Bleeding risk stratification in acute coronary syndromes. Is it still valid in the era of the radial approach?

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Bleeding is the most common adverse event after percutaneous coronary intervention (PCI). It can occur either as a direct complication of the index procedure or spontaneously during the antithrombotic treatment for secondary prevention. Hemorrhagic complications significantly impact the prognosis independently from their timing and have been associated with a poorer quality of life [1]. In addition, anti-thrombotic therapies are now becoming more potent than in the past, and an increase in hemorrhagic events can easily be anticipated in clinical practice with state-of-the-art drug combinations. International guidelines endorse a careful evaluation of the bleeding risk, in order to lower the risk of the devastating consequences of hemorrhagic events with the simultaneous effort to maintain ischemic protection. However, no specific methodology has ever been standardized to assess bleeding risk in patients undergoing PCI, although several bleeding risk scores [2–8], addressing risk stratification in diverse clinical situations, have gained popularity (Table I). They are based on readily available clinical and laboratory values and could improve clinicians' ability to standardize bleeding risk assessment. Among these, the CRUSADE score [8] was developed from a large registry, which included 71,277 patients with non-ST segment elevation myocardial infarction (NSTEMI), and is recommended by European guidelines for the bleeding stratification of patients with NSTEMI [9]. The CRUSADE score estimates the risk of in-hospital bleeding irrespective of the initial therapeutic strategy, and also confirms its discriminatory capacity in the subgroup of patients managed invasively with PCI [8]. Similarly, the ACUITY score has been developed to appraise in-hospital bleeding risk in a wider acute coronary syndrome (ACS) patient population [3]. Importantly, this score also takes into account the type of anticoagulant used during PCI (i.e. heparin + glycoprotein IIb/IIIa inhibitors or bivalirudin), considering the protective effect of bivalirudin on peri-procedural bleeding as compared to heparin plus glycoprotein IIb/IIIa inhibitors [3].

In the current issue of *Postępy w Kardiologii Interwencyjnej/Advances in Interventional Cardiology*, the performance of different bleeding risk scores in the PCI scenario is broadly assessed in a meta-analysis [10]. The authors conclude that the appraised risk scores performed similarly in patients with ACS [10]. This result suggests that more important than which score to apply it is to apply at least one. In fact, although these scores focus on slightly different patient populations and clinical/procedural variables, anyone of them can help clinicians to standardize bleeding risk assessment and objectively point out those individuals with a higher bleeding risk. Especially in such patients, the use of all available mechanical and pharmacological bleeding avoidance strategies appears appropriate.

The implementation of radial access has proved to reduce procedural bleeding during cardiac catheterization and PCI in different clinical subsets, and this holds particularly true in patients with non-cardiac conditions, high risk of bleeding and low probability of coronary artery disease [11, 12]. The recent MATRIX-Access trial, which included an unselected patient population presenting with ACS, demonstrated a significant net clinical benefit in patients receiving invasive management through the radial as compared to the femoral access [13]. This benefit was mainly driven by a definite reduction of access-site bleeding complications and also by a reduction in all-cause mortality. The possibility to reduce mortality with implementation of the radial access is of utmost importance in ST segment elevation myocardial infarction (STEMI) patients, and it has been speculated that the reduction of vascular complications and major bleeding with the radial approach may be the driver of the consis-

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tent prognostic benefit that patients with STEMI receive from radial access [14]. The MATRIX-Access trial [13], on top of the previous evidence in the literature, now represents the proof of concept of the benefit of the radial access, which should be considered the default strategy for patients presenting with ACS, irrespective of the baseline bleeding risk.

Similarly, bivalirudin is known to reduce peri-procedural bleeding during PCI, both access site- and non-access site-related, while this benefit translated into a mortality benefit only in a single trial [15]. Importantly, bivalirudin was associated with an increase of early stent thrombosis. The incremental value of bivalirudin during PCI in terms of bleeding risk reduction is provided by the direct inhibition of thrombin activity, which allows a more predictable anticoagulant effect as compared to unfractionated heparin. However, bivalirudin's half-life is shorter than that of heparin, and its anticoagulant effect dissipates early after the end of the procedure, exposing the patient to a possible higher ischemic risk, especially in those situations (i.e. in STEMI) in which the effect of oral antiplatelet drugs is slowed by the slow absorption and a pro-inflammatory status is present [15]. Accordingly, newer studies are needed to confirm the net clinical benefit profile of bivalirudin.

Despite bleeding risk scores (Table I) being focused on the prevention of events that may occur early after PCI, the majority of bleeding events are observed during long-term treatment with antiplatelet drugs, which are used for secondary prevention of both stent- and non-stent-related ischemic events. The optimal duration of dual antiplatelet therapy (DAPT) after PCI is a matter of great debate, considering that the longer the duration of antithrombotic treatment after PCI, the higher is the chance to incur bleeding complications [16]. This is of particular interest in view of the recent DAPT trial, which tested 30- vs. 12-month DAPT with thienopyridines in patients treated with drug-eluting stents [17]. A longer DAPT course reduced the rate of the composite ischemic endpoint of death, myocardial infarction and stroke and the co-primary endpoint of definite or probable stent thrombosis. The ischemic benefit was mainly driven by a reduction of myocardial infarction, which was not stent-related in almost 50% of cases. Nonetheless, this advantage came at the expense of a significant increase in major bleeding events in the arm receiving a prolonged DAPT regimen, which also showed a borderline increase of all-cause mortality and a significant increase in non-cardiovascular mortality. Importantly, a similar adverse results were also observed in an independent meta-analysis, which included all the available trials randomizing patients to different DAPT durations [18]. These results generated considerable uncertainty in the cardiological community with respect to the appropriateness of the extension of DAPT beyond the recommended period in all patients [19]. Accordingly, it is of paramount importance to identify the appropriate patient to receive prolonged DAPT, as a more thorough selection of the patients might maximize the ischemic benefit without an exaggerated bleeding trade-off. In this matter, the clinical presentation of the patient at the time of PCI could be a piece of the puzzle. In the all-comer population of the PRODIGY trial, patients presenting with stable coronary artery disease (CAD), as compared to those presenting with ACS, showed a signifi-

Table I. Bleeding risk scores in patients treated with percutaneous coronary intervention

Score	Population	Type of bleeding	Variables	External validation	AUC
CRUSADE [8]	NSTEMI	In-hospital	Baseline hematocrit < 36%, CrCl, heart rate, female sex, CHF at presentation, SBP < 110 or > 180 mm Hg, PVD, diabetes mellitus	Yes	0.71
ACUITY [3]	ACS	In-hospital	Female sex, age, baseline serum creatinine, white blood cell count, anemia, clinical presentation, procedural anticoagulation	No	0.74
ACTION [2]	ACS	In-hospital	Heart rate, baseline hemoglobin, female sex, baseline serum creatinine, age, electrocardiographic changes, heart failure/shock, diabetes mellitus, PVD, body weight, SBP, home warfarin use	Yes	0.71
STEEPLE [4]	Stable CAD	In-hospital	Female sex, procedural anticoagulation, GPI use	Yes	0.67
NCDR [7]	All PCI	In-hospital	STEMI presentation, age, BMI, previous PCI, CKD, dialysis, shock, cardiac arrest within 24 h, female sex, hemoglobin at baseline, PCI urgent or emergent	Yes	0.77
RISK-PCI [5]	STEMI	30-day bleeding	Female sex, prior peptic ulcer, Killip > 1 at presentation, hemoglobin at baseline, CrCl	Yes	0.76
REPLACE [6]	All PCI	All post-PCI bleeding events	Age, female sex, CrCl, prior anemia, LMWH prior PCI, GPI use, IABP use	Yes	0.62

CrCl – Creatinine clearance, CHF – congestive heart failure, SBP – systolic blood pressure, PVD – peripheral vascular disease, GPI – glycoprotein IIb/IIIa inhibitor, BMI – body mass index, CKD – chronic kidney disease, LMWH – low molecular weight heparin, IABP – intra-aortic balloon pump, PCI – percutaneous coronary intervention.

cantly higher bleeding risk when treated with a prolonged DAPT course (i.e. 24- vs. 6-month DAPT) [20]. Importantly, when ischemic and bleeding events were combined in the overall net clinical benefit, a stable clinical presentation discouraged the use of prolonged DAPT, whereas patients presenting with ACS did not show significant adverse effects of prolonged therapy. This result is complemented by a recent sub-group analysis from the DAPT trial. In this study, patients presenting with myocardial infarction (MI) during the initial PCI showed a numerically higher benefit from prolonged DAPT as compared to those not presenting with MI [21]. Although this study did not demonstrate a significant interaction between clinical presentation and DAPT duration, the rate of death for all causes was significantly increased in stable but not unstable patients after prolonged treatment, suggesting that patients with stable presentation at the time of the index PCI might not be ideal candidates for extension of the antithrombotic treatment. Interestingly, in a recent sub-group analysis from the PRODIGY trial, patients presenting with or without lesions in the left main or the proximal left anterior descending coronary artery were compared to investigate a possible benefit of the prolonged DAPT regimen in patients with higher risk anatomy [22]. The study showed that the subgroup of patients with lesions in one of these coronary segments benefitted from a prolonged course of DAPT because of a reduction of definite, probable or possible stent thrombosis, which was not replicated in the subgroup with less important coronary lesions [22].

Taken all together, these data suggest that it is crucial to tailor DAPT duration according to the single-patient bleeding profile, taking into account clinical or even anatomical variables. However, a risk score estimating bleeding liability late after hospitalization in patients treated with DAPT is yet to be proposed.

In conclusion, a comprehensive evaluation of the bleeding risk in patients undergoing PCI could greatly help in reducing both procedural and post-procedural hemorrhagic complications on top of the established benefit of radial access. While numerous studies have already explored predictors for in-hospital bleeding, an important challenge for future studies is to unravel bleeding predictors of events occurring late after PCI, during the long-term antiplatelet treatment for secondary prevention of ischemic events.

Conflict of interest

The authors declare no conflict of interest.

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