



Bleeding risk assessment in elderly patients with acute coronary syndrome

Lucía Riobóo-Lestón, Sergio Raposeiras-Roubin, Emad Abu-Assi, Andrés Iñiguez-Romo

Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain

Abstract

Nowadays, elderly people represent a growing population segment with a well known increased risk of both ischemic and bleeding events. Current acute coronary syndrome guidelines, strongly recommend dual antiplatelet therapy (DAPT) with few specific references for aged patients due to lack of evidence. Patients aged ≥ 75 years are misrepresented in the classic derivation trials cohorts. Strategies to reduce the bleeding risk in this group of patients are urgently needed for the daily clinical practice. Identify the specific age related bleeding risk factors and the importance of an integral geriatric assessment remains challenging. Some of the available in-hospital and out-hospital bleeding risk scores have shown a lower to moderate predictive ability in older patients and no specific tools are developed in elderly population. The importance of an appropriate vascular access choice, type and duration of antiplatelet drugs is crucial to reduce the bleeding risk. Increase radial approaches and short DAPT duration leads to reduce hemorrhages. One interesting subgroup of patients is those who need chronic anticoagulation therapy after percutaneous coronary intervention, due to their very high risk of bleeding. New alternatives as dual therapy with oral anticoagulation and only one antiplatelet drug should be considered. In current review, we evaluate the available evidence about bleeding risk in elderly.

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1 Introduction

Each year, 17.9 million people die from cardiovascular disease, which is the main cause of loss of quality of life and dependency, especially in elderly people who represent a growing population segment.^[1]

Nowadays, the cornerstones of the acute coronary syndrome (ACS) treatment are the new antithrombotic therapies and the percutaneous coronary intervention (PCI), exposing our patients to a higher risk of bleeding. Dual antiplatelet therapy (DAPT) is the standard care in ACS patients underwent PCI.

Elderly patients have been under-represented in the main ACS trials derivation cohorts which makes difficult to extrapolate the available information.^[2] Currently, several studies have studied the effectiveness of an invasive strategy in elderly patients.^[3–6] Results were controversial, especially in non-ST segment elevation ACS (NSTEMI-ACS), probably because of the heterogeneous basal characteristics of the groups like the degree of comorbidity or frail. The man-

agement of DAPT in elderly people remains challenging, with few specific recommendations in current guidelines, being an important gap of knowledge.^[7]

It is known that elderly patients have increased both ischemic and bleeding risk.^[8] It could be related to their intrinsic characteristics as: comorbidity, complex coronary disease, physical disabilities and frail. Recent studies have demonstrated that hemorrhagic risk exponentially rise from the seventh decade, increasing mortality, length of hospitalization and costs.^[9,10] This is the reason why the evaluation of hemorrhagic risk plays a crucial role when faced the treatment of ACS in elderly patients. The use of bleeding risk scores identifies high risk patients and it helps clinicians to determine the DAPT regime and duration. At the present time, we have in the literature multiple bleeding classifications (Table 1); generating difficulties to compare the available bleeding risk scores.

The aim of this paper is summarizing the available information that it could help the clinicians facing the bleeding risk assessment of elderly people.

2 Factors associated with bleeding risk in elderly

Historically, factors related to the risk of bleeding have

Correspondence to: Lucía Riobóo-Lestón, MD, Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain. E-mail: lucia.rioboo.leston@sergas.es

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Table 1. Bleeding classifications and definitions.

Classifications	Definitions
BARC	
0	No bleeding.
1	Bleeding is not actionable.
2	Any overt, actionable bleeding.
3a	Overt bleeding plus hemoglobin drop 3 to < 5 g/dL and any transfusion with overt bleeding.
3b	Overt bleeding plus hemoglobin drop 3 to \geq 5 g/dL; includes cardiac tamponade and bleeding requiring surgical intervention or vasoactive agents.
4	CABG-related bleeding: perioperative intracranial bleeding within 48 h; reoperation after closure of sternotomy for the purpose of controlling bleeding; transfusion of \geq 5U whole blood or packed red blood cells within 48 h; chest tube output \geq 2 L within 24 h.
5	Fatal bleeding.
GUSTO	
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding.
Moderate	Bleeding that requires blood transfusion but does not result in haemodynamic compromise.
Severe or life threatening intracranial	Intracranial hemorrhage or bleeding that cause hemodynamic compromise and requires intervention
TIMI	
Minimal	Overt hemorrhage associated with a fall in hemoglobin < 3 g/dL (hematocrit of < 9%).
Minor	Any clinically overt sign of hemorrhage associated with a fall in hemoglobin of 3 g/dL to \leq 5 g/dL (hematocrit of 9% to \leq 5%).
Major	Intracranial or clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of > 5 g/dL (hematocrit > 15%).

BARC: bleeding academic research consortium; CABG: coronary artery bypass graft; GUSTO: global use of strategies to open occluded arteries; TIMI: thrombolysis in myocardial infarction.

been identified, some of them closely related to age. Broadly speaking, we could classify them as non modifiable, potentially modifiable and modifiable factors.

2.1 Non modifiable

The principal non modifiable bleeding risk factors are age and female sex. Most of them are generally related to patient comorbidity as peripheral arteriopathy, diabetes mellitus, hypertension, stroke, malignancy and previous bleeding.

2.2 Potentially modifiable

Within the potentially modifiable factors, we include those that vary during the time and they may be affected by the medical therapies. For example: anticoagulation, use of chronic steroid or non steroid antiinflammatory drugs, renal function, hemoglobin, and a very frequent finding in elderly patients, thrombocytopenia. Patients with thrombocytopenia were excluded from the derivation trials, but there is evidence that the risks of mortality and bleeding correlated directly with the thrombocytopenia severity.^[11]

2.3 Modifiable

The modifiable factors are the cornerstone of the bleeding assessment. The type and duration of dual antiplatelet

therapy, the invasive management, and the choice of vascular access, favours radial, femoral, are the most relevant ones.^[12]

3 Bleeding risk assessment tools

In this section, we will summarize the main available scores in the literature up to the current time. The most relevant limitations of these tools are that the average age of the patients in the referral cohorts does not exceed 70 years old, the use of different bleeding definitions, the different presentation of coronary artery disease, and the heterogeneous clinical management in the studies. As we will see some of them have been specifically studied in elderly patients.

3.1 Inhospital bleeding

As is known that hemorrhagic events increase in-hospital mortality.^[13] Current guidelines recommend the use of bleeding risk scores in ACS patients to predict in-hospital bleeding.^[14] The most widespread scores are summarized in Table 2.

Ariza, *et al.*^[15] evaluated the predictive ability of CRUSADE, MEHRAN and ACTION bleeding risk scores in 2,036 consecutive ACS patients aged \geq 75 years old. They

Table 2. Inhospital bleeding risk scores.

	CRUSADE ^[15]	ACTION ^[16]	ACUTY-HORIZONS ^[17] (MEHRAN)
Variables	Gender	Gender	Gender
	HR at admission	Age	Age
	Systolic arterial pressure at admission	Weight	Creatinine
	HF	Systolic arterial pressure at admission	White blood cell
	DM	HR at admission	Anemia
	Peripheral artery disease	Hemoglobin	Type of ACS
	Hematocrit	Creatinine	Type of antitrombotic medication (bivalirudin vs. non-bivalirudin)
	Creatinine	DM	
		Peripheral artery disease	
		Previous oral anticoagulation	
Derivation cohort age, yrs	67 ± 13	64.0 (54.0–76.0)	62.1 ± 11.7

Data are presented as means ± SD or median (interquartile ranges). ACS: acute coronary syndrome; DM: diabetes mellitus; ECG: electrocardiogram; HF: heart failure; HR: heart rate.

found a consistent lower ability for all of them to predict in hospital major bleeding in this group. The vascular access was the most common location for in-hospital bleedings in elderly people, followed by urinary and intracranial, instead of digestive and urinary that they are more common in younger patients. Likewise, Faustino, *et al.*^[16] consistently observed a poor predictive ability of the CRUSADE score in a cohort of patients aged ≥ 80 years with NSTEMI-ACS.

Most of the previously described scores were validated in the pre ticagrelor-prasugrel era, which is not the real clinical practice nowadays. We need further investigation according to actual approaches: early invasive PCI strategies, high percentages of radial vascular access, use of fondaparinux and limited glycoprotein IIb/IIIa inhibitors.

3.2 Outhospital bleeding

In recent years, there has been a growing concern about the evaluation of the hemorrhagic risk in the medium-long term. It is known that the scores created for the intrahospital bleeding risk assessment, they have low capacity when predicting bleeding in the extrahospitalary phase.^[17] At the time of the newest antiplatelet treatments and last generation stents, knowing the probability of presenting a hemorrhagic event in the follow-up is of great relevance to help us to select the best therapeutic strategy including type and duration of antiplatelet therapy.

Recent DAPT guidelines recommend the use of risk scores to evaluate the benefits and risks of different DAPT durations.^[18] Table 3 summarizes the main characteristics of the scores used for the hemorrhagic risk assessment at discharge. As we can see in the derivation cohorts mean and median ages (Table 2), patients older than 75 years are clearly underrepresented, which makes uncertain the application of these tools in an elderly population.

Regarding to PRECISE-DAPT score, a recent study showed no significant differences regarding the incidence of bleeding according to the recommended cut-off point ≥ 25. However, a progressive increase in the incidence of bleeding was observed across PRECISE-DAPT quartiles. These results suggest that the need for adapting of the PRECISE-DAPT score in non-selected elderly patients with ACS for an accurate assessment of bleeding risk.^[19]

One recent study also assessed the predictive ability of the BleemACS score in elderly patients.^[20] They analyzed 3,376 patients aged ≥ 75 years old, 5.6% presented hemorrhagic events during follow-up with a mean time to the episode shorter than younger patients (134 vs. 159 days). There were no differences in the bleeding location being the most frequent gastrointestinal, genitourinary and intracranial. They found a moderately lower ability for predicting out-hospital bleeding events in the ≥ 75 years old group (0.652 vs. 0.691). So far there are no more studies that specifically evaluate the hemorrhagic risk in elderly patients with ACS.

4 Role of integral geriatric assessment in hemorrhagic risk stratification

Due to the specific characteristics and complexity of the elderly patients, the need for a comprehensive geriatric assessment in the ACS has been studied in the last years. The integral geriatric assessment is a dynamic and structured diagnostic process including functional, clinical, mental and social valuation in order to optimize resources and achieve the highest degree of independence and quality of life.

Nowadays, there are controversial findings about the usefulness of parameters such as frailty to assess the risk of bleeding in the ACS. In the insights from the LON-GEVO-SCA registry, Ariza, *et al.*^[21] explored the role of a

Table 3. Outhospital bleeding risk scores.

	PARIS ^[22]	DAPT ^[23]	PRECISE-DAPT ^[24]	TRILOGY ACS ^[25]	BLEEMACS ^[26]
Clinical context	DAPT after PCI TT included	DAPT after PCI After 12 months eventsfree	DAPT after PCI TT not included	DAPT without revascularization	DAPT after PCI TT included.
Variables	Age BMI Current smoking Anemia Renal dysfunction TT at discharge	Age Current smoking DM MI at presentation Prior PCI or Prior MI Paclitaxel eluting stent Stent diameter < 3 mm CHF or LVEF < 30% Vein graft stent	Age White blood cells Hemoglobin Creatinine clearance Prior bleeding	Age Gendre Angiography performed before randomisation Creatinine Hemoglobin	Age Hypertension Vascular disease Prior bleeding Malignancy Creatinine Hemoglobin
Classification	Low risk: 0–2 Intermediate risk: 4–7 High risk: ≥ 8	Score ≥ 2: long DAPT (30 months) Score < 2: standar DAPT (12 months)	Score ≥ 25: short DAPT (3–6 months) Score < 25: standar/long DAPT (12–24 months)		Very low risk: ≤ 7 Low risk: 8–16 Moderate risk: 17–25 High risk: ≥ 26
Prediction	From discharge to 24 months	From 12 months to 36 months	From discharge to 24 months	From discharge to 14 months	From discharge to 12 months
Derivation cohort age, yrs	CTE: 64 ± 12 No CTE: 63 ± 10.9 MB: 67.8 ± 10.7 No MB: 63.6 ± 11.0	CTE: 61.7 ± 10.8 No CTE: 61.3 ± 10.3 MB: 66.4 ± 10.3 No MB: 61.2 ± 10.3	65.0 (56.9–73.0)	66 (59–74)	63.6 ± 12.5

Data are presented as means ± SD or median (interquartile ranges). BMI: body mass index; CHF: congestive heart failure; CTE: coronary thrombotic events; DAPT: dual antiplatelet therapy; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; MB: major bleeding; MI: myocardial infarction; PCI: percutaneous coronary intervention; TT: triple therapy.

comprehensive geriatric assessment to predict in-hospital bleeding. Geriatric assessment included: functional capacity for basic activities of daily living (Barthel index), cognitive status (Pfeiffer test), frailty (Frail scale), comorbidity (Chalson index) and nutritional risk assessment (MNA-SF). They found from all of previous age-related variables, only comorbidity was significantly associated with in hospital major bleeding (MB). In the same way, White, *et al.*^[22] in a substudy of TRILOGY ACS, they found that it is no association between frailty defined by Fried criteria and bleeding. On the other hand, Alonso Salinas, *et al.*^[23] have done a study to determine if frailty measured by SHARE-FI index increases bleeding risk in patients with ACS. They included 190 patients ≥ 75 years old. 37.9% were categorized like frail patients. On multivariate analysis, frailty was an independent predictor for MB.

Some explanations for these different findings could be the use of different index to measure fragility and hemorrhagic events, it also makes them difficult to compare.

4.1 Antitrombotic therapy

Current guidelines general recommend 12 months of DAPT in ACS patients but it emphasized on the importance of individualize according hemorrhagic risk, it being able to choose short patterns of DAPT(3-6 months) in patients at

high bleeding risk.^[24] The management of DAPT in elderly people remains challenging and we have little specific recommendations in guidelines.^[25,26] Recent trials in old people using drug eluting stents with biodegradable polymers and short DAPT duration shows to reduce the risk of bleeding events with no significant increase of ischemic complications.^[27,28]

Age-related organ changes affect to drug pharmacokinetics and pharmacodynamics.^[29] The decrease in intestinal absorption, hepatic metabolism, body mass index, free water and muscle mass as well as the increase in fat, influences drugs efficacy and safety in this group of patients.

4.2 Chronic oral anticoagulation

Triple therapy (TT) is the standard care in patients with ACS ongoing to PCI and atrial fibrillation (AF). It is known that this strategy can triple the risk of bleeding.^[30] Sambola, *et al.*^[31] analyzed the efficacy and safety of TT in patients ≥ 75 years old with atrial fibrillation undergoing PCI in one study. They found lower thromboembolism rate in TT group than in DAPT one (0.6 % vs. 6.9%) but at the expense of increased MB events (11.7 % vs. 2.4%).

Current guidelines recommend different strategies depending if the main concern is the ischemic or the hemorrhagic events and propose strategies to reduce the risk in

anticoagulated patients including: use of HAS-BLED score, shorten the time of DAPT considering oral anticoagulation and clopidogrel instead of triple therapy in high bleeding risk patients, use of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKA), if VKA is needed consider a lower target international normalized ratio (INR), use less than 100 mg daily atomic absorption spectrometry (AAS) and routine use of proton pump inhibitors (PPIs). The DAIGA score system (DAPT continuation, age > 75 years, INR > 2.2, gastrointestinal ulcer history, Anemia) proved usefulness for predicting bleeding complications and risk stratification of AF patients after drug-eluting stent (DES) implantation with triple antithrombotic therapy (TAT). The score showed better predictive ability for bleeding complications than the HAS-BLED score in this context.^[32]

In a recent meta analysis, Cavallari, *et al.*^[33] includes 6036 patients from four controlled randomized trials (ISAR TRIPLE, PIONER AF-PCI, RE-DUAL-PCI and WOEST) with chronic oral anticoagulation indication after PCI. They conclude that in these patients dual antithrombotic therapy compared with TT, it reduces bleeding events without significant increased in ischemic events.

5 Conclusions

Age is an independent risk factor for bleeding. The management of ACS in this group of patients is challenging because they are misrepresented in trials and the evidence is scarce. The identification of different bleeding risk factors and bleeding risk assessment tools can help the clinician to optimize the therapeutic decisions. Few bleeding scores were validated in elderly population who paradoxically constitutes one of the higher bleeding risk groups. Despite the appearance of new antiplatelet treatments as well as strategies to reduce the hemorrhagic events in high risk patients (short term DAPT or dual therapy post PCI in patients' requiring chronic anticoagulation), further investigation is needed in all these fields for elderly population.

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