,18]. Fourth, different coronary stents and antithrombotic agents were used. Yet, this corresponds to a "real-world" scenario where patients are treated with different antiplatelet drugs, anticoagulants, and stents according to clinical setting, operator choice, and drug/device availability. Fifth, no information was available regarding patients' adherence to treatment during follow-up. In particular, patients were considered to be on dual antiplatelet therapy according to the discharge treatment. Finally, the overall bleeding risk was probably underestimated as mild and moderate events where not collected.

4.2. Conclusions

We developed and validated a simple score based on the PEGASUS-TIMI 54 criteria for the prediction of death and non-fatal AMI in patients discharged after AMI. Our score may allow physicians to early identify patients who are at high risk of recurrent ischemic events and may benefit from thorough preventive strategies.

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Disclosures

None.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.142.

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