Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes

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Introduction

Antithrombotic therapy and invasive risk stratification in selected high-risk patients have improved outcomes from non-ST-segment elevation acute coronary syndromes (NSTE-ACS), but carry a risk of bleeding and blood transfusion. Although the true incidence of bleeding depends on the population studied (i.e. clinical trial vs. registry), the definition used, and the use of invasive procedures, it is becoming clear that bleeding is associated with an increased risk for adverse outcomes including myocardial infarction and death. Blood transfusion itself may carry a risk for ischaemic outcomes that is independent of bleeding. Therefore, therapies that provide an adequate level of anticoagulation to reduce ischaemia while simultaneously minimizing the risk of bleeding and transfusion have the potential to improve outcomes among patients with NSTE-ACS. Anticoagulants studied in recent clinical trials that have focused on bleeding reduction include fondaparinux and bivalirudin. In this review, we discuss the clinical trial evidence for these agents, the association between bleeding and clinical outcomes, the biology of blood transfusion and potential mechanisms underlying its association with adverse outcomes, and propose strategies to deal with bleeding complications. Future directions for research and clinical practice are also discussed.

Methods

The primary purpose of this paper is to provide a narrative review of data related to bleeding complications among patients with NSTE-ACS. Formal meta-analytic techniques were not employed; however, a comprehensive literature review was performed to identify all relevant clinical and experimental studies. We included both observational and randomized clinical studies as well as in vitro and in vivo experimental studies. The review is divided into 2 parts: (i) a discussion of the incidence, predictors, and outcomes associated with bleeding; and (ii) a discussion of therapeutic options to deal with bleeding and bleeding risk. A systematic search of the MEDLINE database was performed using subject headings appropriate to each part of the review. For example, the subject headings 'anaemia', 'haemorrhage', 'coronary artery disease', 'MI', 'unstable angina', and 'outcomes' were used to identify relevant studies for part 1, and the subject headings 'anaemia', 'haemorrhage', 'coronary artery disease', 'MI', 'unstable angina', 'red blood cell transfusion', 'nitric oxide', 'erythropoietin', 'anticoagulants', and 'therapy' were used to identify the relevant literature for part 2. Searches were not restricted to specific journals or time periods, and specific quality criteria were not applied.
**Part 1: Defining the problem**

**How does one define bleeding?**

A discussion of the incidence of bleeding complications among patients with NSTE-ACS cannot begin without a discussion of the various bleeding definitions that have been employed in clinical trials and registries. The two most commonly used classification schemes are the *Thrombolysis In Myocardial Infarction* (TIMI) and *Global Use of Strategies to Open Occluded Coronary Arteries* (GUSTO) scales, or some combination of the two (*Table 1*). Both were developed in the context of fibrinolytic therapy, but have been used to classify bleeding complications in clinical trials of NSTE-ACS and percutaneous coronary intervention (PCI), as well as NSTE-ACS and PCI registries. The TIMI definition of bleeding uses 4 categories: major, minor, minimal, and none. The GUSTO bleeding definition likewise uses four categories: severe or life-threatening, moderate, mild, and none.

The use of different definitions across studies can influence the reported incidence of bleeding (*Table 2*). Rates tend to be higher in registries compared with clinical trials, likely due to a more complex patient population represented in the former. The difference in bleeding definitions (e.g., laboratory-based vs. clinical) also has the potential to create confusion when attempting to assess the safety of antithrombotic therapy. For example, in the *Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy* (PURSUIT) trial, the rate of TIMI major bleeding among patients assigned to the platelet inhibitor eptifibatide was 3.0%, yet the rate of GUSTO severe bleeding in this same group was 1.1%. Moreover, the proportion of patients receiving eptifibatide deemed to have no TIMI bleeding was 84.2%, but the proportion deemed to have no GUSTO bleeding was 68.8%. Similarly, in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial of enoxaparin vs. unfractionated heparin, the rate of TIMI major bleeding was 9.7% among patients assigned to enoxaparin, but the rate of GUSTO severe bleeding was only 2.7%.

Other trials have used variations of the definitions described earlier. For example, the REPLACe-2 trial comparing bivalirudin and heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing urgent or elective PCI used a definition that included both laboratory measures and clinical events. Similarly, the CURE and OASIS trials of patients with NSTE-ACS also used bleeding definitions that included decreases in haemoglobin, as well as clinical bleeding such as retroperitoneal haemorrhage. It is also important to note the variation across trials in the reporting of bleeding associated with coronary artery bypass grafting (CABG). Many NSTE-ACS trials simply report non-CABG major bleeding, while others report both CABG and non-CABG bleeding rates. CABG-related bleeding rates tend to be higher than non-CABG bleeding rates, as would be expected. An association has been found between peri-operative transfusion and increased mortality after CABG, but the relationship between bleeding and mortality is less clear, especially when suspected bleeding is evaluated with prompt re-exploration. However, a full discussion of the incidence, predictors, and outcomes specific to CABG-related bleeding is beyond the scope of this review.

**What is the incidence of bleeding among non-ST-segment elevation acute coronary syndromes patients?**

On the basis of the above data, it is clear that reported estimates of the incidence of bleeding during antithrombotic therapy for NSTE-ACS are dependent on the definition used. In addition, rates of bleeding can vary with the rate of invasive procedures employed across clinical trials. Trials performed in a setting of conservative rather than invasive management will have lower rates of cardiac catheterization, PCI, and CABG, and thus will have correspondingly lower rates of bleeding. Figure 1 displays the reported incidence of ‘major’ bleeding across various trials. The definition of ‘major’ or ‘severe’ bleeding was different in each and incorporated some measure of either decreased haemoglobin or blood transfusion. Estimating the incidence of bleeding is even more difficult in trials where more than one definition is used. For example, in the SYNERGY trial comparing enoxaparin with unfractionated heparin in NSTE-ACS patients, there appeared to be a statistically significant excess of TIMI major bleeding.
in patients receiving enoxaparin; however, there was no significant difference in the incidence of GUSTO severe bleeding between the two arms. Other trials demonstrate congruity in the incidence of bleeding regardless of definition used. In the OASIS-5 trial comparing fondaparinux with enoxaparin in NSTE-ACS patients, incidence of both TIMI major and ‘OASIS’ major bleeding was similar. Another complicating factor is the evolution of NSTE-ACS therapy to include multiple antithrombotic medications. The addition of antiplatelet therapy, oral (clopidogrel) or

<table>
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<th>Trial</th>
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<tr>
<td>SYNERGY</td>
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<td>Major bleeding</td>
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<td>• Life-threatening (fatal, intracranial, requiring surgical intervention, results in hypotension, decrease in Hgb ≥ 5 g/dL, or required ≥ 4 units of blood)</td>
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<td>• Other major bleeding episodes (requiring transfusion of 2 or 3 units, intracocular). Minor bleeding</td>
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<td>• Other major bleeding episodes (requiring transfusion of 2 or 3 units or judged to be disabling).</td>
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<td>All other bleeding events classified as Minor.</td>
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<td>OASIS-5</td>
<td>NSTE-ACS</td>
<td>Fondaparinux vs. enoxaparin</td>
<td>Major bleeding</td>
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<td>• Fatal, intracranial, retroperitoneal, intraocular leading to vision loss</td>
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<td>• Any other clinically significant bleeding not meeting Major criteria leading to study drug interruption, surgery, or transfusion of 1 unit of blood</td>
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<td>OASIS-6</td>
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<td>Fondaparinux vs. placebo or heparin</td>
<td>Major bleeding</td>
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<td>• Fatal, intracranial, retroperitoneal, intraocular leading to vision loss, or bleeding requiring surgery</td>
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<td>• Any other clinically significant bleeding not meeting Major criteria leading to study drug interruption, surgery, or transfusion of 1 unit of blood</td>
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<td>REPLACE-2</td>
<td>PCI</td>
<td>Bivalirudin vs. heparin + GP IIb/Illa</td>
<td>Major bleeding</td>
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<td>• Intracranial, intraocular, or retroperitoneal haemorrhage</td>
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<td>• Clinically overt blood loss resulting in a decrease in haemoglobin of more than 3 g/dL</td>
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<td>• Any decrease in haemoglobin of more than 4 g/dL</td>
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<td>• Transfusion of 2 or more units of packed RBCs or whole blood.</td>
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<td>ESPRIT</td>
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<td>EPIC</td>
<td>PCI</td>
<td>Abciximab bolus vs. abciximab bolus + infusion vs. placebo</td>
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<td>EPILOG</td>
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<td>Abciximab/low dose heparin vs. heparin</td>
<td>TIMI</td>
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<tr>
<td>EPILOG</td>
<td>PCI</td>
<td>Abciximab/low dose heparin vs. heparin</td>
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NSTE-ACS, non-ST-elevation acute coronary syndromes; GP, glycoprotein; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; PCI, percutaneous coronary intervention; std, standard; TIMI, Thrombolysis In Myocardial Infarction (see text for definition).
intravenous (glycoprotein IIb/IIIa inhibitors), increases bleeding rates. Coupled with this is an evolution in the use of antithrombotic drugs. Specifically, it has been recognized that aggressive dosing of unfractionated heparin leads to a higher incidence of bleeding in the ST-segment elevation MI, the NSTE-ACS, and PCI settings. In addition, failure to adjust the doses of renally excreted anticoagulant drugs (e.g. enoxaparin and the glycoprotein IIb/IIIa inhibitor epifibatide) in patients with chronic kidney disease may increase the risk of bleeding. Finally, many trials use blood transfusion as a marker for bleeding, which is easily quantifiable but can prove problematic, considering the variability in transfusion practice across centres. Given these limitations, as well as the variability in the definitions used, the incidence of ‘major’ or ‘severe’ bleeding can be estimated as being between <1 and 10%.

In registry or administrative databases, bleeding rates also tend to vary from those in clinical trials not only because of the definitions used, but also due to differences in patient characteristics and practice patterns. In the Global Registry of Acute Coronary Events (GRACE) Registry, Moscucci et al. reported that the rate of major bleeding among NSTE-ACS patients was 3.9%. Major bleeding was defined as life-threatening bleeding requiring transfusion of ≥2 units of packed red cells, or leading to an absolute haematocrit decrease of ≥10%, or subdural haematoma. In the U.S. CRUSADE registry of NSTE-ACS patients, bleeding is measured by the incidence of blood transfusion. Yang et al. found that the 10.3% of patients in the CRUSADE registry who did not undergo CABG received at least one blood transfusion during hospitalization.

The issue of using transfusion as a measure of bleeding deserves discussion. The advantage of using transfusion as an indicator of bleeding is that it captures a clearly defined event related to a bleeding event significant enough to warrant intervention. However, as mentioned earlier, use of blood transfusion as a surrogate for bleeding can be problematic due to variations in transfusion practice. Indeed, the optimal transfusion strategy in patients with ischaemic heart disease remains elusive and is controversial.

It should be noted that all measures of bleeding are influenced by practice variation. For example, decisions on the timing of phlebotomy to monitor haemoglobin values, use of crystalloid that may result in dilutional anaemia, and how closely one looks for a site of bleeding can all influence whether a bleeding event is identified.

**Does bleeding matter?**

Until recently, bleeding was considered an inevitable complication of NSTE-ACS therapy. An increased risk of bleeding seemed acceptable provided that antithrombotic agents reduced the incidence of recurrent ischaemic events (e.g. MI). A growing body of literature, however, suggests that bleeding itself is associated with adverse outcomes, including MI and death. For example, Kinnaird et al. examined 10 974 PCI patients treated at three centres to determine the association between TIMI major bleeding, TIMI minor bleeding, and transfusion and in-hospital and 1-year mortality. There was a numerically higher incidence of major adverse cardiac events (including death, recurrent MI, and repeat revascularization) as bleeding severity worsened. After adjustment for potential confounders, TIMI major bleeding and transfusion were independently associated with in-hospital mortality, and transfusion was independently associated with 1-year mortality.

Rao et al. examined 26 452 patients with NSTE-ACS from the PURSUIT, PARAGON B, and GUSTO IIb studies and used a statistical technique known as ‘time-dependent covariate analysis’ to determine the relationship between levels of GUSTO bleeding and short and intermediate-term outcomes. The time-dependent covariate technique takes into account the timing of events so that only outcomes occurring after the bleeding event are considered. They found a stepwise increase in risk of 30-day death, 30-day death or MI, and 6-month death as bleeding worsened. Even GUSTO mild bleeding was associated with a significantly worse prognosis compared with no bleeding.

Eikelboom et al. evaluated the impact of bleeding on prognosis among 34 146 NSTE-ACS patients enrolled in the OASIS trials. They too found a significant association between major bleeding (as defined in the trials) and 30-day mortality. This association was present across patient subgroups and co-interventions administered in the hospital. Importantly, this study also found an association between major bleeding and other ischaemic events such as MI and stroke.

These studies demonstrate the association between bleeding and other adverse outcomes and suggest that bleeding reduction is an attractive therapeutic goal that may lead to improved survival among patients with NSTE-ACS, provided that ischaemic events are also reduced. One issue that bears further clarification relates to the different bleeding definitions used in the studies mentioned earlier. When considered separately, it appears that both TIMI and GUSTO scales identify bleeding complications that place patients at risk for increased mortality. It is also important to note that the findings of the above studies demonstrate an association between bleeding and adverse outcomes. These data should not be taken to imply causality. Indeed, the mechanisms behind the associations are likely complex and may relate to hypotension, anaemia, ineffective oxygen delivery, vasoconstriction, platelet dysfunction, or cessation of evidence-based antithrombotic or antiplatelet therapies.

**Which bleeding definition should be used?**

The variability in the definitions used across clinical trials and studies examining outcomes associated with bleeding raises two questions: (i) should the definition be standardized and (ii) if so, which definition is the ‘best’? There are several advantages to using a standard definition for
bleeding. First, from a research perspective, it allows for comparison of bleeding rates across therapies as the ‘cocktail’ of drugs and interventions for NSTE-ACS treatment becomes more complex. Secondly, the use of a data standard streamlines development of future clinical trials and registries. Thirdly, existence of a standard bleeding definition could potentially evolve into a measure that could be used as part of the definition for a quality indicator. Fourthly, from a clinical standpoint, a standardized bleeding definition facilitates the risk-benefit assessment of therapies for certain patient subgroups. Finally, standardization of a bleeding definition reduces the possibility of ‘gaming’ clinical trials of newer anticoagulants to make them appear safe.

If one assumes that a consistent bleeding definition should be used, the issue then becomes which of the myriad definitions already used in prior clinical studies should be adopted. As outlined in the previous section, the risk associated with TIMI bleeding has been explored in the PCI population and the risk associated with GUSTO bleeding has been explored in the NSTE-ACS population. The American College of Cardiology task force on clinical data standards recommends that the TIMI classification of bleeding be used as the standard.33 Although the TIMI definition is commonly used in trials and registries, there has only been one study comparing the clinical effect of TIMI bleeding with the clinical effect of GUSTO bleeding. Rao et al.13 examined data from two large international clinical trials involving 15 454 patients to determine the association between the degrees of TIMI bleeding or GUSTO bleeding and 30-day death or MI. In this analysis, both definitions were used in the same patients, thereby minimizing confounding due to different patient populations. After adjustment for baseline characteristics and blood transfusion, there was a stepwise increase in the risk for death or MI with worsening GUSTO bleeding. In contrast, all degrees of TIMI bleeding were associated with a similar risk. Finally, after adjustment for differences in patient characteristics and presentation as well as blood transfusion, there was a stepwise increase in the risk of 30-day and 6-month death or MI with worsening GUSTO bleeding; in contrast, TIMI bleeding had no prognostic value (Figure 2A and B).

This study suggests that clinically evident bleeding is more important for prognosis than bleeding detected only through laboratory measurements. Therefore, it seems reasonable that, based on the available evidence, a definition of bleeding that incorporates both clinical indices (e.g. bleeding with hypotension) and some measure of need for transfusion may be the most comprehensive. We must recognize, however, that ‘need for transfusion’ is highly subjective. In addition, transfusion may confer a risk that is separate from bleeding (see in what follows). At a minimum, use of standard data elements (which could allow generation of more than one definition) is warranted.

Who bleeds?

Although the incidence of bleeding can vary across trials and registries, a surprisingly consistent message has emerged with respect to risk factors for developing bleeding complications. Almost every study that has examined predictors of bleeding in ST-segment elevation MI, NSTE-ACS, and PCI has found that older age, female gender, lighter body weight, use of invasive procedures, and renal insufficiency all are powerful predictors of bleeding complications.15,34 Age, renal function, and use of invasive procedures appear to be the most predictive, regardless of antithrombotic strategy.10,15,35 This consistency suggests that these patient subgroups are most likely to benefit from treatment strategies that reduce bleeding risk while maintaining an antithrombotic effect.

One interesting predictor of bleeding and blood transfusion that has been noted in recent studies is delivery of care in the United States.9,10 Although several papers have examined transfusion practice within specialties,11,36,37 there are few data on international variations in bleeding and transfusion rates. Two issues emerge from this variation in practice: (i) the suggestion that there are biological differences in the response to antithrombotic therapies across regions and (ii) the lack of guidance on the use of blood transfusion in patients with NSTE-ACS. Further study is needed to address these concerns.
Part 2: Dealing with the problem

Therapeutic options

The occurrence of bleeding complications may lead to a number of events that place the patient at risk for death. Foremost among these is cessation of anticoagulant therapy, potentially leading to an increased risk for thrombosis. Other sequelae of bleeding include hypotension, anaemia, and reduction in oxygen delivery. Despite the potential risks, anticoagulant therapy should be discontinued if bleeding leads to hypotension or if bleeding is brisk. This should be followed by haemodynamic support with fluid repletion and vasopressor therapy as necessary. All of these actions, however, clearly place the patient at risk for recurrent ischaemia and infarction. Once anaemia occurs as a result of bleeding, the patient continues to be at risk.38–40 Anaemia has several effects on the myocardium. Mild-to-moderate anaemia (Hgb 7.0–10.0 g/dL) leads to increased cardiac output, primarily through reduced blood viscosity leading to reduced afterload. Under these conditions, myocardial oxygen demand does not change.41 The myocardium has a high oxygen-extraction ratio, however, and can augment oxygen delivery only by increasing coronary blood flow. Such an increase may not be possible in patients with fixed coronary stenoses. In the normal healthy heart, oxygen consumption and oxygen extraction are relatively constant at haematocrit levels between 20–60%.42 There are considerable experimental data suggesting that a haemoglobin level of 7 g/dL is tolerated without myocardial ischaemia if there is no obstructive coronary artery disease (CAD). With coronary artery obstruction, however, ischaemia can occur with even mild anaemia in experimental circumstances.43

One target for therapy, therefore, is to raise haematocrit levels in order to augment oxygen delivery. Two currently available options to increase haemoglobin levels are erythropoietin and red blood cell (RBC) transfusion. Erythropoietin is a 165 amino acid glycoprotein secreted in response to hypoxia. Although aggressive use of erythropoietin in patients with end-stage renal disease has been associated with an increase in cardiovascular events,44 there is substantial interest in its role as therapy for congestive heart failure;45 trials are currently ongoing. There are no data, however, on the use of recombinant erythropoietin for acute anaemia that occurs in the setting of therapy for NSTE-ACS. RBC transfusion is the most readily available method to increase haematocrit in anaemic patients. Because reduced blood volume and reduced oxygen delivery can lead to myocardial ischaemia in the setting of CAD, it is commonly believed that patients with ischaemic heart disease require a higher haemoglobin level in order to prevent adverse events. While clinical studies suggest that raising haemoglobin levels via transfusion increases oxygen delivery,42,46,47 studies also show that measures of tissue oxygenation either decrease or do not change.42,47,48 The reason for this paradox (greater oxygen delivery but no improvement in tissue use) is unclear, but alterations in erythrocyte nitric oxide biology in stored blood may provide a partial explanation. Nitric oxide (NO), a gas essential to oxygen exchange,49 is depleted in stored RBCs, which may cause them to function as NO ‘sinks,’ leading to vasoconstriction and platelet aggregation.50

Two recent non-randomized studies came to different conclusions regarding optimal haematocrit level in patients with acute cardiac ischaemia or infarction. Wu et al.29 examined outcomes after RBC transfusion among 78 974 Medicare beneficiaries with acute MI. Both in-hospital and 30-day mortality were significantly lower among patients with a higher haematocrit level at admission. In logistic regression analysis, blood transfusion was associated with lower 30-day mortality among patients with an admission haematocrit concentration between 5 and 33%, but it was associated with a non-significant increase in mortality among patients with a baseline haematocrit >33%. In contrast, Rao et al.10 examined the association between RBC transfusion and mortality among 24 111 patients with NSTE-ACS and found that transfusion increased mortality when administered for a nadir haematocrit above 25% (Figure 3). The potential harm associated with RBC transfusion in patients with NSTE-ACS is further supported by an analysis of 74 271 patients enrolled in the CRUSADE registry.41 Patients who received an RBC transfusion during hospitalization had a higher risk for in-hospital death and death or MI.

It is important to note that despite the apparent contradictions in the findings of these studies, all affirm the danger with aggressive transfusion of RBCs. The largest randomized trial comparing aggressive and conservative RBC transfusion strategies included 838 critically ill patients with a haemoglobin concentration of <9.0 g/dL within 72 h of admission to the ICU.51 By an intention-to-treat analysis, there was no difference in 30-day all-cause mortality between the groups, but 30-day mortality was significantly higher with the liberal strategy of transfusion in patients who were younger than age 55 or had an Acute Physiology And Chronic Health Evaluation (APACHE) II score <20. There also were significantly more MIs and cases of pulmonary oedema with the liberal transfusion strategy. This trial included only 77 patients with unstable angina or MI, and in a post hoc subgroup analysis of patients with CAD, there was no difference in 30-day mortality between strategies. These data are underscored by a systematic overview of 10 randomized trials of transfusion strategies that found that a restrictive transfusion strategy is associated with non-significant trends towards decreased mortality, MI, and congestive heart failure.52 Until further randomized data are available, aggressive use of blood transfusion to maintain predefined haemoglobin levels in stable patients with CAD cannot be recommended. This is consistent with published guidelines on the appropriate use of RBC transfusion that do not recommend transfusion in stable patients regardless of nadir haemoglobin or haematocrit value; however, these guidelines do acknowledge the lack of randomized data to guide use of RBC transfusion in patients with ischaemic heart disease.41

Pharmacological strategies to prevent bleeding complications

Given that the use of erythropoietin to treat anaemia due to bleeding complications is unproved and that the use of blood transfusion in stable patients is controversial, the best strategy may be to prevent bleeding complications altogether. This is not easily accomplished in all patients, and may be particularly difficult in patients at higher risk for bleeding,
such as the elderly and those with renal insufficiency. It is important to note that foundation for the treatment of NSTE-ACS is antithrombotic and antiplatelet therapy along with revascularization in high-risk patients, and use of these strategies has led to decreased morbidity and mortality. These outcomes could be further improved by strategies that maintain an anticoagulant effect sufficient to reduce ischaemia while simultaneously minimizing bleeding. A variety of options are available to achieve this goal: judicious dosing of antithrombotic medications, careful selection of patients for invasive risk stratification, and incorporation of newer anticoagulant strategies into treatment algorithms.

With regard to antithrombin therapy, inappropriate dosing has been implicated as one reversible cause of bleeding among patients with NSTE-ACS. This is true for antithrombin therapies and glycoprotein IIb/IIIa inhibitors. For example, weight-adjusted dosing of unfractionated heparin is associated with a reduced risk for bleeding. When low-molecular-weight heparins are used, careful attention must be paid to renal function because these agents are renally excreted. Even mild-to-moderate chronic kidney disease can lead to an increased risk for bleeding, which has led to interest in modest dose adjustment for these patients. Similarly, renal function affects dosing of glycoprotein IIb/IIIa inhibitors, and either downward dose adjustment or avoidance appears to be the prudent strategy for patients with moderate to severe renal dysfunction. Unfortunately, these dose adjustments are not often implemented in clinical practice. Review of medication data from the CRUSADE registry of over 140,000 patients with NSTE-ACS demonstrates that both antithrombin therapy and glycoprotein IIb/IIIa inhibitors are often overdosed in elderly patients, leading to a significant increase in bleeding complications (Figure 4A and B).

Other dosing strategies that appear to reduce the risk of bleeding deal with the oral antiplatelet agents aspirin and clopidogrel. Peters et al. performed a post hoc analysis of 12,562 NSTE-ACS patients enrolled in the CURE trial that compared aspirin alone with the combination of aspirin and clopidogrel to determine the effect of aspirin dose on efficacy and bleeding. There was a stepwise increase in the incidence of major bleeding as aspirin dose increased in both treatment groups (aspirin alone: dose ≤ 100 mg = 1.9%, 101–199 mg = 2.8%, ≥ 200 mg = 3.7%, P < 0.0001; aspirin + clopidogrel: dose ≤ 100 mg = 3.0%, 101–199 mg = 3.4%, ≥ 200 mg = 4.9%, P < 0.0009). Importantly, there was no increase in efficacy at higher doses, suggesting that aspirin doses between 75–100 mg daily represented the optimal risk-benefit balance. In terms of clopidogrel, another post hoc analysis of the CURE trial demonstrated a higher rate of peri-CABG bleeding in the aspirin plus clopidogrel arm until clopidogrel had been discontinued for 5 days pre-operatively. Although caution must be exercised in interpreting these retrospective non-randomized comparisons, lowering aspirin dose and waiting 5 days after clopidogrel discontinuation before performing CABG appears to be associated with reduced bleeding complications.

Two anticoagulants that have been studied in clinical trials that specifically focused on reductions in bleeding as well as ischaemia are the direct thrombin inhibitor bivalirudin and the synthetic pentasaccharide fondaparinux. Bivalirudin is a specific and direct inhibitor of thrombin with a half-life of 25 min (in subjects with normal renal function). It is cleared from plasma by a combination of renal mechanisms and proteolytic cleavage and does not bind to plasma proteins. It is currently approved for use in unstable angina patients undergoing balloon angioplasty and with provisional use of glycoprotein IIb/IIIa inhibitors in patients undergoing PCI. This latter indication was based on results from the REPLACE-2 trial that randomly assigned 6010 patients undergoing urgent or elective PCI to receive conventional therapy with unfractionated heparin and planned glycoprotein IIb/IIIa inhibitor or bivalirudin with provisional glycoprotein IIb/IIIa inhibitor. The primary endpoint was the composite of 30-day death, MI, target vessel revascularization, and major bleeding (so-called 'net clinical

![Figure 3](image-url) The relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. From Alexander et al., with permission.)
outcome'). As stated earlier, the definition of ‘major’ bleeding included both clinical as well as laboratory parameters (e.g. intracranial or retroperitoneal bleeding, transfusion of ≥2 units of blood, a decrease in haemoglobin of > 4 g/dL). The trial was powered to show non-inferiority of bivalirudin with regard to the primary ‘quadruple’ endpoint. The composite endpoint did demonstrate non-inferiority, with no statistically significant difference in death, MI, or target vessel revascularization between arms, but a statistically significant reduction in major bleeding was seen in patients randomized to bivalirudin. Long-term results of the REPLACE-2 trial demonstrated no significant difference in 12-month survival between arms, but a trend towards lower mortality in the bivalirudin arm was seen that potentially could be explained by the lower in-hospital bleeding rates.57

The REPLACE-2 trial has been controversial because of the inclusion of safety (bleeding) with efficacy (death, MI, or TVR) in the primary endpoint.58 Another issue was the dose of unfractionated heparin used in the control arm, which resulted in higher activated clotting time (ACT) values than those recommended by PCI guidelines.59 These limitations were addressed in the PROTECT-TIMI 30 trial comparing bivalirudin with either heparin or enoxaparin plus eptifibatide in high-risk NSTE-ACS patients undergoing PCI.60 The trial was powered to show superiority of enoxaparin or heparin plus eptifibatide with regard to coronary flow reserve; the safety endpoint was TIMI major haemorrhage. The heparin dosing used in this trial was lower than that in REPLACE-2 and resulted in median ACT values of 200–250 s. In terms of efficacy, coronary flow reserve favoured bivalirudin, whereas TIMI myocardial perfusion grade favored eptifibatide. In terms of safety, the rates of TIMI minor haemorrhage (heparin/enoxaparin + eptifibatide: 2.5%, bivalirudin: 0.4%, P = 0.027), TIMI major haemorrhage (heparin/enoxaparin + eptifibatide: 0.7%, bivalirudin: 0%, P = 0.308), and transfusions (heparin/enoxaparin + eptifibatide: 4.4%, bivalirudin: 0.4%, P < 0.001) were lower in the bivalirudin arm, even with the lower heparin dose.

Whether this benefit extends to the treatment of acute coronary syndromes was examined in the ACUITY trial.21 The ACUITY trial randomly assigned 13,819 moderate-to-high-risk NSTE-ACS patients to one of three arms: a heparin (either unfractionated heparin or
enoxaparin) with a glycoprotein IIb/IIIa inhibitor, bivalirudin with a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone with provisional glycoprotein IIb/IIIa inhibitor given for recurrent or refractory ischaemia or for PCI-related complications. Similar to the REPLACE-2 trial, the primary endpoint was the 30-day composite of death, MI, ischaemia-driven revascularization, or non-CABG major bleeding. The definition of non-CABG major bleeding in ACUITY was unique to the trial and included clinical as well as laboratory parameters. The trial demonstrated superiority of the bivalirudin-alone strategy with respect to the 'net clinical outcome' (‘heparins’+GP IIb/IIIa: 11.7%, bivalirudin+GP IIb/IIIa: 11.8%, bivalirudin alone: 10.1%, P < 0.001). This was driven by a 47% reduction in non-CABG major bleeding. The trial has been controversial due to a generous non-inferiority margin (25% compared with conventional 10% in other trials), a rapid time to cardiac catheterization (median time from study drug administration to angiography ~4.0 h), and for a potential interaction between thienopyridine pre-treatment and outcomes that suggested an increase in ischaemic events with bivalirudin monotherapy among patients who had not received a thienopyridine prior to angiography or PCI. Despite these limitations, the ACUITY trial provides support for the use of bivalirudin in the management of NSTE-ACS in the context of rapid invasive risk management and bleeding reduction.

Another agent that has demonstrated efficacy in the treatment of NSTE-ACS while simultaneously reducing bleeding is fondaparinux. Fondaparinux is a synthetic pentasaccharide that selectively binds to antithrombin III to potentiate its neutralization of Factor Xa. It is cleared through the kidney and has an elimination half-life of 17–21 h. The OASIS-5 trial compared fondaparinux 2.5 mg subcutaneously per day with enoxaparin 1 mg/kg subcutaneously twice daily in 20 078 patients with acute coronary syndromes. Patients with a creatinine level of ≥265 μmol/L were excluded from the study. The mean duration of treatment was 6 days. The trial demonstrated non-inferiority of fondaparinux compared with enoxaparin with respect to the primary outcome of MI, refractory ischaemia, or death at 9 days (5.8 vs. 5.7%, HR 1.01: 95% CI: 0.90–1.13). However, the risk of major bleeding at 9 days was substantially lower in patients treated with fondaparinux compared with enoxaparin (2.2 vs. 4.1%, HR 0.52: 95% CI: 0.44–0.61) and by 30 days, there was a statistically significant 17% reduction in 30-day death among patients treated with fondaparinux (2.9 vs. 3.5%, HR 0.83: 95% CI: 0.71–0.97). The effect of fondaparinux on survival remained evident at the end of follow-up at 180 days. Importantly, 95% of the difference in mortality occurred among the patients who suffered bleeding, suggesting that the lower mortality with fondaparinux may have directly resulted from the lower bleeding. A safety signal noted in OASIS-5 concerned patients who underwent PCI. There was a higher rate of catheter thrombus formation among patients treated with fondaparinux compared with those treated with enoxaparin (although it was noted in both arms). The rate of this complication was lower in both arms (but still numerically higher among those assigned to fondaparinux) after the protocol was amended to include administration of intravenous unfractionated heparin to patients undergoing PCI. It should be noted that the dose of heparin needed to prevent thrombus formation during PCI on a background of fondaparinux therapy is unclear.

The role of fondaparinux in ST-segment elevation MI was evaluated in the OASIS-6 randomized trial that compared fondaparinux 2.5 mg subcutaneously per day with usual care, consisting of either placebo or unfractionated heparin (depending on local investigator preference) in 12 092 patients. Patients allocated to receive unfractionated heparin were treated for up to 48 h, after which they were switched to placebo. Fondaparinux significantly reduced risk of death or reinfarction at 30 days compared with usual care (9.7 vs. 11.2%, HR 0.86; 95% CI: 0.77–0.96); these benefits were preserved to study end at day 180. Fondaparinux was again associated with a trend towards reduced risk of major bleeding (1.8 vs. 2.1%, hazard ratio 0.83; 95% confidence interval: 0.64–1.06), despite the fact that the majority of patients in the control group did not receive an active comparator drug beyond 48 h. The safety issues raised among patients undergoing PCI in OASIS-5 were seen again in patients undergoing primary PCI in OASIS-6: there was a non-significant higher incidence of 30-day death or MI among patients treated with fondaparinux compared with those treated with unfractionated heparin or placebo, suggesting that fondaparinux should not be the sole anticoagulant used during PCI.

Future directions

Despite the recognition of bleeding risks with NSTE-ACS therapy over a decade ago, there remain several areas of therapeutic uncertainty. Although there are studies that show a consistent association between bleeding and mortality (as discussed earlier), the causal mechanisms to explain this association remain unclear. The OASIS-5 study suggests that the lower mortality observed with fondaparinux may have directly resulted from lower rates of bleeding. More data regarding the mechanisms underlying the bleeding-mortality association can lead to the development of strategies to further improve NSTE-ACS outcomes. In addition, there is a state of equipoise regarding the role of blood transfusion in patients with ischaemic heart disease and bleeding or anaemia. There are no randomized clinical trials of transfusion strategies in patients with CAD and the appropriate 'transfusion trigger,' if one exists, is unknown. Furthermore, investigation into additional blood-based alternatives for raising haematocrit levels (e.g. erthropoietin) or improving oxygen delivery in anaemia is warranted.

With regard to antithrombotic agents, there should be detailed studies on the pharmacokinetics and pharmacodynamics of new and existing drugs in patients at high risk for bleeding, such as the elderly and patients with renal insufficiency. At the same time, efforts to improve appropriate prescribing of antithrombotic medications to these at-risk populations should be implemented. Development of new drugs that provide reliable anticoagulation across treatment strategies (i.e. invasive vs. conservative) while simultaneously reducing bleeding may provide important advances in management of NSTE-ACS.

Concomitant with the development of new treatment strategies or therapeutic agents must be an evolution of clinical trial designs. The excellent outcomes with current PCI technology have resulted in some important clinical
trials being underpowered to address their primary efficacy hypotheses. Therefore, clinical trial designs should evolve to accommodate improved outcomes. Although efficacy as it has been classically described (death, MI, TVR) should still be the primary focus, there are emerging data that the traditional safety endpoint of bleeding affects at least two components of the efficacy composite (death and MI). This is the rationale for the quadruple endpoint, or composite clinical benefit, which includes death, MI, TVR, and bleeding. It is important to note that inclusion of bleeding in the efficacy endpoint does not mean that a sacrifice should be made with respect to death or MI. Rather, it means that one must be willing to accept a potentially small decrease in efficacy for a large benefit in safety. This approach has been used to design non-inferiority trials, in which the trial design accepts a small decrement in efficacy with an experimental agent if it has other advantages over the control (e.g. ease of use, cost savings, etc.).

Conclusions

The evolution of management of NSTE-ACS over the past two decades has consistently led to improved ischaemic outcomes, but at the cost of increased risk of bleeding and blood transfusion. Variability in definitions of bleeding across clinical trials and registries makes it difficult to accurately compare the true rates of bleeding, but it is clear that certain groups, such as the elderly and those with renal insufficiency, are at high risk for bleeding complications. Strategies to deal with bleeding complications once they occur include cessation of antithrombotic therapy and/or blood transfusion, both of which are associated with worse clinical outcomes; therefore, prevention appears to be the most prudent approach. This includes judicious dosing of antithrombin therapy and careful assessment of patient risk when using antithrombolic medications, but even these strategies are not without their limitations. The number of unanswered questions in the realm of bleeding and its treatment, there is an immediate need for more research into transfusion medicine (e.g. transfusion triggers, non-transfusion alternatives, blood substitutes) among patients with CAD, the study of high-risk populations, and new antithrombotic agents that decrease bleeding risk and/or allow better control of coagulation. Significant effort needs to go into reaching a professional consensus on how to weigh the risk of bleeding with the benefits of potent antithrombotic agents.

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References


Clinical vignette

Infarct-related left ventricular diverticulum

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A 64-year-old woman presented with sudden onset central chest pain. Her ECG showed dynamic anterior, inferior, and lateral ST changes, suggestive of ischaemia. Her 12 h troponin I was 17.04 ng/mL (normal <0.1).

She was treated with enoxaparin, aspirin, clopidogrel, and atenolol, and in view of recurrent pain, tirolbant was started 2 days later. She subsequently underwent coronary angiography. This showed moderate disease in the proximal LAD and RCA with severe disease in the small but non-dominant circumflex artery. Left ventricular (LV) angiography showed good LV function with filling of a diverticulum (Image); contrast cleared rapidly from the diverticulum, indicating contractile function.

To assess further, she had a CT scan. This demonstrated a narrow-necked diverticulum extending from the LV into the posterior wall. Her condition was managed conservatively. She was discharged pain free.

LV diverticula following myocardial infarction are rarely reported. The pathogenesis is unclear but such diverticulae are believed to result from incomplete LV rupture caused by haemorrhagic dissection extending outwards from the endocardium but arrested within the infarcted LV wall. Resorption and organization of the haematomata leads to diverticulum formation.

Supplementary movies are available at European Heart Journal online.

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