Major bleeding after PCI. Where is our crystal ball?

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This editorial refers to ‘Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach’ by E. Nikolsky et al., on page 1936

Over the last three decades, there have been remarkable advances in percutaneous coronary intervention (PCI). Utilization of coronary stents and combination antiplatelet/antithrombotic therapy have led to significant improvements in revascularization success rates as well as marked reductions in thrombotic complications. Patients considering elective procedures are now routinely quoted a <1% risk of incurring a myocardial infarction or of requiring urgent revascularization. These advances have led to exponential increases in the utilization of PCI in patients with both stable and unstable coronary artery disease (CAD) over the last decade—it is now estimated that >800 000 PCI procedures are performed annually in Europe.¹ In addition, PCI is being performed in increasingly complex patients, including the elderly and those with multiple co-morbidities, who are at higher risk for incurring procedural complications.

However, with increased utilization of PCI, increased use of combinations of multiple antithrombotic agents, and the reduction in the occurrence of ischaemic/thrombotic complications of PCI, there has emerged recognition that post-procedural bleeding complications remain all too common and result in significant morbidity and mortality.

In a retrospective analysis of >10 000 patients undergoing PCI at a single centre between 1991 and 2000, major bleeding occurred in 5.4% of patients and was associated with a 3.5-fold increased adjusted risk of in-hospital mortality.² Similarly, in an analysis of >24 000 patients with acute coronary syndromes enrolled in the Global Registry of Acute Coronary Events (GRACE), major bleeding occurred in 5.5% of patients undergoing PCI and was associated with a significant increase in hospital death.³ Finally, it has been estimated that the incremental cost of prolonged hospitalization and treatment associated with bleeding complications exceeds US$10 000/hospital stay.⁴

Although a number of studies have identified clinical and procedural variables associated with PCI-related bleeding, a global assessment of the impact of different risk factors on the development of major haemorrhagic complications has not been performed.

The development of a simple assessment tool to predict a patient’s risk of bleeding with PCI would be of great clinical value to physicians and their patients as they consider percutaneous revascularization. In patients with unstable CAD, estimates of a high risk of procedural bleeding could greatly affect decisions about vascular access (e.g. radial vs. femoral) and dosing and type of adjunctive antithrombotic therapy. In patients with stable CAD, an accurate prediction of procedural-associated bleeding risk would certainly factor into any decision concerning elective PCI. Indeed, given the results of the recently published COURAGE trial, in which elective PCI failed to reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical management,⁵ deferring PCI may be most appropriate in patients deemed at highest risk for procedure-associated bleeding.

Nikolsky et al. take an important first step towards providing clinicians with such an assessment tool.⁶ In a post hoc analysis of two large multicentre randomized clinical trials evaluating bivalirudin as an adjunctive therapy for PCI,⁷ ⁸ the authors identified seven independent correlates of major bleeding, assigned a weight to each variable based on its contribution to bleeding risk, and then developed a simple scoring system based on summation of each weighted variable. Application of this risk score allowed for separation of patients into groups with very low, low, moderate, and high rates of bleeding. This risk assessment tool was then validated using the data set from REPLACE-1—the pilot study preceding REPLACE-2. Despite differences between patient populations, their tool demonstrated a reasonable ability to discriminate between patients with varying risk of bleeding (C-statistic 0.62). As noted by the authors, this tool may be useful to determine which patients are at highest risk for bleeding after angioplasty and thereby require closer and perhaps more prolonged observation following the procedure.

Recognizing that the ability to estimate bleeding risk prior to intervention would be of equal or even greater clinical importance, the authors also provide a modified ‘clinical’ model utilizing the same pre-procedural variables but peri-procedural use of an intra-aortic balloon pump (IABP) or glycoprotein (GP) IIb/IIIa inhibitors. This model showed
a similar discriminatory power in the validation cohort (C statistic = 0.65) and appeared to work equally well both in patients receiving bivalirudin alone and in those receiving heparin and GP IIb/IIIa inhibitors.

The models described demonstrate that despite the heterogeneity of patients undergoing PCI, better estimates of procedural bleeding risk are possible. That said, although the current version of their instrument demonstrates statistically adequate discriminatory power, its clinical utility must still be considered limited. Given the relatively low rate of bleeding in REPLACE-2, derivation of the model was based on only 155 major bleeding events (and validated in a data set consisting of only 26 major bleeding events). In addition, the number of variables considered for inclusion in the model was limited and did not include several clinical variables (e.g. body mass index, prior history of bleeding, peripheral arterial disease previously shown to be associated with bleeding). Similarly, a number of important procedural variables (e.g. sheath size, delay time until sheath removal) previously shown to be independently associated with peri-procedural bleeding were not examined. As such, the ability of the model to provide more clinically relevant risk stratifications is diminished.

Using the comprehensive model (clinical and PCI-related variables), the difference in bleeding risk between very low (1%), low (1.5%), and moderate (2.6%) categories is not large enough to drive clinical decision-making. On the other hand, the mean rate of bleeding in patients in the high-risk category (score ≥10) was 5%, but with a range of 3.4% (score = 11) to >14% (score >18). This high-risk category comprised >25% of the total sample. The 'clinical' model suffers from the same limitations. Further refinement of the model (e.g. inclusion of additional variables, testing in larger data sets) to achieve improved stratification of risk within the broadly termed 'high-risk' category will be necessary.

It is also important to recognize that the risk stratification tools presented were derived and validated in a 'mixed' cohort of patients—approximately 25% of patients enrolled in REPLACE-1 and -2 had an acute coronary syndrome, whereas 75% were less urgent or even elective patients. Unfortunately, we are not provided data about the performance of the risk factor tools in each of these patient subsets. One would expect that three of the seven risk factors comprising the final model (IABP, GP IIb/IIIa inhibitor, and recent low molecular weight heparin use) were most prevalent in the cohort of patients with acute coronary syndrome. It is also likely that this group contributed disproportionately to the number of bleeding events. As such, the utility of the risk factor tool in patients undergoing non-urgent PCI is not clear.

Finally, it should be noted that these models were derived in patients undergoing PCI via femoral access and as such will not apply to procedures performed through a radial approach. In fact, given the lower rate of major bleeding with radial access, estimates of high bleeding risk using the present tool may warrant a change from planned femoral access to a radial approach.

In summary, the work performed by Nikolsky et al. represents an important starting point for the development of clinically useful tools to predict bleeding in patients undergoing PCI. Refinement of their tool(s) will require consideration of additional patient, health care provider (operator, hospital volume, etc.), and procedural variables. Derivation and validation of resulting models should be performed separately for patients requiring PCI for acute coronary syndrome and those undergoing non-urgent PCI given differences in patient profile, utilization of adjunctive therapies, overall bleeding risk, and PCI efficacy (compared with medical therapy) between these groups. Finally, given the selection bias inherent in randomized clinical trials, any resulting bleeding risk tool will require validation in the 'real-world' setting. Analysis of patient profiles within the GRACE registry has demonstrated that patients enrolled in randomized clinical trials differ markedly in terms of baseline characteristics, hospital treatment, and outcomes from the patients who are not eligible for such trials. Validation of future risk assessment tools in a broader selection of patients may be accomplished using data from large community-based registries of patients with stable and unstable CAD.

References

Clinical vignette

Intra-atrial course of the right coronary artery: a previously missed anomaly

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A 77-year-old woman with recurrent episodes of atypical chest pain was referred to computed tomography (CT) coronary angiography to rule out coronary artery disease. Her history was remarkable with regard to the risk factors arterial hypertension, hyperlipidaemia, and a positive family history for cardiovascular disease. Contrast-enhanced, retrospectively electrocardiography-gated dual-source CT coronary angiography (Siemens Medical Solutions) demonstrated no significant coronary stenoses with normal anatomy of the left main, left anterior descending, and left circumflex artery, whereas the right coronary artery showed an anomalous course. Although origin and proximal segment of the right coronary artery was normal with an epicardial course from the right coronary sinus along the anterior atrioventricular groove (Panel A), it passed through the anterior right atrial wall proximal to the acute angle (Panel B) and entered the cavity of the right atrium (Panel C). It then followed a completely intra-cavitary course over ~5.5 cm in length (Panel D). The distal right coronary artery then re-emerged into the epicardium proximal to the crux (Panels E and F).

Cardiac CT represents a cross-sectional imaging modality that allows the simultaneous depiction of coronary arteries, surrounding tissue, and cardiac chambers. The intra-cavitary course of a coronary artery is very rare and has been previously encountered only accidentally at coronary bypass surgery or autopsy. Owing to the purely luminographic nature of conventional coronary angiography, it is highly likely that such a vessel course has been previously missed and that the growing clinical use of cardiac CT may increasingly uncover this rare anomaly.

Panel A. Dual-source CT coronary angiography (cross-sectional image) demonstrating the normal epicardial course of the proximal right coronary artery within the anterior atrioventricular groove (arrow).

Panel B. Dual-source CT coronary angiography (cross-sectional image) illustrating the entrance of the right coronary artery through the anterior right atrial wall (white arrowhead).

Panel C. Dual-source CT coronary angiography (cross-sectional image) showing the intra-atrial course of the right coronary artery (black arrowheads).

Panel D. Dual-source CT coronary angiography (cross-sectional image) demonstrating the distal intra-cavitary course (black arrowheads) of the artery until exiting the right atrium (white arrowhead).

Panel E. Dual-source CT coronary angiography (maximum intensity projection along the right coronary artery) demonstrating the normal proximal segment (arrow), the intra-atrial course (black arrowheads), and the distal epicardial portion of the artery eventually reaching the crux (asterisk).

Panel F. Dual-source CT coronary angiography 3D image (volume rendering technique) showing the entry and exit (white arrowheads) of the right coronary artery. Note the origin of the acute marginal branch immediately proximal to the entry.