



Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: The BleeMACS score

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ABSTRACT

Background: Accurate 1-year bleeding risk estimation after hospital discharge for acute coronary syndrome (ACS) may help clinicians guide the type and duration of antithrombotic therapy. Currently there are no predictive models for this purpose. The aim of this study was to derive and validate a simple clinical tool for bedside risk estimation of 1-year post-discharge serious bleeding in ACS patients.

Methods: The risk score was derived and internally validated in the BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registry, an observational international registry involving 15,401 patients surviving admission for ACS and undergoing percutaneous coronary intervention (PCI) from 2003 to 2014, engaging 15 hospitals from 10 countries located in America, Europe and Asia. External validation was conducted in the SWEDEHEART population, with 96,239 ACS patients underwent PCI and 93,150 without PCI.

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Results: Seven independent predictors of bleeding were identified and included in the BleeMACS score: age, hypertension, vascular disease, history of bleeding, malignancy, creatinine and hemoglobin. The BleeMACS risk score exhibited a C-statistic value of 0.71 (95% CI 0.68–0.74) in the derivation cohort and 0.72 (95% CI 0.67–0.76) in the internal validation sample. In the SWEDEHEART external validation cohort, the C-statistic was 0.65 (95% CI 0.64–0.66) for PCI patients and 0.63 (95% CI 0.62–0.64) for non-PCI patients. The calibration was excellent in the derivation and validation cohorts.

Conclusions: The BleeMACS bleeding risk score is a simple tool useful for identifying those ACS patients at higher risk of serious 1-year post-discharge bleeding.

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1. Introduction

Dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 receptor inhibitor is the standard regimen to prevent atherothrombotic events in patients after acute coronary syndrome (ACS) [1], especially after percutaneous coronary intervention (PCI) with stenting [2]. In the current era, the clinical cardiologist has to face every day to two important issues when prescribing DAPT: Which P2Y12 inhibitor has to be associated with aspirin? And how long DAPT has to be prescribed [3]?

Because thrombotic risk is increased after ACS, guidelines recommend DAPT with the new more potent P2Y12 inhibitors (ticagrelor or prasugrel) [4]. There is no doubt that both prasugrel and ticagrelor are of choice—versus clopidogrel—in patients with not-high bleeding risk [5,6]. Regarding the duration of DAPT, the guidelines establish a reference standard of 12 months [4]. Recent evidence suggests that treatment with DAPT beyond the first year may be beneficial in selected groups of patients with low bleeding risk [7], particularly when the ischemic risk is high [8]. However, guidelines state that shorter DAPT regimens might be considered in patients deemed at high bleeding risk [4].

With this background, it is clear that bleeding risk has an important role as a limiting factor for the choice of the type of DAPT (clopidogrel versus ticagrelor/prasugrel) and for the selection of candidates for shorter DAPT regimens (<versus ≥12 months). With this study, we aimed to develop a simple risk prediction tool that would allow physicians to objectively estimate the bleeding risk within the first year after hospital discharge for an ACS.

2. Methods

2.1. Study design and population

The BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) is a retrospective, observational, multicenter cohort study involving 15,401 consecutive patients. BleeMACS inclusion and exclusion criteria, data collection, and variables have been described previously [9]. Briefly, eligible patients were all consecutive adult patients (≥18 years old) discharged with the definitive diagnosis of ACS and underwent in-hospital PCI, with data of follow-up during at least 1 year. Participants were recruited from 15 hospitals with different health care patterns, from North- and South-America (Canada and Brazil), Europe (Germany, Poland, Netherlands, Spain, Italy, and Greece), and Asia (China and Japan). Enrollment occurred from November 2003 through June 2014 (Supplementary data, pages 2–4: eText; eFig. 1).

The study complied with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [10]. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by each center ethical committee. The study was registered on ClinicalTrials.gov (NCT02466854).

2.2. Follow-up and outcomes

The primary endpoint of the BleeMACS study was to examine the bleeding risk within the first year after hospital discharge, in order to create a bleeding risk score to accurately stratify patients according to their risk of developing serious spontaneous bleeding. Serious spontaneous bleeding was defined as any intracranial bleeding or any other bleeding leading to hospitalization and/or red blood transfusion (≥1 unit), occurring within the first year after hospital discharge. Bleeding and/or red blood transfusions related to procedures or surgeries were not considered spontaneous bleeding and were not included in the present study.

Patients were systematically followed during 1 year to assess vital status and bleeding complications ascertained by trained research coordinators at each participating site. Data on vital status and information about bleeding were obtained from hospital and/or

administrative (vital statistics records, hospital discharge data, and emergency department data) data records, by contacting the patients or their relatives by phone, and/or by contacting the primary care physicians for additional information, when necessary. For patients treated for adverse events at other medical institutions, the medical records and discharge reports were systematically collected and reviewed.

2.3. Statistical analysis

Model development and risk score derivation.

The study population was randomly split into a derivation sample consisting of 70% of patients ($n = 10,750$), and an internal validation sample consisting of the remaining 30% of patients ($n = 4651$).

In the derivation cohort, using a competing risk framework for bleeding occurrence—accounting for death as a competing episode—, uni- and multivariate predictors of bleeding risk we assessed by Fine-Gray proportional hazards regression analysis [11]. For the multivariate analysis, we used covariates with $p < 0.10$ in the univariate analyses, in addition to sex regardless of its p -value. Fractional polynomials were used to determine the functional form of the quantitative covariates (i.e. age, baseline hemoglobin and creatinine), and plots of each continuous covariate versus rates of bleeding were reviewed to create cut points and categorizing continuous covariates when appropriate. The final fitted model included the main effect of the predictors, without any interaction term, adjusting for calendar year. There was a clustering effect present because patients admitted to the same country were represented by similar characteristics. As a result, the observations could not be considered independent. Accordingly, we adjusted the model estimates for the country-clustering effect by using a sandwich estimate of the variance–covariance matrix to obtain standard errors allowing to accommodate the clustering of observation on subjects.

The proportional hazard assumption was confirmed by testing for time-by-covariate interaction in the multivariate analysis, and the adjusted hazard of bleeding was expressed as subhazard ratios (sHR) with their corresponding 95% confidence intervals (95% CI).

The BleeMACS risk score was developed by assigning a weighted integer to each independent predictor in the basis of its coefficient in the final model [12]. A point score for each patient was calculated by summing the weighted integers. The risk equation for the predicted probability of bleeding: $1 - e^{-\text{baseline CIF of bleeding} \cdot \exp(P)}$, in which CIF was the cumulative incidence function and PI the prognostic index. Patients were classified further into quartiles of the BleeMACS risk score: Very low-risk (≤7 points; $n = 2873$ patients, 26.7%), low-risk (8 to 16 points; $n = 2785$ patients, 25.9%), moderate-risk (17 to 24 points; $n = 2120$ patients, 19.7%), and high-risk (≥25 points; $n = 2972$ patients, 27.6%). The adjusted rate of 1-year bleeding was calculated and reported as cumulative incidence function (CIF).

2.3.1. Risk score validation

The BleeMACS risk score was internally validated in 4651 patients randomly selected after dividing the BleeMACS population into two samples.

An external validation was performed using data from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, which has been described in detail previously [13]. In this registry, consecutive patients who underwent PCI ($n = 96,239$) and not ($n = 93,150$) during index hospitalization from 2003 to 2012 were included using the same inclusion and exclusion criteria as for the derivation cohort. Data about prior hospitalization due to bleeding was obtained from the National Patient Register and data about serious bleeding (TIMI major and minor) during index hospitalization was entered by the treating physician as part of the SWEDEHEART registry. The outcome (post-discharge serious bleeding) was defined as any bleeding resulting in hospitalization or blood transfusion within the first year after discharge according to the National Patient Register or SWEDEHEART. These events were not adjudicated. Date of death was obtained from the Swedish Population Register.

2.3.2. Risk score performance assessment

The performance of the BleeMACS bleeding risk score was tested by assessing its discrimination and calibration capacity in both BleeMACS derivation and internal validation cohort, and in the SWEDEHEART external validation dataset. Discrimination was evaluated by calculating the C statistic [14] using the function *c-index* of the R package *pec*. Calibration was assessed by comparing observed against predicted probability; calibration slopes, and $\times 2$ plus p -values of the Hosmer–Lemeshow test were calculated, as metrics of calibration. Clinical usefulness and net benefit were estimated with decision curve analysis [15].

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