Risk Stratification for Bleeding in the Elderly with Acute Coronary Syndrome: Not So Simple

Davide Capodanno[1]   Antonio Greco[1]

[1] CAST, A.O.U. "Policlinico-Vittorio Emanuele," Catania, Sicily, Italy

Address for correspondence Davide Capodanno, MD, PhD, CAST, A.O.U. "Policlinico-Vittorio Emanuele," P.O. Rodolico, Ed. 8, Via Santa Sofia 78, Catania, Italy (e-mail: dcapodanno@gmail.com).

Acute coronary syndromes (ACSs) are more prevalent in the elderly, who benefit from early invasive management and antithrombotic therapy similar to younger individuals but are also more prone to bleeding in the aftermath of percutaneous coronary intervention (PCI).[1] Indeed, the management of ACS has advanced greatly over the years,[2] but determining the risk of post-discharge bleeding in the elderly remains a primary clinical challenge, because bleeding impacts on mortality and increases with the intensity and duration of dual anti-platelet therapy.[3] This issue is even more complex in elderly patients who have co-existing reasons to assume oral anticoagulant medications (e.g. atrial fibrillation, venous thromboembolism).[4]

Recognizing that 'there is elderly and elderly' with respect to the risk of serious and life-threatening out-of-hospital bleeding is important to tailor guideline-directed antithrombotic strategies for ACS.[5] In recent years, several risk scores have become available in the field of bleeding risk assessment (►Table 1).[6–12] Risk stratification for post-discharge bleeding is a tricky undertaking in general, and particularly in elderly ACS patients who were under-represented or over-selected in development cohorts of contemporary risk models such as the PARIS (Patterns of Non-Adherence to Dual Anti-Platelet Regimen In Stented Patients) and PRECISE-DAPT (Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) scores.[13] In a recent study of 1,927 ACS patients undergoing PCI, where the median age was 65 years, the PARIS and PRECISE-DAPT scores displayed equal c-statistics of 0.73, corresponding to fair-to-moderate discrimination for predicting Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.[14]

In the previous issue of *Thrombosis and Haemostasis*, Garay et al report on the discrimination accuracy of the BleeMACS (Bleeding complications in a Multicenter registry of patients discharged after an ACS) score in elderly patients.[15] Notably, at variance with the PARIS and PRECISE-DAPT models, the Blee-MACS score is ACS-specific (►Table 1).[12] The score, which is computed from seven clinical and laboratory predictors of severe bleeding at 1-year post-discharge (age, hypertension, vascular disease, history of bleeding, malignancy, creatinine, haemoglobin), was previously derived from a multi-centre cohort of 10,750 PCI patients and validated first internally with a c-statistic of 0.72 (95% confidence interval [CI], 0.67–0.76), and then externally in the large SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry, with a c-statistic of 0.65 in the sub-group of 96,239 ACS patients undergoing PCI (95% CI, 0.64–0.66).[12] Elderly (≥ 75 years) patients in the BleeMACS registry were 3,376 (21.9%). The relative increase in serious bleeding episodes at 1 year was 131% compared with younger patients, and the mean time to bleeding was approximately 1 month shorter (134 vs. 159 days, $p < 0.001$). A lower discrimination was observed in older compared with younger patients (c-statistics 0.65 [95% CI, 0.62–0.68] versus 0.69 [95% CI, 0.67–0.72]; $p = 0.001$) in parallel with a loss in the predictive ability for some components of the score, including age itself, vascular disease and malignancy.

The authors should be commended for their investigation of a risk stratification tool for decision-making in a very uncertain clinical scenario.[16] Indeed, when analysing the BleeMACS risk score, some strengths are not deniable: the model was derived from a large multi-centre cohort, it was externally validated and it is made of variables that are easy to obtain and do not require complex computation. Also importantly, the score has been built with the scope of predicting sizeable and clinically meaningful events (e.g. intracranial bleeding or bleeding leading to hospitalization or transfusions). The BleeMACS elderly sub-group was inclusive and representative, encompassing more ACS patients than the derivation cohorts of the PARIS and PRECISE-DAPT scores, which supports the generalizability of the findings.

Unfortunately, several limitations also prevent the Blee-MACS score to become a broadly accepted companion to daily practice in tailoring antithrombotic decisions for elderly ACS

Table 1 Bleeding risk assessment tools

Score	Variables	Setting	Predicted outcome	Development cohort				Validation cohort		
				N	Age[a]	ACS	c-Statistic	Type	N	c-Statistic
Peri-procedural										
ACTION[6]	Age, creatinine, systolic blood pressure, haemoglobin, heart rate, weight, gender, home warfarin use, DM, heart failure ± shock, electrocardiographic changes, previous peripheral artery disease	ACS	In-hospital major bleeding	72,313	64	100%	0.73	Internal	17,960	0.71
CRUSADE[7]	Haematocrit, glomerular filtration rate (Cockroft–Gault), heart rate, systolic blood pressure, prior vascular disease, DM, signs of CHF, gender	ACS	In-hospital major bleeding	71,277	67	100%	0.71	Internal	17,857	0.70
Mehran et al[8]	Age, gender, creatinine, white blood cell count, anaemia, clinical presentation, antithrombotic medication	ACS	30-day major bleeding	17,421	62	100%	0.74	NA	NA	NA
Post-discharge										
DAPT[9]	Age, DM, prior myocardial infarction or PCI, myocardial infarction at presentation, stent diameter > 3 mm, stenting of vein graft, history of congestive heart failure or left ventricular ejection fraction < 30%, current cigarette smoker or smoker within past year, paclitaxel-eluting stent	PCI	Moderate or severe bleeding at 12–30 months	11,648	61.3 ± 10.3[b]	79%	0.68	External	8,136	0.64
PARIS[10]	Age, body mass index, current smoking, anaemia, creatinine clearance < 60 mL/min, triple therapy on discharge	PCI	BARC 3 to 5 bleeding at 24 months	4,190	63.8 ± 10.9[b]	37.8%	0.72	External	8,130	0.65
PRECISE-DAPT[11]	Age, haemoglobin, white blood cells, creatinine clearance, prior bleeding	PCI	TIMI major or minor bleeding at 12 months	14,963	65	55.6%	0.73	External	8,595 and 6,172	0.70 and 0.66
BleeMACS[12]	Age, hypertension, vascular disease, history of bleeding, malignancy, creatinine, haemoglobin	ACS-PCI	Severe bleeding at 12 months	10,750	63.6	100%	0.71	External	96,239	0.65

Abbreviations: ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CHF, congestive heart failure; DAPT, dual anti-platelet therapy; DM, diabetes mellitus; NA, not available; PCI, percutaneous coronary intervention.

[a]Median.

[b]Mean ± standard deviation.

patients. First, the development cohort was well suited for risk modelling but concerns with respect to data quality and completeness, as well as to endpoints reporting and adjudication apply to any large retrospective data collection. Second, age-specific factors (e.g. frailty, disability, cognitive status) that were not found to impact on in-hospital bleeding of elderly with ACS[17] but might impact on the risk of bleeding post-discharge were not collected and analysed in the model. Third, creatinine (one of the score's most influential components) may represent an inaccurate parameter in lean or frail old people due to its relationship with muscular mass resulting in over-estimation of renal function. Fourth, determining the predictive value of the score in the elderly sub-group of the development cohort corresponds to a sort of internal and therefore over-optimistic validation. Taking this caveat into account, with a c-statistic of 0.65, the discrimination of the BleeMACS score was far from ideal and not too far from to the flip of a coin. In the study from Garay et al, even the best fitted model for bleeding risk prediction in elderly patients did not exceed a c-statistic of 0.66. Rendering unto Caesar, these numbers are in line with c-statistics reported in validation cohorts of the PARIS and PRECISE-DAPT scores (►Table 1). Unfortunately, a head-to-head comparison of c-statistics for the BleeMACS, PARIS and PRECISE-DAPT scores, which would have been insightful, was not provided.

Loss of performance of the BleeMACS score in the elderly population is not surprising and can be explained by several contributing factors, including the multifactorial nature of bleeding in the elderly but also the inescapable statistical conundrums that occur when a score is validated in a sub-group of patients who are homogeneous based on a variable of the score itself. Because the BleeMACS risk score assigns different integer values below 75 years but not above, the discriminatory ability of age as a categorical risk factor is lost when the score is applied in the elderly. By default, all elderly patients (> 75 years) in this sub-study received nine points, corresponding to more than one-third of the points required to enter the highest risk category, whereas the lowest risk category (score ≤ 7) was missing by definition. Clearly, in validation studies, heightening the level of clinical complexity translates into diluting the ability of a score to discern across risk sub-groups.

Age is a major determinant of the risk of severe bleeding.[18] Indeed, in existing and upcoming trials of PCI strategies for high bleeding risk patients, older age is a key entry factor.[19,20] Bleeding risk scores perform modestly and their value is foremost to 'flag up' high-risk patients with a focus on modifiable risk factors.[21] Although some strengths and opportunities of the available models are obvious, it seems risky to conclude that decision-making for dual anti-platelet therapy in elderly ACS patients can be safely guided by relying entirely on any of the available risk stratification systems. Nonetheless, the important efforts in the understanding of bleeding risk stratification made by investigators such as Garay et al should be acknowledged, and it seems reasonable to move towards refinements of existing models to attain a better discrimination accuracy in the elderly setting. In the case of the BleeMACS score, this aim could be obtained by removing or granularizing the age variable, by substituting creatinine with more accurate metrics of renal function (e.g. glomerular filtration rate) and by introducing other variables (e.g. frailty, tendency to fall, concomitant use of oral anticoagulants) that have been shown to influence the specific aetiology of post-discharge bleeding in the elderly.

References

1 Roffi M, Patrono C, Collet J-P, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37(03):267–315
2 Sibbing D, Angiolillo DJ, Huber K. Antithrombotic therapy for acute coronary syndrome: past, present and future. Thromb Haemost 2017;117(07):1240–1248
3 Valgimigli M, Bueno H, Byrne RA, et al. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J 2018;39(03):213–260
4 Capodanno D, Angiolillo DJ. Triple antithrombotic therapy at the intercept between threats and opportunities: don't throw out the baby with the bath water. JACC Cardiovasc Interv 2017;10(11):1086–1088
5 Capodanno D, Angiolillo DJ. Antithrombotic pharmacotherapy in the elderly: general issues and clinical conundrums. Curr Treat Options Cardiovasc Med 2012;14(01):57–68
6 Mathews R, Peterson ED, Chen AY, et al. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™. Am J Cardiol 2011;107(08):1136–1143
7 Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009;119(14):1873–1882
8 Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55(23):2556–2566
9 Yeh RW, Secemsky EA, Kereiakes DJ, et al; DAPT Study Investigators. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315(16):1735–1749
10 Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016;67(19):2224–2234
11 Costa F, van Klaveren D, James S, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389(10073):1025–1034
12 Raposeiras-Roubín S, Faxén J, Íñiguez-Romo A, et al. Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the BleeMACS score. Int J Cardiol 2018;254:10–15
13 Capodanno D, Angiolillo DJ. Tailoring duration of DAPT with risk scores. Lancet 2017;389(10073):987–989
14 Abu-Assi E, Raposeiras-Roubin S, Cobas-Paz R, et al. Assessing the performance of the PRECISE-DAPT and PARIS risk scores for predicting 1-year out-of-hospital bleeding in acute coronary syndrome patients. EuroIntervention 2018;13(16):1914–1922

15 Garay A, Ariza-Solé A, Formiga F, et al. Prediction of post-discharge bleeding in elderly patients with acute coronary syndromes: insights from the BleeMACS registry. Thromb Haemost 2018;118(05): 929–938

16 Ariza-Solé A, Guerrero C, Formiga F, et al. Global geriatric assessment and in-hospital bleeding risk in elderly patients with acute coronary syndromes: insights from the LONGEVO-SCA Registry. Thromb Haemost 2018;118(03):581–590

17 Alegre O, Ariza-Solé A, Vidán MT, et al. Impact of frailty and other geriatric syndromes on clinical management and outcomes in elderly patients with non-ST-segment elevation acute coronary syndromes: rationale and design of the LONGEVO-SCA Registry. Clin Cardiol 2016;39:373–377

18 Capodanno D, Angiolillo DJ. Antithrombotic therapy in the elderly. J Am Coll Cardiol 2010;56(21):1683–1692

19 Urban P, Meredith IT, Abizaid A, et al; LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med 2015;373(21): 2038–2047

20 Varenne O, Cook S, Sideris G, et al; SENIOR investigators. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet 2018;391 (10115):41–50

21 Lip GYH, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. J Thromb Haemost 2016;14(09):1711–1714