Barking up the right tree at last: another step closer to a universal definition of bleeding

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This editorial refers to ‘Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial†, by P. Vranckx et al., on page 2524

Over the last 10 years, bleeding has become a matter of concern for clinicians and a subject of intense debate. It is now widely accepted that bleeding is not a neutral event devoid of clinical significance, since many concordant reports have shown that bleeding in acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI) leads to a four- to five-fold increase in the risk of death and also in the risk of myocardial infarction and stroke at 30 days and in the longer term, depending on the severity and location of the bleed. Bleedings linked to instrumentation seem to carry a different impact on prognosis compared with bleeding that occurs spontaneously. In rare cases, bleeding per se may lead to death through massive, uncontrollable haemorrhage, inducing shock, or due to bleeding in critical areas, e.g. intracranial bleeding. However, the negative impact of bleeding is usually observed in patients who survive the bleeding event itself.

Although several hypotheses exist, the mechanisms by which bleeding influences outcome are as yet poorly understood and remain a subject of research. It is accepted that the negative impact of bleeding is multifactorial: haemodynamic compromise through hypovolaemia, or a hyperadrenergic state, which can have deleterious consequences on an already ischaemic myocardium. Discontinuation of antithrombotic drugs and, more particularly, dual antiplatelet therapy in this context can also have catastrophic consequences, with a risk of recurrence of thrombotic events and of acute stent thrombosis, also known to have a particularly deleterious impact on outcome. The role of blood transfusion is also hotly debated. It has been shown in multiple post-hoc analyses of clinical trials and registries that a liberal transfusion policy may lead to an excess of events, especially death. All these points are now well established, and have been taken into account in appropriate recommendations for bleeding avoidance and transfusion policies, first incorporated into practice guidelines already several years ago.1

Importantly, it is now established that a lower rate of bleeding leads to improved outcome, as observed in OASIS 5 and Horizons-AMI.3 In these two trials addressing different populations and testing different pharmacological environments and invasive strategies, a major reduction in bleeding translated into a significant reduction of death at 30 days and in the long term. In both trials, the reduction in death rate was attributable to the reduced bleeding rate. The loop is therefore closed—an increased risk of bleeding leads to an increased risk of death, but a risk reduction for bleeding leads to a risk reduction for death. Prevention of bleeding has become equally as important as the prevention of ischaemic events.

Interestingly enough, over the last decade, a trend towards a gradual decline in bleeding has been observed. In the GRACE registry, the frequency of bleeding was shown to have declined over time, despite the fact that the rate of intervention increased over the 7-year observation period.4 The reasons why bleeding is declining are unknown, and may be linked to changes in the definitions of bleeding used over time, or greater physician awareness of the risk of bleeding.5 Furthermore, an analysis of temporal trends in post-PCI bleeding from 2005 to 2009 in over a million patients from the National Cardiovascular Data Registry confirmed that there has been a gradual decrease in the rate of bleeding over the years, possibly driven by changes in antithrombotic therapy.5

However, quantification of bleeding is not an easy task. Bleeding rates depend mainly on the clinical setting, the baseline characteristics of the population, the pharmacological environment, the management strategy (invasive or not), and the definition of bleeding events. Indeed, several definitions, each categorizing bleeding complications of the population, the pharmacological environment, the management strategy (invasive or not), and the definition of bleeding events differently, are used to grade the severity of bleeding complications. This implies that the same term may represent different bleeding severity, and have a different clinical impact. It also implies that different bleeding complication rates may be observed within the same study population depending on the definition used to grade bleeding severity (Figure 1). Similarly, it renders comparisons of bleeding rates across trials or registries difficult. Thus, there is a pressing need for a universal definition of bleeding, which would...
make it possible to compare the risk of bleeding across trials and registries. A universal definition would necessarily be based on the following criteria: location of the bleed and relationship with the procedure, if any; drop in haemoglobin associated with the bleed, including pre-bleed and nadir haemoglobin levels; consequences of the bleed, such as death, permanent disability, or a decrease in blood pressure; and, finally, the number of units of blood transfused, if any. In order to improve our understanding of the mechanisms by which bleeding impacts on outcome, it would also be necessary to document whether the bleeding event led to the interruption of active drugs. Most bleeding scales are already based on some of these data, but combined in different ways. A universal definition recommending that all these points be taken into account would make it possible to compare bleeding rates on an equal footing between trials and registry studies.

The Bleeding Academic Research Consortium (BARC) proposed a new definition taking into account many of the requirements mentioned above, while still maintaining a certain degree of subjectivity. To date, the BARC definition of bleeding has been validated in a patient-level pooled analysis of 12 459 patients recruited in six randomized trials of patients undergoing PCI. A close association between bleeding events, as defined by the BARC, and mortality at 1 year after PCI was shown. However, the predictive accuracy of the BARC scale was not shown to be superior to that of the TIMI (Thrombolysis in Myocardial Infarction) or REPLACE2 definitions. Vranckx et al. now provide further confirmation of the predictive value of the BARC definition of the impact of bleeding on outcome.

The question now is, what is the added value of the BARC definition compared with existing bleeding scales used to quantify bleeding risk in clinical trials and registries? Close examination of the data of the study by Vranckx et al. clearly reveals that, compared with previous bleeding scales, the BARC definition has the same predictive value, as mirrored by the hazard ratios (HRs) for the different components of the BARC scale (BARC type III particularly), and those of the TIMI and GUSTO scales. It also has the same predictive accuracy when judged by Harrell’s C-statistic. This is hardly surprising, since the components of BARC type III bleeding are more or less the same as those used in the TIMI scale, and to a lesser extent in the GUSTO scale, namely a decrease in haemoglobin and the need for transfusion, amongst others. Therefore, it is not unexpected that the predictive value of the BARC definition should be equally as good as that of the TIMI and GUSTO scales. The only added value of the BARC definition is its potential to become a universally accepted bleeding scale, just like the ARC definition of stent thrombosis gradually came to be accepted as a standard. If the BARC scale were to enter into mainstream practice as the standard definition for bleeding in the future, this would represent a major advancement in the quantification of bleeding complications. Moreover, it would make it possible to compare bleeding rates between trials and registries more reliably.

However, a number of shortfalls remain. So far, the BARC definition has only been validated in the setting of coronary interventions. External validation in ACS with or without ST-segment elevation is lacking. One can assume that the validity would hold in ACS, but it is obviously necessary to obtain confirmation from clinical trials in the setting of ACS before declaring that this new definition should become universal. Secondly, validation has always been carried out on retrospective cohorts. There is a need to validate this new definition in prospective cohorts, i.e. ongoing randomized trials, vs. the conventional TIMI and GUSTO scales. In addition, previous validation was performed only in the setting of randomized clinical trials, which include highly selected and homogeneous patient populations that are not representative of routine practice. Validation in a registry setting would probably reveal whether this scale is accurate to quantify bleeding and predict its impact on outcome in a real-life population of all-comer patients. There are several registries ongoing in the field of ACS at the moment. For the sake of simplicity, some have chosen their own bleeding definitions, as it might be hard to impose such a complex measure as the BARC definition on investigators in a registry. The apparent complexity of the BARC definition may be a major obstacle to its use in this context. However, widespread validation in registries would be the only way to determine its real predictive value and accuracy in the future, in all sorts of populations—not only trial populations but also in real-life practice. Full validation of this kind would definitely confirm the universal validity of this bleeding scale.

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References

Giant primary right ventricular synovial sarcoma

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A 61-year-old man without prior medical history presented with progressive dyspnoea on exertion and right hypochondrial discomfort since 2 months. Clinical examination showed markedly dilated jugular and upper extremity veins without other signs of congestion, congruent with a vena cava superior syndrome. A transoesophageal echocardiogram (Panels A1 and 2) revealed a giant inhomogeneous intracavitary mass with broad insertion to the interventricular septum, obliterating the dilated right ventricle and extending into the right atrium and pulmonary trunk. Magnetic resonance imaging (MRI) depicted the large (10 × 4.5 cm) lobulated tumour with early and late inhomogeneous gadolinium contrast enhancement (Panels B1 and 2). An endovascular biopsy was performed and morphological analysis was consistent with a diagnosis of a poorly differentiated synovial sarcoma (Panel C). This diagnosis was confirmed with a fluorescence in situ hybridization test, which showed a translocation involving the SYT gene on chromosome 18. Positron emission tomography (PET) depicted the cardiac tumour, but no metastasis (Panel D). Because complete tumour resection was not feasible, palliative chemotherapy with doxorubicin and ifosfamide was started with clear regression of the tumour on MRI (Panels E1 and 2) and disappearance of PET avidity (Panel F) as a result. However, after chemotherapy discontinuation, the sarcoma progressed again.

Primary cardiac synovial sarcoma is an extremely rare malignancy, with a very poor prognosis. Complete macroscopic resection is usually not possible, and maintains a high local recurrence and metastasis rate.

There is no relationship with industry.