

# Impact of anaemia, bleeding, and transfusions in acute coronary syndromes: a shift in the paradigm

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**This editorial refers to 'Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction'<sup>†</sup> by D. Aronson *et al.*, on page 1289**

Over the last two decades, major improvements in clinical outcome have been achieved in the management of acute coronary syndromes (ACS), with or without ST-segment elevation. In both these clinical settings, the pharmacological approach comprising anti-platelet agents, (or a combination thereof), anticoagulants, thrombolytic treatment in case of ST-elevation MI (STEMI) combined with mechanical or surgical revascularization or reperfusion, has led to a dramatic reduction in the rate of ischaemic events, namely death, death/myocardial infarction (MI), or death/MI/stroke. However, this has been achieved at the cost of a higher risk of bleeding complications, which were considered, until recently, to be inherent to ACS management, and to be a side effect devoid of serious clinical implications, except for intra-cranial bleeding. Bleeding complications were thought to be the price to pay for the improvement in the risk of ischaemic events, and were considered to be easily controlled, particularly thanks to a liberal transfusion policy. In this context, the risk factors for bleeding have been identified, and include baseline characteristics, such as age, female gender, renal failure, diabetes, and heart failure. In addition, the number and dosage of anti-thrombotic drugs, the use of fibrinolytic treatments, and the use of invasive strategies, required to achieve mechanical reperfusion or revascularization, also play an important role.<sup>1,2</sup>

However, over the last 5 years, it has become clear that bleeding complications occurring during the initial phase of ACS have a considerable impact on prognosis, especially in terms of death, MI, and stroke, both in the short- and long-term. A four- to five-fold increase in the risk of death, MI, and stroke at 30 days has been observed in patients with bleeding events, as compared to those without.<sup>2–4</sup>

The potential mechanisms by which bleeding leads to a deterioration of prognosis are multiple, and include haemodynamic compromise, hyperadrenergic state triggered by blood loss and blood pressure drop, worsening of myocardial ischaemia, exaggeration of the inflammatory response, and also discontinuation of anti-thrombotics. In addition, transfusion may also add to the risk. A three- to four-fold increase in the risk of death at 30 days was observed in patients who were transfused, as compared to those who were not, in a meta-analysis of several trials in the setting of ACS.<sup>5</sup> Depletion of 2,3-diphosphoglycerate and nitric oxide in stored blood cells leading to reduced oxygen delivery at tissue level, an exaggeration of myocardial ischaemia, and generalized vasoconstriction are thought to be the main factors explaining the potential deleterious effects of transfusion on outcome.<sup>6,7</sup> Lastly, anaemia at baseline has also been shown to be a predictor of the risk of ischaemic events, with a 'J-shaped' relation between baseline haemoglobin levels and the rate of ischaemic events. Higher rates of ischaemic events have been observed with both high and low baseline haemoglobin levels, with the lowest rate of events being observed for haemoglobin levels in the range of 14–16 g/dL.<sup>8</sup> Decreased oxygen supplies to the myocardium, compounded by increased myocardial oxygen demand because of the higher cardiac output required to maintain adequate systemic oxygenation, are the potential mechanisms by which anaemia exerts its deleterious effects. Inadequate remodelling may also play a role in the risk.

Interestingly, data from a large trial in the setting of NSTEMI-ACS showed that the risk reduction for bleeding at 9 days had a huge impact on the risk of death, death/MI, and death/MI/stroke, shown to be significantly reduced at 30 days and 6 months.<sup>9</sup> In this trial, almost the entire reduction in the risk of death was explained by the risk reduction for bleeding. In other words, the loop is closed—an excess of bleeding leads to an excess of ischaemic events, but a reduction in bleeding complications leads to a risk reduction for ischaemic events. A new concept is therefore born—bleeding carries a high risk of death and MI, and transfusion could be potentially deleterious. Prevention of bleeding has the potential to reduce the risk of death, MI, and stroke, and has become as equally as important as the prevention of ischaemic events.

In this regard, the paper by Aronson *et al.*<sup>10</sup> sheds further light on this issue. This is a prospective study assessing the

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impact of admission, nadir, and discharge haemoglobin levels during hospital stay, on the in-hospital, and long-term outcome in terms of ischaemic events and occurrence of congestive heart failure. In this paper, anaemia at admission, according to the WHO definition, was observed in only 17.8% of patients. Major and minor bleedings occurred in 3.7 and 9.7%, respectively. However, more than 50% of patients experienced a drop in haemoglobin of  $>1.3$  g/dL during hospitalization, which means that many of them may have had occult bleeding, or oozing, not serious enough to be reported as an adverse event, but sufficient to lead to a significant decrease in haemoglobin levels.

This paper confirms that baseline haemoglobin level has an impact on prognosis—the lower the haemoglobin, the higher the rate of events. However, after adjustment on baseline characteristics and left ventricular function, the relation between baseline haemoglobin level and rate of events becomes weak. In contrast, nadir and discharge haemoglobin levels were shown to have a strong impact on death and occurrence of heart failure in the short- and long-term. The study by Aronson *et al.*<sup>10</sup> also confirms another known fact, namely that renal function, use of thrombolytic treatment, or revascularization procedures, diabetes, and heart failure are all independent predictors of development of anaemia during hospital stay. Unfortunately, the impact of blood transfusion on outcome could not be rigorously assessed in this study. According to the authors, many factors may explain the deterioration of prognosis induced by anaemia, or worsening of anaemia, during hospital stay. These include increased inflammatory response, inappropriate excentric remodelling of the myocardium, higher oxygen consumption, increased diastolic wall stress, and accelerated myocyte loss. Furthermore, greater neuro-hormonal activation may also play a role.

Above all, the paper by Aronson *et al.*<sup>10</sup> demonstrates that even in the absence of clinically overt bleeding, a drop in haemoglobin frequently occurs during the course of ACS, and leads to adverse events, in terms of both death and heart failure post-discharge, incurred by several different mechanisms. This is further evidence that bleeding, whatever the mechanism and intensity, has a strong impact on prognosis. Prevention of bleeding has become equally as important an objective in the treatment of ACS as the prevention of ischaemic events. Recent evidence has shown that a reduction of bleeding events has a positive impact on prognosis, and leads to a risk reduction for death, death/MI, and death/MI/stroke.<sup>9</sup>

The risk factors for bleeding and ischaemic events considerably overlap, with the result that patients at high risk of ischaemic events are also at high risk of bleeding complications. Risk stratification for ACS should therefore involve careful evaluation of both ischaemic and bleeding risks, with a view to reducing both through a judicious choice of pharmacological environment and reperfusion/revascularization strategies. The choice of the pharmacological environment (dual or triple antiplatelet therapy and anticoagulants) has become critical, as has the dosage of the drugs. Registry data have shown that the risk of bleeding increases as a function of the number of anti-platelet and anticoagulants agents used in combination. In addition, excessive doses are frequently used in clinical practice,

particularly in elderly patients and in renal dysfunction.<sup>1</sup> Reducing the risk of bleeding implies that the anti-thrombotic agents must be carefully selected, favouring those that reduce bleeding risk. Particular attention has to be paid to renal dysfunction, known to be frequent in elderly and diabetic patients. The risk of bleeding is already seriously increased for moderate renal dysfunction, with creatinine clearance between 30 and 60 mL/min.<sup>2</sup> In this range corresponding to moderate renal failure, the pharmacokinetics of drugs with complete or partial renal elimination have to be reassessed and the dosage reduced accordingly. Last but not least, as an invasive strategy is a main contributor to the risk of bleeding, the choice of the vascular approach in patients at high bleeding risk is also critical. The choice of a radial route over the femoral route may help to reduce bleeding risk.

In conclusion, a complete shift in the paradigm has occurred. From now on, clinicians will have to take into account not only the ischaemic risk, but also the risk of bleeding complications in patients with ACS. They will have to do their best to reduce both. The time has come to hammer home this message!

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