Prediction of Post-Discharge Bleeding in Elderly Patients with Acute Coronary Syndromes: Insights from the BleeMACS Registry

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Abstract

Background A poor ability of recommended risk scores for predicting in-hospital bleeding has been reported in elderly patients with acute coronary syndromes (ACS). No study assessed the prediction of post-discharge bleeding in the elderly. The new BleeMACS score (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome), was designed to predict post-discharge bleeding in ACS patients. We aimed to assess the predictive ability of the BleeMACS score in elderly patients.

Methods We assessed the incidence and characteristics of severe bleeding after discharge in ACS patients aged $\geq$ 75 years. Bleeding was defined as any intracranial bleeding or bleeding leading to hospitalization and/or red blood transfusion, occurring within the first year after discharge. We assessed the predictive ability of the BleeMACS score according to age by Fine–Gray proportional hazards regression analysis, calculating receiver-operating characteristic (ROC) curves and the area under the ROC curves (AUC).

Keywords
- acute coronary syndromes
- elderly
- bleeding
- risk prediction

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Results The BleeMACS registry included 15,401 patients of whom 3,376/15,401 (21.9%) were aged ≥ 75 years. Elderly patients were more commonly treated with clopidogrel and less often treated with ticagrelor or prasugrel. Of 3,376 elderly patients, 190 (5.6%) experienced post-discharge bleeding. The incidence of bleeding was moderately higher in elderly patients (hazard ratio [HR], 2.31, 95% confidence interval [CI], 1.92–2.77). The predictive ability of the BleeMACS score was moderately lower in elderly patients (AUC, 0.652 vs. 0.691, $p = 0.001$).

Conclusion Elderly patients with ACS had a significantly higher incidence of post-discharge bleeding. Despite a lower predictive ability in older patients, the BleeMACS score exhibited an acceptable performance in these patients.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 receptor blocker is the standard regimen to prevent atherothrombotic events in patients after acute coronary syndromes (ACS).[1,2] Antiplatelet drugs decrease the rate of ischaemic events in patients with ACS, but with a significant increase in the rate of bleeding.[3] There is strong evidence about the association between bleeding complications and increased mortality in this scenario.[4] Therefore, bleeding risk is the limiting factor for the choice of the type and duration of DAPT after discharge in patients with ACS.

While several bleeding scores[5–7] have been developed and widely used for the prediction of in-hospital bleeding, little information exists about the prediction of bleeding after discharge in this setting. The BleeMACS registry[8] (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) was conducted to develop and validate a score to predict post-discharge bleeding in patients with ACS. This score exhibited a good ability for predicting serious bleeding 1 year after discharge in an extensive series of patients with ACS.

On the other hand, incidence of ACS increases with age, and it is particularly high in elderly patients.[9,10] These patients are at higher risk both for ischaemic and bleeding complications, prolonged hospital stay and increased consumption of health resources.[11] Elderly are poorly represented in clinical trials and registries from whom currently recommended bleeding risk scores were developed. In fact, a poorer predictive ability of these bleeding risk scores for predicting in-hospital bleeding has been reported in elderly patients with ACS.[12] To our knowledge, no study assessed the prediction of post-discharge bleeding in elderly patients with ACS.

Therefore, the aim of this sub-study was to analyse, in the BleeMACS database, the incidence and characteristics of bleeding complications after medical discharge according to age, and to assess the predictive ability of the BleeMACS score in elderly patients as compared with the younger population.

Methods

This study is a sub-analysis of the international multi-centre BleeMACS registry. Full study protocol has been already published.[13] In brief, the BleeMACS registry enrolled 15,401 consecutive patients undergoing percutaneous coronary intervention (PCI) for ACS, including ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) and unstable angina (UA). Recruitment was conducted between 2003 and 2014 in 15 hospital centres from 10 countries from North America (Canada), South America (Brazil), Europe (Germany, Poland, Netherlands, Spain, Italy, Greece) and Asia (China and Japan). DAPT was prescribed during at least 12 months, except in patients treated with oral anticoagulants, in whom antiplatelet therapy was prescribed based on clinical judgment of the responsible physician. Baseline clinical characteristics, in-hospital procedures and adverse events were recorded for all patients.

A one-year follow-up after the discharge from index hospitalization was conducted and data about vital status, bleeding complications, cardiovascular events and other adverse events were collected from hospital records, by telephonic contact with patients or their relatives or their primary care physician if deemed necessary.

The primary end-point of the study was the incidence of serious bleeding complications within the first year after hospital discharge, defined as intracranial bleeding or any other bleeding leading to hospitalization and/or red blood cell transfusion. Bleeding and/or red blood transfusions related to procedures or surgeries were not considered for the purpose of this study.

The BleeMACS score[8] was compound by seven independent predictors of bleeding (age, hypertension, vascular disease, history of bleeding, malignancy, creatinine and haemoglobin). The score was developed by assigning a weighted integer to each independent predictor on the basis of its coefficient in the final model. A point score for each patient was calculated by summing the weighted integers (►**Table 1**). Patients were classified further into quartiles of the BleeMACS risk score: very low-risk (≤ 7 points), low-risk (8–16 points), moderate-risk (17–24 points) and high-risk (≥ 25 points). This risk score exhibited a good ability for predicting spontaneous serious bleeding after discharge (*c*-statistic value of 0.71 in the derivation cohort and 0.72 in the internal validation sample).

Definitions

NSTEMI was defined as the presence of chest pain in the previous 48 hours accompanied by electrocardiographic

Table 1 Composition of the BleeMACS score

BleeMACS score		Points
Age	< 67.0	0
	67.0–74.9	7
	≥ 75	9
Hypertension		7
Vascular disease		6
History of bleeding		19
Malignancy		8
Creatinine	mg/dL or mmol/L	
	<1.0, < 88.4	0
	1–1.49, 88.4–131.9	3
	≥1.5, ≥132.0	12
Haemoglobin	g/dL	
	< 11.0	18
	11–13.9	9
	> 14.0	0

Abbreviation: BleeMACS score, Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome score.

abnormalities suggestive of ischaemia or blood troponin value above the higher normal laboratory limit. STEMI was defined as chest pain with persistent ST-segment elevation of 0.1 mV or more in at least two contiguous leads or new left bundle branch block in the electrocardiogram.

Hypertension was defined as prior history of diagnosed and/or treated hypertension. Vascular disease included prior stroke/transient ischaemic attack, and/or peripheral artery disease (in the external validation dataset, vascular disease was defined as stroke and/or peripheral artery disease, because data on transient ischaemic attack were not available). Malignancy was defined as any active cancer or any non-active cancer treated during the past 3 years of the index ACS. History of bleeding included any hospitalization due to a bleeding event prior to the qualifying ACS and/or any serious bleeding occurring during hospitalization for the index ACS. For the purpose of this study, elderly patients were defined as patients aged 75 years or older.

Statistical Analysis

Categorical variables were expressed as number and percentage. Quantitative variables were expressed as mean and standard deviation. The variables with non-normal distribution were expressed as median and interquartile range. Analysis of the normality of the distribution was conducted by the Kolmogorov–Smirnoff test. Comparisons between categorical variables were performed with the chi-square test or Fisher's exact test, when appropriate. Comparisons between quantitative variables were performed with the Student's *t*-test.

The performance of the BleeMACS risk score was assessed using the Fine–Gray proportional hazards regression analysis,[14] using a competing risk framework for bleeding occurrence—accounting for death as a competing episode.

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 sub-hazard ratios (sHRs) with their corresponding 95% confidence intervals (95% CIs). The adjusted rate of 1-year bleeding was calculated and reported as cumulative incidence function (CIF).

Additionally, the ability of the BleeMACS score for predicting the composite of post-discharge serious bleeding or death was assessed by a Cox regression model.

The performance of the BleeMACS score according to age status was tested assessing its discrimination separately in elderly patients and young patients from the BleeMACS database. Discrimination was evaluated by calculating the area under the receiver-operating characteristic (ROC) curve (AUC), and by assessing CIF curves between the four established BleeMACS score risk categories. The AUCs between elderly and young patients were compared using the DeLong method.[15] A two-sided *p*-value equal to or less than 0.05 was considered as statistically significant.

Finally, a predictive model for post-discharge bleeding was built specifically in patients aged 75 years or older. This analysis was also performed using the Fine–Gray proportional hazards regression model, considering death as a competing episode. Variables included in the multivariate analysis were those with an association ($p < 0.05$) with bleeding in univariate analysis. The best model was selected taking into account the criteria of the best AUC.

All analyses were undertaken using the statistical software PASW Statistics 18 and the STATA 14.1 version.

Results

The BleeMACS registry included 15,401 patients, of whom 11,809 (76.7%) were male. Mean age was 63.6 (±12.7) years, and 3,376/15,401 patients (21.9%) were aged 75 years or older. The characteristics of patients according to age are shown in ►**Table 2**.

Patients aged 75 years or older were less often males and had a higher prevalence of cardiovascular risk factors and other comorbidities, such as previous stroke, malignancy or previous bleeding. These patients had significantly lower glomerular filtration and lower haemoglobin values at admission as compared with younger patients. In addition, clinical presentation with STEMI was less common in the elderly. Older patients had also poorer left ventricular ejection fraction and more severe coronary artery disease as compared with the rest of the patients. Bleeding complications, need for transfusion, heart failure and reinfarction during hospitalization were more common in patients aged 75 years or older.

Significant differences were also observed regarding post-discharge antithrombotic treatment according to age subgroups (►**Table 3**). Elderly patients were more commonly treated with clopidogrel and less often treated with ticagrelor or prasugrel. Oral anticoagulants were more commonly prescribed in the elderly. Triple therapy was also more

Table 2 Baseline clinical characteristics and in-hospital clinical course according to age sub-groups

	Elderly patients ($n = 3,376$)	Young patients ($n = 12,025$)	*p*-Value
Continent			0.001
Europe	2,471 (73.2)	7,533 (62.6)	
Asia	421 (12.5)	1,911 (15.9)	
North America	465 (13.8)	2,477 (20.6)	
South America	19 (0.6)	104 (0.9)	
Age	80.6 (4)	58.9 (10)	0.001
Male sex	2,002 (59.3)	9,807 (81.6)	0.001
Hypertension	2,475 (73.3)	6,561 (54.6)	0.001
Diabetes mellitus	981 (29.1)	2,718 (22.6)	0.001
Dyslipidaemia	1,597 (47.6)	6,426 (53.9)	0.001
Previous MI	524 (15.5)	1,318 (11)	0.001
Previous PCI	494 (14.7)	1,427 (12)	0.001
Previous CABG	171 (5.1)	340 (2.8)	0.001
Previous stroke	384 (11.4)	523 (4.3)	0.001
PAD	326 (9.7)	580 (4.8)	0.001
CHF	202 (6.6)	246 (2.3)	0.001
Malignancy	383 (11.3)	543 (4.5)	0.001
Previous bleeding	260 (7.8)	540 (4.5)	0.001
LVEF	52 (12)	54 (11)	0.001
Haemoglobin at admission	13 (2)	14.3 (2)	0.001
Haemoglobin at discharge	11.9 (2)	13.4 (3)	0.001
Creatinine at admission	1.07 (0.6)	0.92 (0.5)	0.001
STEMI	1,671 (49.5)	7,266 (60.4)	0.001
UA	484 (14.3)	1,574 (13.1)	0.032
Killip class II or higher	631 (22.3)	1,016 (11)	0.001
Femoral access	1,765 (60)	6,370 (57.8)	0.037
Multi-vessel disease	1,424 (57.4)	3,922 (45.9)	0.001
DES	1,153 (34.2)	4,891 (40.7)	0.001
Thrombolysis	29 (0.9)	210 (1.7)	0.001
Complete revascularization	1,402 (52.5)	5,647 (62.3)	0.001
In-hospital bleeding	365 (10.8)	554 (4.6)	0.001
In-hospital transfusion	213 (6.6)	252 (2.3)	0.001
In-hospital reinfarction	59 (1.8)	141 (1.2)	0.011
In-hospital heart failure	209 (6.9)	376 (3.6)	0.001
BleeMACS score	27 (11)	12 (10)	0.001

Abbreviations: BleeMACS score, Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome score; CABG, coronary artery bypass grafting; CHF, congestive heart failure; DES, drug eluting stents; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

commonly used in older patients. Beta-blockers and statins were less commonly used in older patients. No significant differences were observed regarding the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor (AR) blockers.

Post-Discharge Bleeding

During 1-year follow-up, 489/15,401 patients (3.2%) presented serious spontaneous bleeding. The incidence of bleeding episodes was moderately higher in elderly patients (HR, 2.31, 95% CI, 1.92–2.77, $p < 0.001$, ►**Fig. 1**).

Table 3 Post-discharge treatment according to age sub-groups

	Elderly patients ($n = 3,376$)	Young patients ($n = 12,025$)	*p*-Value
Aspirin	3,312 (98.1)	11,898 (98.9)	0.001
Clopidogrel	3,071 (91)	10,334 (85.9)	0.001
Ticagrelor	107 (3.2)	524 (4.4)	0.002
Prasugrel	24 (0.7)	641 (5.3)	0.001
OAC	302 (9.5)	448 (3.7)	0.001
SAPT	162 (4.8)	518 (4.3)	0.217
DAPT	3,152 (93.4)	11,394 (94.8)	0.002
Triple therapy	260 (7.7)	335 (2.8)	0.001
OAC only	14 (0.4)	23 (0.2)	0.027
Beta-blockers	2,490 (74.7)	9,785 (82.4)	0.001
ACEI/ARB	2,482 (74.5)	8,591 (75.4)	0.297
Statins	3,015 (89.8)	11,188 (93.9)	0.001
PPI	1,485 (66.2)	4,267 (53.4)	0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; PPI, proton pump inhibitor; SAPT, single antiplatelet therapy.

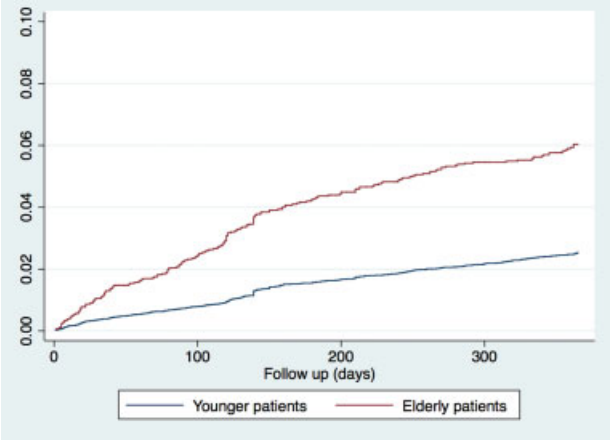

Fig. 1 Cumulative incidence of bleeding according to age sub-groups.

Mean time to bleeding episodes was significantly shorter in the elderly (134 days [95% CI, 119–149] vs. 159 days [95% CI, 147–171], $p < 0.001$). No significant differences regarding bleeding location according to age sub-groups were observed. The most common locations were gastrointestinal, genitourinary and intracranial in both groups (►**Fig. 2**).

Clinical Characteristics and Antithrombotic Management According to Post-Discharge Bleeding in Elderly Patients

Clinical characteristics according to post-discharge bleeding status in elderly patients are shown in ►**Table 4**. Some comorbidities such as congestive heart failure, malignancy and previous bleeding were more common in patients who presented post-discharge bleeding. These patients had worse Killip class at admission, lower left ventricular ejection fraction and more severe coronary artery disease. In addition, patients with post-discharge bleeding had lower haemoglobin value at admission, poorer renal function and higher incidence of in-hospital bleeding and need for transfusion.

On the other hand, post-discharge use of clopidogrel was less common and use of ticagrelor was more common in patients who presented post-discharge 1 year bleeding episodes. No significant differences were observed regarding the post-discharge use of the rest of treatments (►**Table 5**).

Predictive Ability According to Age

The ability of the BleeMACS score for predicting post-discharge bleeding was moderately lower in elderly patients as compared with the rest (AUC, 0.652 [95% CI, 0.624–0.679] vs. 0.691 [95%

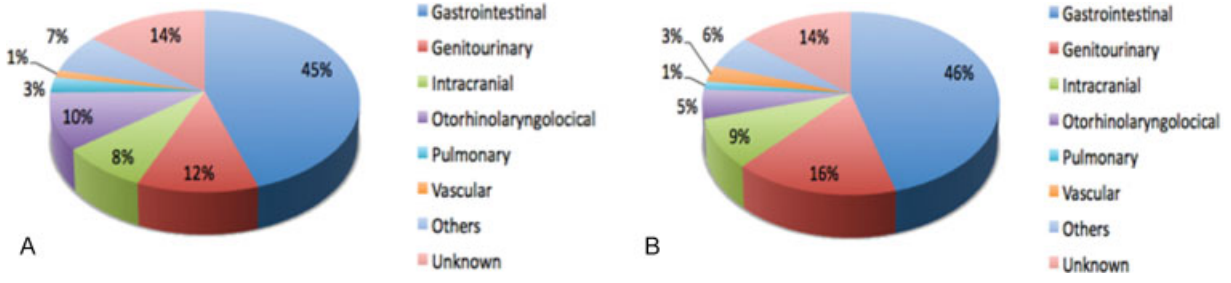

Fig. 2 Post-discharge bleeding location according to age sub-groups.

Table 4 Clinical characteristics and in-hospital clinical course according to post-discharge bleeding status in elderly patients

	Bleeding post-discharge ($n = 190$)	No bleeding ($n = 3,186$)	*p*-Value
Continent			0.958
Europe	137 (72.1)	2,334 (73.2)	
Asia	24 (12.6)	397 (12.5)	
North America	28 (14.7)	437 (13.7)	
South America	1 (0.5)	18 (0.6)	
Age	80.6 (4)	80.6 (4)	0.939
Male sex	120 (63.2)	1,882 (59.1)	0.288
Hypertension	154 (81.1)	2,321 (72.8)	0.013
Diabetes mellitus	55 (28.9)	926 (29.1)	0.972
Dyslipidaemia	93 (49.2)	1,504 (47.5)	0.643
Previous MI	31 (16.3)	493 (15.5)	0.756
Previous PCI	30 (15.9)	464 (14.6)	0.644
Previous CABG	6 (3.2)	16 (5.2)	0.217
Previous stroke	20 (10.5)	364 (11.4)	0.705
PAD	30 (15.8)	296 (9.3)	0.003
CHF	21 (12.1)	181 (6.3)	0.003
Malignancy	31 (16.3)	352 (11)	0.026
Previous bleeding	29 (15.4)	231 (7.3)	0.001
LVEF	52 (12)	52 (12)	0.594
Haemoglobin at admission	12.2 (2)	13.1(2)	0.001
Haemoglobin at discharge	11.3 (2)	11.9(2)	0.001
Creatinine at admission	1.28 (1)	1.06 (0.6)	0.002
STEMI	103 (54.2)	1,568 (49.2)	0.181
UA	21 (11.1)	463 (14.5)	0.184
Signs of congestive heart failure	44 (28)	587 (22)	0.077
Femoral access	105 (63.6)	1,660 (59.7)	0.320
Multi-vessel disease	73 (53.3)	1,351 (57.7)	0.311
DES	66 (34.7)	1,087 (34.1)	0.861
Thrombolysis	3 (1.6)	26 (0.8)	0.222
Complete revascularization	76 (50.3)	1,326 (52.7)	0.574
In-hospital bleeding	58 (30.5)	307 (9.6)	0.001
In-hospital transfusion	37 (20.7)	176 (5.8)	0.001
In-hospital reinfarction	6 (3.2)	53 (1.7)	0.127
In-hospital heart failure	19 (11)	190 (6.7)	0.027
BleeMACS score	25 (15)	15 (12)	0.001

Abbreviations: BleeMACS score, Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome score; CABG, coronary artery bypass grafting; CHF, congestive heart failure; DES, drug eluting stents; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

CI, 0.666–0.716], $p = 0.001$). The ROC curves of the BleeMACS score for predicting bleeding after discharge in both age subgroups are shown in ►**Fig. 3**. ►**Fig. 4** shows the cumulative incidence of post-discharge bleeding according to the BleeMACS categories in young (A) and elderly patients (B).

The ability of the BleeMACS score for predicting the composite of death or post-discharge bleeding was also moderately lower in elderly patients (AUC, 0.635 [95% CI, 0.606–0.664] vs. 0.673 [95% CI, 0.647–0.699], $p = 0.001$).

Prediction of Bleeding in the Elderly

The best model for predicting bleeding in elderly patients included hypertension, previous bleeding, haemoglobin at admission and previous heart failure. This model showed an

Table 5 Post-discharge treatment according to post-discharge bleeding status in elderly patients

	Bleeding at discharge ($n = 190$)	No bleeding ($n = 3,186$)	*p*-Value
Aspirin	189 (99.5)	3,123 (98)	0.154
Clopidogrel	162 (85.3)	2,909 (91.3)	0.005
Ticagrelor	13 (6.8)	94 (3)	0.003
Prasugrel	1 (0.5)	23 (0.7)	0.755
OAC	23 (12.1)	299 (9.4)	0.215
SAPT	12 (6.3)	150 (4.7)	0.314
DAPT	175 (92.1)	2,977 (93.4)	0.473
Triple therapy	20 (10.5)	240 (7.5)	0.133
OAC only	0	14 (0.4)	0.360
Beta-blockers	134 (70.9)	2,356 (74.9)	0.215
ACEI/ARB	142 (75.1)	2,340 (74.4)	0.829
Statins	173 (91.5)	2,842 (89.7)	0.420
PPI	93 (71.5)	1,392 (65.9)	0.188

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; PPI, proton pump inhibitor; SAPT, single antiplatelet therapy.

acceptable predictive ability (AUC, 0.666 [95% CI, 0.62–0.712]), without significant differences as compared with the BleeMACS score ($p = 0.276$).

Finally, ►**Table 6** shows the specific contribution of each component of the BleeMACS score for predicting post-discharge bleeding according to age. The contribution of age, vascular disease and malignancy was not statistically significant in elderly patients. In contrast, the predictive role of hypertension, previous bleeding, renal function and haemoglobin levels remained significant in both sub-groups.

Discussion

The main findings from our study are: (1) elderly patients from this series patients had a moderately higher incidence of serious spontaneous bleeding at 1 year and a shorter time to bleeding episodes, without significant differences regarding bleeding location; and (2) despite a moderately lower predictive ability in patients at older ages, the BleeMACS score showed an acceptable performance in these patients.

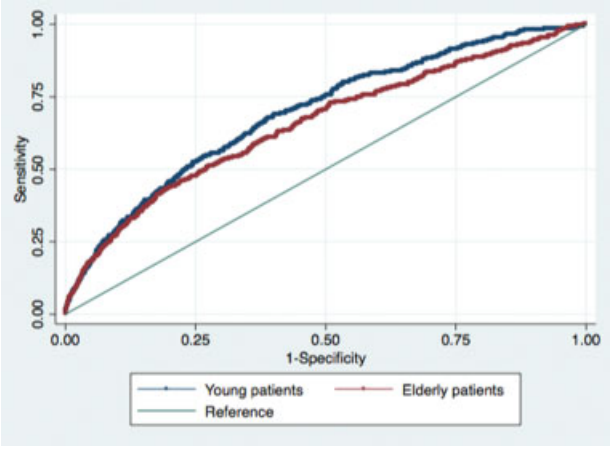

Fig. 3 Receiver-operating characteristic (ROC) curves for the prediction of post-discharge bleeding by the BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) score according to age sub-groups.

Haemorrhagic complications are associated with a higher mortality in patients with ACS, especially in the elderly.[16–18] Current guidelines establish a reference standard duration of DAPT of 12 months.[2] However, recent evidence suggests that treatment with DAPT beyond the first year may be beneficial in selected groups of patients with low bleeding risk,[19] particularly when the ischaemic risk is high.[20] On the other hand, guidelines state that shorter DAPT regimens may be considered in patients deemed at high bleeding risk.[2] Therefore, bleeding risk is one of the main factors in choosing the type and duration of antiplatelet therapy after an ACS.

Several bleeding risk scores have been developed and widely used for predicting major in-hospital bleeding.[5–7] These recommended risk scores seem to not adequately predict post-discharge bleeding in patients with ACS.[21] The bleeding profile for in-hospital phase (predominance of access site bleeding, related with the coronary intervention and parenteral antithrombotic drugs) is clearly different than for post-discharge period (predominance of gastrointestinal bleeding, related with oral antiplatelet therapy).[22–24] Recent studies have demonstrated that bleeding after discharge is also associated with a significant increase in the risk of death and myocardial infarction.[25–27] Available information about the prediction of bleeding after discharge in patients with ACS is scarce.

Baber et al[19] developed a risk score for predicting major bleeding at 2 years in 4,190 patients undergoing successful PCI with stent implantation from the PARIS registry. Independent predictors of bleeding included older age, body mass index, triple therapy at discharge, anaemia, current smoking and renal dysfunction, and the predictive model showed an acceptable ability for predicting major bleeding. In a sub-study of the

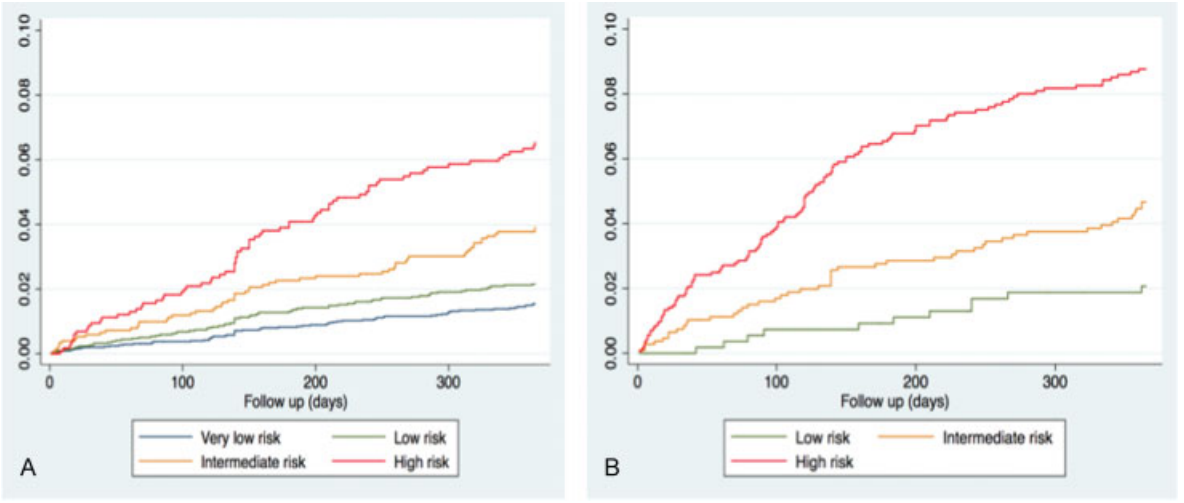

Fig. 4 Cumulative incidence of bleeding according to the BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) score categories in young patients (**A**) and elderly patients (**B**).

DAPT trial, Yeh et al[20] derived a risk score for predicting ischaemic and bleeding events in 11,648 patients not sustaining major bleeding or ischaemic events 1 year after PCI. The predictors included in the model were myocardial infarction at presentation, prior myocardial infarction or PCI, diabetes, stent diameter < 3 mm, smoking, paclitaxel-eluting stent, history of congestive heart failure/low ejection fraction, vein graft intervention and age. Derivation cohort model predicting bleeding events had *c*-statistics of 0.68.

More recently, Costa et al[28] studied a series of 14,963 patients treated with DAPT after coronary stenting from eight multicentre randomized clinical trials. A predictive score for out-of-hospital thrombolysis in myocardial infarction (TIMI) major or minor bleeding was derivated from this series. This score (so-called PRECISE-DAPT score) included age, creatinine clearance, haemoglobin, white blood cell count and previous spontaneous bleeding, and showed a *c*-index for out-of-hospital bleeding of 0.73. This score was validated in patients treated with PCI from the PLATelet inhibition and patient Outcomes (PLATO) trial (*c*-statistic of 0.70) and BernPCI registry (*c*-statistic of 0.66).

It is important to note that patients included in these studies were at relatively low bleeding risk, since more than 60% of patients from the PARIS registry[19] underwent PCI for stable angina, and in a not negligible proportion of patients included in the PRECISE-DAPT score and in the DAPT study,[20] the reason for performing PCI was not an ACS. In addition, patients suffering bleeding events during the first 12 months on DAPT and patients requiring oral anticoagulation were not included in the DAPT study.

Table 6 Contribution of each predictor of the BleeMACS score according to age sub-groups

	Younger patients		Elderly patients	
Predictor	**sHR (95% CI)**	***p*-Value**	**sHR (95% CI)**	***p*-Value**
Age (per y)	1.03 (1.02–1.05)	0.001	1 (0.98–1.02)	0.390
Hypertension	1.30 (0.99–169)	0.053	1.49 (1.01–2.20)	0.045
Vascular disease	1.49 (1.07–2.07)	0.017	1.18 (0.83–1.69)	0.351
History of bleeding	1.49 (0,96–2.32)	0.074	2.12 (1.41–3.19)	0.001
Malignancy	1.81 (1.21–2.69)	0.003	1.35 (0.92–1.99)	0.130
Creatinine (g/dL)		0.065		0.005
< 1.0	Ref		Ref	
1–1.49	1.05 (0.79–1.41)		1.43 (1.02–2.01)	
> 1.5	1.59 (0.97–2.59)		1.82 (1.20–2.75)	
Haemoglobin (g/dL)		0.001		0.001
< 11.0	2.65 (1.69–4.17)		2.71 (1.71–4.32)	
11–13.9	1.28 (0.98–1.65)		1.49 (1.01–2.21)	
> 14.0	Ref		Ref	

Abbreviations: BleeMACS score, Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome score; CI, confidence interval; sHR, sub-hazard ratio.

The BleeMACS score[8] was the first risk score designed to estimate the probability of developing a serious haemorrhagic event within the first year after hospital discharge for an ACS. The score was developed in an extensive series of all corners ACS patients from routine clinical practice, obtaining a good predictive ability in this clinical setting.

On the other hand, the incidence of ACS is particularly high in the elderly, and the number of elderly patients who are hospitalized for ACS is increasing.[9,10] These patients are at increased risk both for ischaemic and bleeding complications. However, information about the real incidence of post-discharge bleeding in non-selected elderly patients with ACS from routine clinical practice is scarce. Data from this series showed a higher incidence of post-discharge bleeding in elderly patients. However, this increase of risk was moderate, despite the clearly higher prevalence of comorbidities of patients at older ages.

On the other hand, a poorer ability of the recommended risk scores for predicting in-hospital bleeding in elderly patients with ACS has previously been reported.[12,29,30] The prediction of bleeding after discharge in patients at older ages is also an important issue, since the antithrombotic management of these patients is often complex, due to a more severe and complex coronary artery disease, higher prevalence of comorbidities and more common concomitant indication of oral anticoagulants because of conditions such as atrial fibrillation or previous stroke. To date, no study assessed the prediction of post-discharge bleeding episodes in elderly patients with ACS.

The ability of the BleeMACS score for predicting post-discharge bleeding was lower in patients aged 75 years or older from this series. However, this loss of performance was moderate, in contrast to other studies assessing in-hospital bleeding risk in elderly patients.[12] The lower predictive ability observed in elderly patients from our study could be mostly due to the fact that age accounts for more than 10% of points of the total score. Despite this, in our opinion the BleeMACS score exhibited an acceptable performance also in elderly patients. In fact, the predictive model specifically performed in elderly patients did not significantly improve the prediction of bleeding as compared with the BleeMACS score.

Interestingly, the predictive role of each of the components of the score differed according to age. While several predictors remained significant or increased its level of significance in the elderly (renal function, haemoglobin, hypertension, previous bleeding), others reduced its predictive contribution to the model (age, vascular disease, malignancy). A different antithrombotic management in patients with these conditions or different types of neoplasm at older ages (not so aggressive or with a lower likelihood for bleeding) may partially explain these findings. However, the type of neoplasm was not recorded in the BleeMACS database, so these data should be confirmed in other populations.

Aging is a heterogeneous process and risk assessment in elderly patients might be conditioned by the presence of frailty and other aging-related variables.[31–33] Recent data suggest a modest contribution of a comprehensive geriatric assessment for predicting in-hospital bleeding in elderly patients with ACS.[34] However, the role of these variables for predicting bleeding after discharge could be more important.

This article has several limitations. The BleeMACS score was derived from a cohort of a retrospective registry, carrying the limitations inherent to this type of studies. Changes in antithrombotic therapy were not assessed, such as switch between antiplatelet drugs or DAPT discontinuation. On the other hand, information about frailty, disability and other aging-related variables was not available. However, despite these limitations we believe that this article retrieves novel and important data about characteristics and prediction of bleeding complications after discharge in elderly patients with ACS from routine clinical practice.

Conclusions

Elderly patients from this series had a moderately higher incidence of post-discharge bleeding. In spite of a moderate loss of predictive ability in patients at older ages, the BleeMACS exhibited an acceptable performance also in these patients.

What is known about this topic?

- Elderly patients are at higher risk for ischaemic and bleeding complications, prolonged hospital stay and increased consumption of health resources.
- The elderly are poorly represented in clinical trials and registries from whom currently recommended bleeding risk scores were developed. A poorer ability of these risk scores for predicting in-hospital bleeding has been reported in elderly patients with ACS.
- Information about prediction of post-discharge bleeding is scarce. The BleeMACS score exhibited a good ability for predicting serious bleeding 1 year after discharge in non-selected patients with ACS. No study assessed the prediction of post-discharge bleeding in elderly patients with ACS.

What does this paper add?

- In this extensive series ($n = 15{,}401$) of ACS patients, patients aged ≥ 75 years (21.9%) were more commonly treated with clopidogrel and less often treated with ticagrelor or prasugrel. A total of 489/15,401 patients (3.2%) presented serious spontaneous bleeding at 1 year. The incidence of bleeding was moderately higher in elderly patients (HR, 2.31, 95% CI, 1.92–2.77, $p < 0.001$).
- Mean time to bleeding episodes was significantly shorter in the elderly (134 vs. 159 days, $p < 0.001$), without significant differences regarding bleeding location according to age.
- Despite a moderate loss of predictive ability in patients at older ages (AUC, 0.652 vs. 0.691, $p = 0.001$), the BleeMACS score exhibited an acceptable performance also in the elderly. The specific contribution of each of the components of the score was significantly different according to age.

Conflict of Interest
None.

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