Anticoagulants and antiplatelet therapies, and revascularisation/reperfusion with percutaneous coronary interventions (PCIs) or surgery are the mainstay of modern treatment of acute coronary syndromes (ACS) with and without ST-segment elevation. In addition, depending on the clinical presentation, thrombolytic therapy may be necessary in patients with ST-elevation myocardial infarction (MI) who do not have access to primary PCI. The use of multiple antiplatelet agents or anticoagulants combined with revascularisation has led to an increased rate of bleeding complications, which were once thought to be inherent to the modern therapeutic approach in ACS and PCI, and seen as the price to pay for an improvement in outcome. Bleeding complications were more or less considered to be a non-event that could easily be fixed with appropriate measures, and blood transfusion if needed. However, it has recently been shown that bleeding has a strong impact on the risk of death, MI and stroke in patients with ACS. In addition, the role of transfusion has been criticised because it may actually have a deleterious effect, which could compound the risk.1–4

**Frequency of Bleeding Complications and Predisposing Factors**

The frequency of bleeding complications in the setting of ACS and PCI is difficult to assess and almost impossible to compare across trials and registries, because of the lack of universal definition of bleeding. Indeed, the rate of bleeding complications is highly dependent on the definition used, and also varies according to the setting and the population under consideration. In light of these restrictions, the rate of major bleeding varies from 1 to 5% and the rate of minor bleeding from 2 to 7%, depending on the source of the data (trials or registries). The rate of bleeding reported in registries is generally higher than that of clinical trials, because the populations included in registries are usually sicker and older than those included in clinical randomised trials.5,6

Many factors have been identified as being independent predictors of bleeding (see Table 1). Undoubtedly, the most potent predictors are age, low bodyweight, female gender, renal failure, use of glycoprotein (GP) IIb/IIIa inhibitors and a previous history of bleeding. Of course, invasive procedures are a major predictor of bleeding complications in the setting of ACS. In addition, inadequate dosage of drugs may lead to an excess of bleeding. This has been shown in particular with anticoagulants and intravenous antiplatelet agents, and was more frequently observed among the elderly, females and patients with impaired renal function; all groups that are known to be already at a particularly high risk of bleeding.7

**Risk Stratification for Bleeding**

Contrary to risk stratification for ischaemic events where a range of validated risk scores exist, there is currently no universally accepted risk score for the stratification of bleeding risk at the initial phase of ACS.8,9 A risk score has recently been described to characterise risk of bleeding in the setting of planned PCI10 and ACS.11 Although ACS patients tend to differ in terms of baseline characteristics (particularly age) from patients submitted to planned PCI, virtually the same variables as those used to calculate the risk score appeared to be predicative of bleeding complications in both risk calculators. However, since only the baseline characteristics were used in the definition of the bleeding score in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry, two major components of the bleeding risk are not taken into account, i.e. previous history of bleeding and use of PCI.

Indeed, the predictors of both ischaemic risk (death, MI and stroke) and bleeding risk largely overlap. Thus, the most frail population is exposed not only to the highest risk of death and MI in the short and long term, but also to the highest risk of bleeding. In practical terms, this means that risk stratification for bleeding should be part of the evaluation process during the initial phase of ACS and PCI. Treatments and procedures should take into account the risk of bleeding, and physicians should give precedence to treatment approaches known to minimise risk of bleeding (see Table 1). This attitude is important, not only for the acute phase, but also for the long term, since after ACS or PCI, patients are submitted to long-term dual antiplatelet therapy, thus exposing them to a long-term risk of bleeding. Recently, it has been shown that in the setting of ACS a higher level of dual antiplatelet therapy leads to a better outcome, but at the cost of a significant increase in bleeding risk.12

Table 1

**Impact of Bleeding and Transfusion in Acute Coronary Syndromes and Percutaneous Coronary Interventions**

A report by

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Impact of Bleeding on Outcome

Several concurrent reports have shown that bleeding at the initial phase of ACS or after PCI leads to a four- to five-fold increase in the risk of death, MI and stroke at 30 days and six months (see Figure 1). The impact of bleeding on outcome varies with the initial severity: the more severe the bleed, the greater the impact on outcome.1,2,14

The mechanisms by which bleeding influences outcome are currently poorly understood. Indeed, bleeding may lead to haemodynamic compromise through hypovolaemia triggering a hyperadrenergic state, which can have deleterious consequences on an already ischaemic myocardium. Discontinuation of antithrombotics and, more particularly, dual antiplatelet therapy in this context can also have catastrophic consequences, with a risk of a recurrence of thrombotic events and of sub-acute stent thrombosis. In addition, bleeding is known to stimulate inflammation, which in turn may lead to further interaction and development of atherosclerosis and plaque instability.1

In fact, it was shown in a large population from the Global Registry of Acute Coronary Events (GRACE) that the excess of events, particularly death after bleeding, is also linked to baseline characteristics, with the most frail patients suffering the highest rate of events.15

The Case for Blood Transfusion

Reports have consistently shown that blood transfusion is associated with detrimental effects. An excess of death and MI has been observed in pooled analyses incorporating several thousand patients who received transfusion versus those who did not, at the initial phase of ACS (see Figure 2). A similar deleterious effect of transfusion has also been reported in the setting of coronary artery bypass graft (CABG) surgery16 and acute (non-cardiac) care.17 A recent report in the setting of CABG surgery showed that there was an increased risk of infection, especially lung infections, and an increased risk of ischaemic events for patients submitted to transfusion compared with those who were not transfused during CABG.16 In this report, there was a stepwise increase in the hazard ratio (HR) for development of infection or further ischaemic events according to the number of units of blood transfused. These results have given rise to a debate about the real utility of transfusing preserved blood, and it is now advocated to limit transfusion to patients in gravely unstable haemodynamic situations. A restrictive blood transfusion strategy tested in the context of acute (non-cardiac) care was shown to lead to better results than a more liberal policy in terms of mortality and organ failure.17,18,19 However, the level of haematocrit or haemoglobin at which transfusion should be given is poorly understood. Indeed, bleeding may lead to haemodynamic compromise through hypovolaemia triggering a hyperadrenergic state, which can have deleterious consequences on an already ischaemic myocardium. Discontinuation of antithrombotics and, more particularly, dual antiplatelet therapy in this context can also have catastrophic consequences, with a risk of a recurrence of thrombotic events and of sub-acute stent thrombosis. In addition, bleeding is known to stimulate inflammation, which in turn may lead to further interaction and development of atherosclerosis and plaque instability.1

Several mechanisms may explain why transfusion of preserved blood may in fact exert a deleterious effect. Storage leads to rapid degradation of the properties of red blood cells. The longer blood is stored in the blood bank, the more its capacity to transport and deliver

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### Table 1: Multivariate Model for Major Bleeding in Patients with Non-segment-type Elevation Myocardial Infarction

| Variable               | Adjusted OR | 95% CI   | p value |
|------------------------|-------------|----------|---------|
| Age (per 10-year increase) | 1.22        | 1.10–1.35 | 0.0002  |
| Female sex             | 1.36        | 1.07–1.73 | 0.0116  |
| History of renal insufficiency | 1.53        | 1.13–2.08 | 0.0062  |
| History of bleeding (per 20 mmHg decrease) | 2.18        | 1.14–4.08 | 0.014   |
| Mean arterial pressure  | 1.14        | 1.02–1.27 | 0.019   |
| Diuretics              | 1.91        | 1.46–2.49 | <0.0001 |
| UFH*                   | 0.72        | 0.52–0.98 | 0.027   |
| GPIIb/IIIa inhibitors only | 1.86        | 1.43–2.43 | <0.0001 |
| Thrombolytics and GPIIb/IIIa inhibitors | 4.19        | 1.68–10.4 | 0.002   |
| Intravenous inotropic agents | 1.88        | 1.35–2.62 | 0.0002  |
| Right-heart catheterisation | 2.01        | 1.38–2.91 | 0.003   |

CI = confidence interval. * referent groups: male gender; unfractionated heparin (UFH) for low-molecular-weight heparin (LMWH) only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor glycoprotein (GP) IIb/IIIa inhibitors for thrombolytics only, LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor glycoprotein (GP) IIb/IIIa inhibitors for thrombolytics only, LMWH only, both LMWH and UFH, and neither LMWH nor UFH.

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### Figure 1: Kaplan-Meier Estimates of 30-day Mortality Among Patients Who Developed and Did Not Develop Major Bleeding

![Kaplan-Meier estimates of 30-day mortality among patients who developed and did not develop major bleeding.](image)

**Randomisation**

| Group            | Number at Risk | Days  |
|------------------|----------------|------|
| No bleeding      | 33676          | 0    |
| Blood transfused | 470            | 10   |
|                  | 419            | 15   |
|                  | 3157           | 20   |
|                  | 32990          | 25   |
|                  | 32079          | 30   |
|                  | 32769          |      |

**Log rank p<0.001**

### Figure 2: Kaplan-Meier Estimates of 30-day Mortality Among Patients Who Did and Did Not Receive Blood Transfusion

![Kaplan-Meier estimates of 30-day mortality among patients who did and did not receive blood transfusion.](image)

**Randomisation**

| Group            | Number at Risk | Days  |
|------------------|----------------|------|
| Transfusion      | 2398           | 0    |
| No transfusion   | 21684          | 10   |
|                  | 2356           | 15   |
|                  | 2317           | 20   |
|                  | 2274           | 25   |
|                  | 2237           | 30   |
|                  | 2217           |      |

**Log rank p<0.001**

Survival data were missing for three patients who received a transfusion and for 27 patients who did not receive a transfusion.
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oxygen is reduced. Depletion of 2,3-diphosphoglycerate (2,3DPG) is practically immediate once fresh blood has been collected and stored. 2,3DPG is intimately linked to oxygen affinity and regulates oxygen transport and delivery at tissue level. Micровascular circulation is impaired by transfused red blood cells, since transfusion induces an important vasoconstrictive reaction, which could be due to depletion in nitric oxide (NO). Red blood cell deformability observed under normal shear stress conditions is altered in preserved blood cells, thereby impairing microcirculation.

**Decreased Bleeding Risk Leads to Improved Outcome**

In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (Oasis-5) study, which compared enoxaparin with a new anticoagulant, fondaparinux, a 50% risk reduction for bleeding at nine days was observed in favour of fondaparinux, leading in turn to a significant risk reduction for death at 30 days and six months. Most of the reduction in the death rate was imputable to the risk reduction for bleeding. Similarly, in the Harmonizing Outcomes with Revascularization and Stents (HORIZONS) study, the use of bivalirudin in the setting of primary PCI for ST-elevation myocardial infarction led to a significant risk reduction of bleeding compared with a combination of anticoagulants plus GPIIb/IIIa inhibitors. In this study, a significant reduction in death at 30 days was observed, probably linked to the risk reduction for bleeding. Therefore, the loop is 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.

The paradigm in the treatment of patients suffering from ACS is now shifting. Prevention of bleeding has become equally important as the prevention of ischemic events. Therefore, when dealing with ACS patients at the time of risk stratification, the risk of bleeding must be considered in the same way as the risk of ischemic events. The most appropriate therapeutic strategy should be chosen depending on the proven capacity of a drug, treatment or procedure to reduce bleeding risk (see Table 1).

In this regard, the choice of vascular approach is critical. It has been shown in a meta-analysis that using a radial approach leads to a significant reduction of bleeding complications at the site of vascular approach. Furthermore, in a large registry involving more than 30,000 patients in Canada, the use of the radial approach was shown to significantly reduce the need for blood transfusion, taken as a surrogate marker for bleeding. The radial approach was also shown to reduce the risk of death at one year by 17% (odds ratio [OR] 0.83 [0.71-0.98]; p=0.001 radial versus femoral).

**Practical Approaches to the Risk of Bleeding**

The management of ACS or PCI patients should incorporate risk stratification for both ischemic and bleeding risk. Risk scores exist for the stratification of both risk of death and risk of bleeding, in both ACS and PCI. However, clinical judgement is critical to the decision-making process. Decisions must be made on a case-by-case basis, particularly among more frail patients. This implies that a careful approach has to be taken when selecting drugs and their dosage and interventions. Since many of the drugs used in the treatment of ACS are eliminated by the renal route, extreme attention has to be paid to renal function. Creatinine clearance or, preferably, the glomerular filtration rate (GFR) must be systematically measured for every patient and monitored during treatment to guide the choice of drug and dose. Renal failure is a major determinant of bleeding complications, with an exponential increase in risk of bleeding with declining renal function, particularly for creatinine clearance <60ml/minute or GFR <60ml/minute/1.73m². As a result, inappropriate dosage or unnecessary prolonging of treatment may lead to an accumulation of the drug in the organism and thereby to a higher risk of bleeding, even for moderate renal dysfunction. The selection of drugs known to reduce the risk of bleeding is necessary to minimise risk of bleeding complications. In summary, the following steps should be taken to address the risk of bleeding:

- evaluation of ischemic risk, according to the presence or absence of predictors of bleeding (see Table 1);
- baseline characteristics must be taken into account, particularly age, female sex and low bodyweight;
- renal function has to be evaluated by calculating creatinine clearance and/or GFR; and
- previous history of bleeding must be recorded, recent and ongoing bleeding must be searched for.

With these simple measures, the bleeding risk of an individual patient can be well evaluated and the treatment strategy can be customised to favour drug associations and duration of therapy that minimise bleeding risk. In addition, the need for invasive strategy has to be evaluated according to the initial ischemic risk of patient, also taking into account co-morbidities and expected beneficial effect in perspective with the bleeding risk. The appropriate vascular access route must be chosen, favouring radial access where possible.

**Management of Bleeding Complications**

No interruption of active treatments is required in cases of minor bleeding. However, major bleeding such as gastrointestinal bleeding, retroperitoneal bleeding, intracranial haemorrhage or severe blood loss requires the interruption of antiplatelet and anticoagulant treatment, and neutralisation where possible, particularly if bleeding cannot be brought under control by specific interventions. If local treatment is successful in controlling active bleeding, such as gastrointestinal bleeding, interruption of anticoagulant and antiplatelet therapy is unnecessary. However, the risk of withdrawing antithrombotic and/or antiplatelet agents must be put into perspective.
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with the risk of thrombotic events, especially if the patient has recently undergone stent implantation. In the latter case, acute thrombotic events can occur in the first five days following withdrawal of active treatment leading to catastrophic complications, but the risk may persist for up to one month.²

Protamine sulphate is a specific inhibitor of unfractionated heparin (UFH), but it has little or no impact on the factor Xa inhibitors. Low-molecular-weight heparin (LMWH) is only partly inhibited by protamine sulphate. For fondaparinux recombinant factor VII is the only possible treatment, but it is particularly costly.

It is impossible to reverse antiplatelet activity, since both aspirin and clopidogrel are irreversible platelet inhibitors. Only the regeneration of platelets, whose turnover rate is about 10–20% per day, can normalise platelet function. In cases of active bleeding the only possibility is platelet transfusion, although there is no firm evidence or recommendations for the optimal usage or dosage in this context.²³

In case of active or acute bleeding occurring under GPIIb/IIIa inhibitor therapy, the only possibility of returning platelet function to normal is by platelet transfusion. As mentioned above, again there is no firm evidence of the efficacy of this procedure and no guidelines exist to stipulate optimum levels of platelets to transfuse in order to restore normal platelet function. The situation is slightly different according to which GPIIb/IIIa inhibitors have been administered. Small molecules (tirofiban and eptifibatide) are rapidly cleared by the renal route, with the result that their effects may disappear within four to eight hours after interruption of therapy. However, with abciximab longer inhibition of platelet function can be anticipated after interruption of treatment.

When active bleeding has been brought under control, anticoagulant and antiplatelet therapy can be resumed, but not until at least 24 hours have elapsed since the last episode of bleeding. In cases of gastrointestinal bleeding linked to peptic ulcer, re-introduction of antiplatelet therapy, particularly aspirin, needs to be associated with proton pump inhibitors.

Conclusion

Until recently, bleeding was considered to be inherent to the therapeutic approach required to treat ACS patients. However, it is now evident that bleeding has a strong impact on outcome in terms of excess risk of death, myocardial infarction and stroke.

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