

A reduction in bleeding in acute coronary syndromes? Let's not rain on the parade!

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This editorial refers to 'Has the frequency of bleeding changed over time for patients presenting with an acute coronary syndrome? The Global Registry of Acute Coronary Events'[†], by K.A.A. Fox *et al.* on page 667

Bleeding is a frequently observed complication in patients suffering from acute coronary syndromes (ACS), as well as in patients submitted to percutaneous coronary interventions (PCI) or coronary artery bypass graft surgery (CABG). The rate of bleeding events varies greatly between reports, and depends mainly on the clinical setting, the baseline characteristics of the patients, the pharmacological environment, and the choice of vascular access in the case of invasive strategy. The rate of bleeding can also vary considerably depending on the scale used to measure haemorrhagic events. Among the many predictors of bleeding, the most powerful are age, sex, renal failure, use of glycoprotein (GP) IIb/IIIa inhibitors, vascular access, previous history of bleeding, and inappropriate dosage of antithrombotic therapies, particularly anticoagulants and GP IIb/IIIa inhibitors. Until recently, bleeding was considered to be inherent to the modern management of ACS, and was thought to be the price to pay to achieve an improvement in outcome. Basically, bleeding was a non-event. However, several reports have shown bleeding to be associated with a higher risk of death, myocardial infarction (MI), or stroke at 30 days and in the long term, irrespective of the clinical setting.^{1,2} In this context, a reduction in the rate of bleeding complications led to an improvement in outcome in at least two trials, and indeed even a reduction in death, MI, and stroke.^{3,4} The loop is therefore closed—more bleeding leads to an excess of death and ischaemic events, but less bleeding reduces the risk of death and ischaemic events.

The exact mechanisms that mediate the deleterious effect of bleeding on outcome are not fully understood. Premature interruption of antithrombotic drugs, amongst other factors, is high on the list of suspected mechanisms. Nevertheless, physicians have come to understand the risks associated with bleeding over the last few years, and it is now considered vital to minimize this

risk by choosing the most appropriate pharmacological environment and the safest vascular access. In addition, blood transfusion has also come under fire in recent times, as it is now suspected to have potentially deleterious effects, and may indeed add to the risk incurred by bleeding rather than providing a solution.⁵ Strong recommendations about how to prevent bleeding and reduce the risks associated with transfusion have been issued in the latest version of the European Society of Cardiology guidelines for the management of non-ST segment elevation ACS.⁶

In the report by Fox *et al.*, the frequency of bleeding observed in the Global Registry of Acute Coronary Events (GRACE) is reviewed in a cohort of >50 000 patients.⁷ A cohort of this size undoubtedly benefits from strong statistical power, conferring credibility on its results. The statistical analysis is robust, with adjustment for all baseline characteristics, clinical setting, pharmacotherapy, and interventions. The main finding of this report is that despite more aggressive management of ACS, shown by a gradual increase in the use of aspirin, thienopyridines, anticoagulants, invasive strategies, and PCI, the risk of major bleeding has declined over the last 7 years. After adjustment, the hazard ratio (HR) for bleeding is 0.94 [95% confidence interval (CI) 0.91–0.98], $P = 0.002$. This is unexpected, in view of the greater potential for bleeding associated with the wider use of aggressive drugs and procedures. The other main finding of this study—confirming previous observations—is that bleeding has quite a strong impact on the risk of death, with a 2- to 3-fold increase in death rate depending on the initial clinical presentation. As a reminder, the same group has previously reported that more aggressive management of ACS in the GRACE registry led to an improvement in clinical outcome. Achieving better outcome in ACS patients without an increase in bleeding—or, better still, with a decrease in bleeding—is certainly good news. These two phenomena might actually be at least partially linked to each other.

The key question is how to interpret these findings. How can we identify the mechanisms that have led to a decrease in bleeding over time, so that we could provide guidance to clinicians? The authors give little information about the use of strategies known

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to influence bleeding and which may have played a role in the observed reduction in risk. We just know that there was an increase in the uptake of antiplatelet therapy, especially aspirin plus thienopyridines, anticoagulant therapy, invasive strategies, and PCI. However, there is no information about vascular access. The authors assume that clinicians probably used smaller catheters and more frequent radial approach over time, but there are no data to support this assumption. We also lack data about the use of anticoagulants and GP IIb/IIIa inhibitors, such as the duration of treatment or the doses used. Registry data have shown that inappropriate dosage may lead to an increased risk of bleeding, especially in the elderly, females, and patients with renal failure.⁸ In the same way, it is not clear whether there was an increase in use of new anticoagulants known to reduce bleeding, such as fondaparinux and bivalirudin, over the study period. The only hard fact is that there is a trend towards decreasing use of GP IIb/IIIa inhibitors, particularly in the setting of ST-segment elevation MI (STEMI), where the greatest decrease in bleeding was observed in this registry. GP IIb/IIIa inhibitors are known to double the risk of bleeding. Can the decline in the use of GP IIb/IIIa inhibitors be entirely responsible for the decrease in bleeding? Probably not.

While the results of this report are interesting and encouraging, there is unfortunately nothing to explain how these results may have come about. We can only assume that physicians have at last begun to assimilate the message that bleeding risk is as important as ischaemic risk, and that they have changed their practices accordingly. The fact that the risk of bleeding varies considerably between the hospitals involved in the registry, despite similar baseline characteristics, could be indirect evidence of this possibility.

However, there is at least one other potential explanation. The problem with the definition of bleeding, regardless of the scale used to grade it, is that it is inextricably linked to blood transfusion. Transfusion is often a component of the scale used to measure bleeding, including the one used in the GRACE registry. This could mean that the reduction in bleeding observed in this registry could be an artefact, if, for example, physicians have moved towards more restrictive use of transfusion with lower triggers for transfusion. If this were the case, then there could be a corresponding, indirect, and somewhat artificial reduction in bleeding events. Here again, the data in the report by Fox *et al.*⁷ are not sufficient to support this theory. There are no data on the rate of transfusion in their report. In any case, if reports about the potentially deleterious effects of blood transfusion are right, then a decrease in blood transfusion rates can only have beneficial effects on outcome.

All in all, there is no message that this report can convey to clinicians except the factual observation that the bleeding rate has decreased over time. As a result, no clear recommendation can be given to clinicians except endless repetition of the fact that bleeding is bad, the factors that lead to an excess of bleeding are well established, and implementation of guidelines may lead to a risk reduction for bleeding and, consequently, improve outcome.⁶

So let's not rain on the parade! Whatever the mechanism, the risk reduction in bleeding cannot be anything other than positive for patients. It might just indicate that physicians are more conscious of the risks of bleeding and transfusion, and treat their patients more cautiously.

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