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EDITORIAL

# Towards a personalized selection of antithrombotic agents in patients undergoing PCI: the role of clinical presentation in tools for risk assessment

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Antithrombotic therapy is the cornerstone for the treatment and prevention of ischemic events among both acute (ACS) or chronic coronary syndromes (CCS) [1, 2]. Nevertheless, its use is inevitably associated with an increased risk of bleeding [3, 4]. The use of different antithrombotic agents, as well as their combinations, have undergone substantial changes during the past years, mainly because of the low thrombogenicity of new stent platforms and the increasing awareness of the prognostic impact of bleeding events [1, 2]. Indeed, a number of antithrombotic strategies have been proposed with the aim of optimizing the balance between ischemic and bleeding risks, representing a step forward towards personalized medicine in the field of antithrombotic therapy [2]. A careful assessment of the bleeding and ischemic risks of the individual patient represents the foundation of such personalized strategy. This can be achieved by a careful assessment of clinical and procedural features known to be associated with increased bleeding and/or ischemic risks, and, as has been more recently proposed, by the use of tools that can measure individual's response to antithrombotic agents, which is known to be broadly variable (Fig. 1) [1, 5, 6].

Against this background, the use of scores has been proposed to provide a better definition of bleeding or ischemic risks for clinical decision-making, but also to provide a better standardization for the design of clinical trials. Table 1 summarizes the main features of the most relevant tools for bleeding risk assessment developed among patients undergoing percutaneous coronary intervention (PCI). Nevertheless, risk scores can be rather heterogeneous, limiting their utility for standardization of risk among clinical studies. To overcome this limitation, the Academic Research Consortium (ARC) has proposed a consensus on the definition of high bleeding risk (HBR) in patients undergoing PCI [7]. This definition is based on 14 major and 6 minor criteria for HBR at the time of PCI. ARC-HBR is defined by at least 1 major or 2 minor criteria. This definition has been validated in several retrospective studies including large cohorts of contemporary patients undergoing PCI, showing the rate of major bleeding at 1-year to be significantly higher in HBR compared with non-HBR patients and that there was a stepwise increase in bleeding risk corresponding to the number of times the ARC-HBR criteria fulfilled [8].

In the present issue of *Journal of Thrombosis and Thrombolysis*, Nicolas and colleagues [9] expand on the performance of ARC-HBR criteria among patients undergoing PCI according to clinical presentation (acute myocardial infarction [AMI] vs. CCS, with unstable angina [UA] excluded). Data from 6,068 patients were analyzed retrospectively. The main finding of the study is that the ARC-HBR framework successfully identified patients with increased risk of bleeding complications at 1-year irrespective of clinical status (AMI or CCS). Moreover, HBR status was more commonly encountered in AMI compared with CCS patients, albeit no significant p-interaction between clinical presentations was found for the included outcomes. Of note, AMI presentation was significantly associated with increased risk for bleeding at 1-year.

The authors should be commended for providing important insights on the validity of the ARC-HBR score across different clinical scenarios. Indeed, while multiple recent studies validated the ARC-HBR criteria in various multinational cohorts [8], there is in the literature conflicting evidence regarding the role of clinical presentation on bleeding

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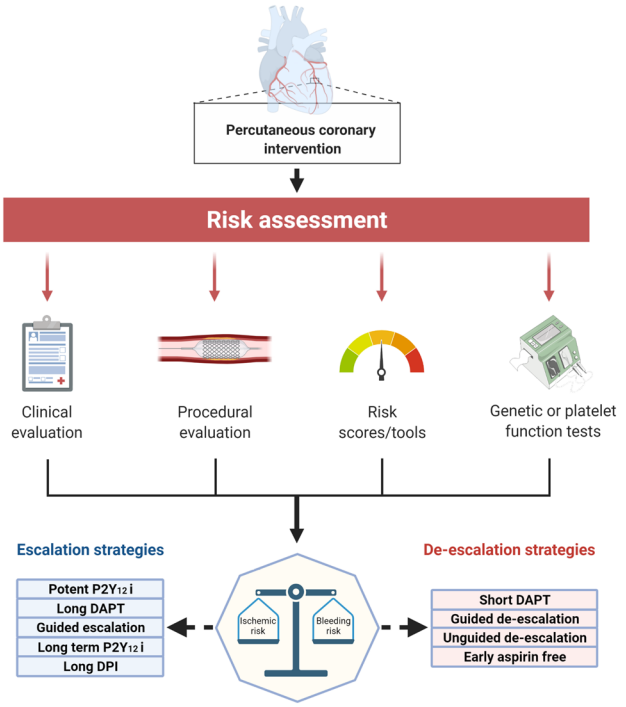


**Fig. 1** Risk assessment as a guidance for a personalized selection of antithrombotic therapy. Risk assessment is based on clinical and procedural evaluation as well as on tools aiming at identifying high bleeding risk patients or impaired effectiveness of antithrombotic therapies. *DAPT* dual antiplatelet therapy, *DPI* dual-pathway inhibition, *I* inhibitors

risk, and none but one of the studies explored this issue in the setting of ARC-HBR validation [10]. Therefore, the present study is of crucial importance to shed further light on this unexplored issue.

Although of clinical relevance, the findings here described should be interpreted in light of some limitations. First, the ARC-HBR status was defined retrospectively and based on a limited number of criteria compared to those originally proposed by the ARC initiative, or modified ones due to the availability of data collected. Second, the bleeding endpoint definition used in this study does not correspond to the BARC scale recommended in the ARC-HBR document. Third, the two populations were imbalanced in numbers (AMI 22.9 % vs CCS 77.1 %) and with the AMI group mainly represented by STEMI patients (78.8 %), thus affecting the power of the analysis. The latter point might at least in part contribute to explain why, despite AMI (of whom only 652 were HBR) was a predictor of bleeding, no significant correlation emerged between clinical status and outcomes. Yet, it is important to note that patients with UA were excluded because considered a "grey zone" between ACS and CCS, therefore, results cannot be generalizable to all ACS patients encountered in clinical practice. Finally, this is a single-center study from a national referral center for complex PCI cases in a densely populated area, thus, these results may not be reflective of clinical practice in many centers worldwide.

The study by Nicolas and colleagues, significantly contributes to highlight that HBR patients are frequent in daily practice among both those with AMI (47 %) or CCS (43 %), and that we should pay attention to adopt all strategies to prevent bleeding complications, including prioritizing the radial access for PCI, that in this study was used in a minority of cases (< 25 %), and selecting the most appropriate DAPT regimen, particularly in AMI patients who might be at even greater risk of bleeding. Although smaller and with different methodology (mainly HBR criteria, adjudication, bleeding definition, focus on AMI instead all ACS), the present study is in line with another recent publication and supports the concept that acute presentation (AMI/ACS) *per se* is associated with greater bleeding risk, thus, further fueling the discussion on this issue and stressing the need for further studies [9, 10].

Eventually, whether or not clinical presentation should be included in current risk scores/tools reflects the major limitation on the use of risk scores/tools in clinical practice: features associated with increased bleeding are often associated with increased ischemic events. Moreover, C-statistics for the majority of available scores do not reach the acceptable boundary of 0.71, resulting in overall low accuracy for predicting outcomes (Table 1).

In conclusion, risk scores/tools are useful for the standardization of the design of clinical trials in HBR patients, but their use in clinical decision-making with the goal of personalizing the selection of antithrombotic therapy, should always be integrated with other available factors which include clinical and procedural characteristics as well as tools proving the effectiveness of antithrombotic agents at the individual patient level (Fig. 1).

Main bleeding risk assessment tools for tailoring antiplatelet in patients undergoing percutaneous coronary intervention

| | DAPT | PARIS | PRECISE-DAPT | BleeMACS | ARC-HBR |
|---|---|---|---|---|---|
| Year | 2016 | 2016 | 2017 | 2018 | 2019–2021 (definition and validation) |
| Data set | DAPT trial (n = 11,684) | PARIS registry (n = 4190) | Pooled 8 RCTs (n = 14,963) | BleeMACS registry (n = 15,401) | 8 registries (n = 70,283) |
| Time of use | After 12 months of uneventful PCI | At the time of PCI | At the time of PCI | At hospital discharge | At the time of PCI |
| Variables included | - Age<br>- Cigarette smoking<br>- Diabetes mellitus<br>- MI at presentation<br>- Prior PCI or MI<br>- Paclitaxel-eluting stent<br>- Stent diameter < 3mm<br>- CHF or LVEF < 30%<br>- Vein graft stent | - Age<br>- BMI<br>- Current smoking<br>- Anemia<br>- Creatinine clearance<br>- Triple antithrombotic therapy at discharge | - Hemoglobin<br>- White blood count<br>- Creatinine clearance<br>- Prior bleeding | - Age<br>- Hypertension<br>- Vascular disease<br>- History of bleeding<br>- Malignancy<br>- Creatinine<br>- Hemoglobin | - Age<br>- Long term OAC<br>- CKD<br>- Hemoglobin<br>- Previous spontaneous bleeding<br>- Thrombocytopenia<br>- Bleeding diathesis<br>- Cirrhosis with portal hypertension<br>- Active malignancy<br>- Previous ICH or stroke or bAVM<br>- Need for major surgery on DAPT<br>- Recent major surgery or trauma<br>- Use of NSAIDs or steroids |
| Score range | -2 to 10 | 0 to 14 | 0 to 100 | 0 to 80 | - |
| Decision making cut-off | ≥ 25 vs < 25 | ≥ 8 vs < 8 | ≥ 2 vs < 2 | ≥ 26 vs < 26 | 1 major or 2 minor criteria |
| Validation discrimination | 0.64 | 0.64 | 0.68 | 0.64 | 0.60–0.72* |

*Ranging according to the study considered: Ueki et al. 0.67, Corpetaux et al. 0.68, Cao et al. 0.64 (HBR vs. non-HBR) or 0.68 (ARC-HBR used as a score), Fujii et al. 0.60 (STE-ACS patients) or 0.72 (excluding patients undergoing mechanical device support), Miura et al. 0.60, Nakamura et al. 0.68

*MI* myocardial infarction, *BMI* body mass index, *OA* oral anticoagulant, *CHF* chronic heart failure, *LVEF* left ventricle ejection fraction, *bAVM* brain arteriovenous malformation, *CKD* chronic kidney disease, *DAPT* dual antiplatelet therapy, *eGFR* estimated glomerular filtration rate, *HBR* high bleeding risk, *ICH* intracranial hemorrhage, *NSAID* nonsteroidal anti-inflammatory drug; *PCI* percutaneous coronary intervention; *ARC* Academic Research Consortium, *STE-ACS* ST-elevation acute coronary syndrome

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## Declarations

**Conflict of interest** Dr. Galli and Dr. Gargiulo have no conflicts of interest to disclose.

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