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High bleeding risk – the clinical context matters

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The selection of optimal antiplatelet therapy following percutaneous coronary intervention (PCI) requires careful consideration, balancing the future risks of ischaemic and major bleeding events. This balance does not remain constant but varies over time depending on the clinical characteristics of the patient, the indication for PCI, lesion and procedural complexity and antithrombotic regimes prescribed[1].

Major bleeding represents one of the most common complications observed following PCI and is associated with a threefold increase in the risk of mortality and major adverse cardiovascular events (MACE)[2], contributing to more than one in ten of all in-hospital PCI deaths[3]. Therefore, avoidance of periprocedural and longer-term bleeding complications following PCI is an important part of PCI procedure planning, necessitating personalisation of antithrombotic regimes at the individual patient level. This requires the ability to quantify future bleeding risk.

Several bleeding risk scores have been developed to quantify the risk of major bleeding complications[4]. Heterogeneity of study populations, differences in candidate variables assessed (e.g., comorbidities, risk factors, laboratory parameters, pharmacotherapy, indications for PCI, and the definition of bleeding events) have led to the development of disparate risk models, with only modest performance in external validation studies and poor agreement between scores. Most of these risk scores were developed in non-acute coronary syndrome (ACS) populations in an era where more potent $P2Y_{12}$ agents were not used[4].

More recently, to minimise heterogeneity, consensus criteria for high bleeding risk (HBR) were defined by the Bleeding Academic Research Consortium (BARC)[5]. Twenty clinical criteria, consisting of major and minor criteria from categories including age, central nervous system, comorbidities, laboratory measures, bleeding history and iatrogenic factors have been used to define HBR[5]. The Academic Research Consortium (ARC)-HBR criteria have been externally validated in numerous patient populations, but to date have not been externally validated in acute and chronic coronary syndrome (CCS) patients.

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In the current issue, Gragnano et al[6] studied 16,821 consecutive patients undergoing PCI at Bern University Hospital between 2009 and 2018 to determine whether clinical presentation *per se* is independently associated with the risk of major bleeding events at one year, and to study the performance of ARC-HBR criteria in predicting major bleeding in ACS and CCS patients undergoing PCI.

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The populations differed significantly: severe anaemia, thrombocytopaenia and recent surgery or trauma were the more prevalent HBR criteria amongst ACS patients undergoing PCI, whilst advanced age, oral anticoagulants, chronic kidney disease, mild anaemia, prior stroke, and use of non-steroidal inflammatory drugs or corticosteroids were more prevalent in patients undergoing PCI for CCS indications. Interestingly, whilst 31% of ACS and 39% of CCS patients were identified as being at high risk of bleeding complications as defined by the ARC-HBR criteria, major bleeding complications were more frequently reported in ACS patients.

The authors reported that at one year, BARC 3 or 5 bleeding occurred in 427 (5.0%) patients with ACS and 248 (3.6%) patients with CCS, with ACS independently associated with a higher risk of BARC 3 or 5 bleeding at one year (HR: 1.21, 95% CI: 1.01-1.43, p=0.03). This excess risk associated with ACS appeared to be limited to the first 30 days following PCI and varied by type of ACS. The greatest risk was observed among ST-segment elevation myocardial infarction (STEMI) patients (HR: 1.92, 95% CI: 1.59-2.31, p<0.001), followed by non-ST-segment elevation myocardial infarction patients (HR: 1.26, 95% CI: 1.04-1.53, p=0.019), with no significant increase in risk observed in patients with unstable angina (HR: 1.10, 95% CI: 0.74-1.66, p=0.63).

When studying the performance of ACR-HBR criteria in predicting major bleeding, the authors report that discrimination of the ARC-HBR criteria for predicting BARC 3 or 5 bleeding was lower amongst patients with ACS compared with CCS patients (c-indexes: 0.67 [95% CI: 0.64-0.69] vs 0.72 [95% CI: 0.69-0.75], p=0.014). The addition of ACS as a minor criterion to the ARC-HBR marginally increased its discrimination (C-statistic) to predict BARC 3 or 5 events from 0.68 (95% CI: 0.66-0.70) to 0.69 (95% CI: 0.67-0.71).

This study highlights the importance of evaluating model performance in higher risk populations and in doing so provides insights into how such models could be updated in future revisions. The current study suggests clinical presentation may be important in the short term (within 30 days following PCI) but perhaps not in the longer term. Whilst the current analysis reports on discrimination – the ability of the ARC-HBR criteria to separate ACS and CCS patients into classes of bleeding risk – it provides no information around calibration. Furthermore, whilst the addition of ACS as a minor ARC-HBR criteria only improves discrimination marginally, the authors provide no information around net reclassification improvement (NRI), an index that quantifies how well a new model reclassifies subjects – either appropriately or inappropriately. Finally, whilst the authors report antiplatelet prescription on discharge, they do not report whether abbreviated dual antiplatelet regimes were utilised or whether de-escalation strategies may have influenced the reported rates of major bleeding.

So where does this leave us? The current work suggests that ACR-HBR criteria do not perform as well in identifying patients at high risk of bleeding complications in ACS patients as they do in CCS patients. Inclusion of ACS as a minor HBR criterion only improves discrimination marginally; whether better gains would be observed through only inclusion of STEMI remains to be seen. The current analysis and previous work[1] suggest that bleeding risk is not constant but varies over time. Accordingly, further efforts to refine HBR criteria should consider the impact of major bleeding in the context of the time frame studied. Finally, many of the criteria used to define HBR are also important determinants of future ischaemic risk. Over 80% of patients with high bleeding risk are also at high risk of ischaemic complications[7]. Future efforts should aim to quantify the trade-off between bleeding and ischaemic risks[8] for each patient to help clinicians tailor the duration and intensity of antithrombotic regimens.

Conflict of interest statement

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