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SPECIAL ARTICLE

Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology

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Bleeding has recently emerged as an important outcome in the management of acute coronary syndromes (ACS), which is relatively frequent compared with ischaemic outcomes and has important implications in terms of prognosis, outcomes, and costs. In particular, there is evidence that patients experiencing major bleeding in the acute phase are at higher risk for death in the following months, although the causal nature of this relation is still debated. This position paper aims to summarize current knowledge regarding the epidemiology of bleeding in ACS and percutaneous coronary intervention, including measurement and definitions of bleeding, with emphasis on the recent consensus Bleeding Academic Research Consortium (BARC) definitions. It also provides an European perspective on management strategies to minimize the rate, extent, and consequences of bleeding. Finally, the research implications of bleeding (measuring and reporting bleeding in trials, the importance of bleeding as an outcome measure, and bleeding as a subject for future research) are also discussed.

Keywords Bleeding • Haemorrhage • Percutaneous coronary intervention • Thrombosis • Acute coronary syndromes • Unstable angina • Myocardial infarction

Rationale

Enormous strides have been made in improving the care of patients with acute coronary syndromes (ACS), resulting in substantial improvements in acute outcomes.[1] Among these developments, key factors appear to be steady refinements in antithrombotic therapy in the acute phase, which nowadays routinely includes oral antiplatelet drugs (aspirin and thienopyridines), a parenteral antithrombin [unfractionated heparin (UFH), low-molecular-weight heparins, fondaparinux, or bivalirudin] given intravenously or subcutaneously, and often an intravenous glycoprotein IIb/IIIa receptor blocker. In addition, the early use of coronary angiography with a view to revascularization has increased and has often become the default management approach. As the efficacy of treatment increased, the residual risk of major adverse cardiac events related to thrombosis, such as death and myocardial infarction, diminished, and the potential for further improvement in efficacy declined. Renewed attention

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Table 1 Examples of frequently used classifications of bleeding events[2,3,6–8]

Classification	Severity	Criteria
TIMI	Major	Intracranial bleeding. Overt bleeding with a decrease in haemoglobin ≥5 g/dL or decrease in haematocrit ≥15%
	Minor	Spontaneous gross haematuria. Spontaneous haematemesis. Observed bleeding with decrease in haemoglobin ≥3 g/dL but haematocrit ≤15%
	Insignificant	Blood loss insufficient to meet criteria listed above
GUSTO	Severe	Deadly bleeding. Intracerebral bleeding or substantial haemodynamic compromise requiring treatment
	Moderate	Bleeding requiring transfusion
	Mild	Other bleeding not requiring transfusion or causing haemodynamic compromise
ACUITY	Major	Intracranial or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma with a diameter of at least 5 cm, a reduction in haemoglobin levels of at least 4 g/dL without an overt bleeding source or at least 3 g/dL with such a source, reoperation for bleeding, or transfusion of a blood product
PLATO	Major life-threatening bleeding	Fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in haemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells
	Other major	Bleeding that led to clinically significant disability (e.g. intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the haemoglobin level of at least 3.0 g per deciliter but less than 5.0 g per deciliter or requiring transfusion of 2 to 3 units of red cells
	Minor	Any bleeding requiring medical intervention but not meeting the criteria for major bleeding
GRACE	Severe	Bleeding requiring transfusion of ≥2 units of packed red blood cells; bleeding resulting in a ≥10% decrease in haematocrit or death; or intracranial/subdural bleeding
STEEPLE	Major	Fatal bleeding; retroperitoneal, intracranial, or intraocular bleeding; bleeding that causes haemodynamic compromise requiring specific treatment; bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event; clinically overt bleeding, requiring any transfusion of ≥1 unit of packed red cells or whole blood; clinically overt bleeding, causing a decrease in haemoglobin of ≥3 g/dL (or, if haemoglobin level not available, a decrease in haematocrit of ≥10%)
ISTH	Major	Fatal bleeding or symptomatic bleeding in a critical area or organ (e.g. intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular), or a bleeding causing haemoglobin decrease of >2 g/dL, or requiring >2 U transfusion

has therefore been drawn to the other side of the risk/benefit equation: bleeding. This article aims to summarize current knowledge regarding bleeding in ACS and percutaneous coronary intervention (PCI), including the epidemiological evidence, basic research issues, and an European perspective on management strategies to minimize the rate and extent of bleeding. In addition, a recent unified effort from stakeholders involved in studies of antithrombotic agents led to a consensus bleeding definition, the Bleeding Academic Research Consortium (BARC), which is presented.

Bleeding definitions

The overall aim of classifications is to systematize the reporting and categorization of bleeding events in a numerical and unequivocal fashion to allow comparisons across data sets. Some of the most widely used bleeding definitions used in clinical trials are the criteria developed by the 'Thrombolysis in Myocardial Infarction' (TIMI)[2] and the 'Global Use of Strategies To Open coronary arteries' (GUSTO) study groups[3] (*Table 1*). The latter are clinically based, while the former definition includes laboratory-based assessments. Many other definitions are used. All have been refined over time to attempt to be as objective as possible and account for blood transfusions, yet the prognostic impact of bleeding may vary across definitions.[4]

Used originally for the study of thrombolytic regimens in acute myocardial infarction, these classifications have subsequently been used in many PCI studies, although they may fail to capture bleeding which is clinically relevant in that setting, such as bleeding at vascular access sites.[5] Conversely, many ACS studies have developed their own scales,[4,6,7] and have sometimes enrolled patients undergoing either conservative (medical) treatment or PCI, with no particular differentiation between non-invasive or invasive treatment algorithms (*Table 1*). The International Society on Thrombosis and Haemostasis (ISTH) has proposed a bleeding scale to increase comparability across studies,[8] which was endorsed by the European Medicines Agency (EMA),[9] with the recommendation, however, of adding the 'cessation' criterion. In addition to these criteria, the Agency demands meticulous recording of haemoglobin (Hb) and haematocrit (Hc) changes, as well as a quantification of blood loss by an objective method.

While most classifications have evolved towards increased reporting details, other scales have attempted a simplification of reporting, as in the classification by the Global Registry of Acute Coronary Events (GRACE) Investigators.[10] Others have argued for an increased focus on minor long-term bleeding events,[11] often either neglected or under-reported in trials, but which may be of importance to patients beyond the acute phase and impact adherence to antithrombotic therapies[12] proposing a bleeding classification that covers the entire spectrum of bleeding

Table 2 Bleed score classification[13]

Severity	Criteria	Points
Superficial	Easy bruising, bleeding from small cuts, petechia, ecchymosis	1
Internal	Haematoma, epistaxis, blood loss from mouth, vagina, melena, eye bleed, haematuria, haematemesis	3
Alarming	Transfusion needed, intracranial, life threatening	6

The minimal BleedScore is 0, each event is added. Points are accrued on an open-ended scale. Bleeding complications are monitored continuously throughout a given trial. For reporting purposes, the 30 contiguous days prior to a given patient assessment (e.g. during a trial study-visit) constitute the index-month for reporting the BleedScore. A subscript-index ('S', 'I' or 'A') is given at the end of the score, reflecting each category from which points were accrued.
Example for scores: 1S, 0I, 0A; 2S, 3I, 6A; etc.
For simplified statistical assessment, e.g. in large-scale trials, points can also be combined into a pooled total BleedScore (e.g. in the examples above: pooled BleedScore 1+0+0 = 1; 2+3+6 = 11 etc.)

complications[13] (*Table 2*). The clinical relevance of the milder bleeding events may vary depending on the clinical setting: it may be minimal when considering life-saving thrombolytic treatment in acute myocardial infarction but important for outpatients beyond the first few months after an ACS.

Defining bleeding is particularly difficult in specific settings such as during the peri-operative period for coronary artery bypass grafting (CABG) surgery where some degree of blood loss and transfusion is extremely common. Because patients undergoing bypass surgery are at high risk of bleeding, CABG-related bleeding may account for a disproportionate number of bleeding events in ACS trials even though only approximately 10% of ACS patients ultimately undergo surgery. Excluding these CABG-related bleeds from safety outcomes in clinical trials violates the intention-to-treat analysis principle, while including them may dilute differences in bleeding risk. Such different approaches were recently used in the TRITON-TIMI38 and PLATO trials.

Because there are multiple definitions and multiple iterations of a given definition, it is often difficult for clinicians to know the clinical relevance of the bleeding risk associated with new therapies. The lack of a common definition also hampers comparison across studies. There have therefore been calls for use of common data elements and for a consensus grading of bleeding events severity.[4,14]

Recently, a consensus effort by academics, research organizations, industry, and regulator representatives resulted in the Bleeding Academic Research Consortium (BARC) standardized bleeding definitions for cardiovascular clinical trials.[15] In developing these definitions, consideration was given to the need to address some of the limitations of some of the classical historical definitions, to capture bleeding events which are meaningful to patients and impact clinical outcomes, while remaining practical and easy to implement. These broadly applicable definitions attempt to describe both CABG-related, non-CABG-related, and total bleeding rates, in a hierarchical manner characterizing severity using an objective graded numerical system nomenclature (*Table 3*). These definitions are based on consensus rather than data driven. Yet, because of the importance of a unified definition, it will be important that they be validated against existing and future data sets in order to be embraced by all the clinical trial community and become routinely used in clinical practice.

Epidemiology of bleeding in acute coronary syndrome

Emerging evidence of a strong and potentially modifiable association of bleeding with subsequent adverse outcomes[10,16,17] has focused the attention of clinicians on the determinants of bleeding and methods to avoid bleeding in patients with an ACS.[4] To this purpose, recommended data collection and reporting of the incidence of bleeding in ACS patients are summarized in *Table 4*.

Most information on the epidemiology of bleeding in ACS patients comes from randomized controlled trials (RCTs) evaluating the efficacy and safety of the different antithrombotic drugs. However, RCTs underestimate the frequency of bleeding for various reasons (*Table 5*), and it has been pointed-out that RCT-eligible patients outside of the context of trials (i.e. patients from routine practice who would fulfil the selection criteria for RCTs) have worse outcomes than participants in RCTs.[18] Interpretation of bleeding data from RCTs is further complicated by differences across studies in definitions of bleeding, the increasing use of combinations of antithrombotic drugs and PCIs, both of which increase the risk of bleeding, and differences in the management strategies for bleeding, for example the use of red blood cell transfusions, which is often used to define the occurrence and severity of bleeding.[4,5,7]

Compared with RCTs, registry studies usually include a more representative sample of patients with ACS, and are therefore more likely to provide reliable estimates of the 'real-world' frequency of bleeding. The interpretation of bleeding data from registry studies is, however, also limited by changes over time in antithrombotic drugs and PCIs, and geographical variability in the management of bleeding, e.g. differences in the use of red blood cell transfusions in North America and Europe. Furthermore, registries may underestimate the frequency of bleeding because data collection is often retrospective and relies on data extraction from clinical records.

Despite more aggressive interventional therapy and more aggressive anti-thrombotic therapy over recent years, a decline in the rate of bleeding has been recently reported in data from the GRACE registry.[19] Although the causes for this are unclear, clinical practice factors may have influenced this decline, which is not accounted for by the risk status of the patients.

Table 3 BARC definition for bleeding[15]

Type 0: No bleeding
Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional
Type 2: Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation
Type 3
Type 3a
Overt bleeding plus haemoglobin drop of 3 to <5*g/dL (provided haemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus haemoglobin drop ≥ 5*g/dL (provided haemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
Bleeding requiring intravenous vasoactive drugs
Type 3c
Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)
Subcategories; confirmed by autopsy or imaging or LP
Intra-ocular bleed compromising vision
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation following closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period**
Chest tube output ≥ 2 L within a 24 h period
If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'
Type 5: fatal bleeding
Type 5a
Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
Type 5b
Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. *Corrected for transfusion (1 unit PRBC or 1 unit whole blood = 1 g/dL Hgb). **Only allogeneic transfusions are considered transfusions for BARC Type 4 bleeding. Cell saver products will not be counted.

Specific groups at risk of bleeding

Despite the variations in incidence and definition of bleeding across studies, older age, female sex, lower body weight, use of invasive procedures, and renal insufficiency have been consistently found to be powerful predictors of bleeding complications in ACS and PCI (*Figure 1*). Increasing age is a strong risk factor for bleeding: in the GRACE registry encompassing the whole spectrum of ACS, the adjusted odds of having a major haemorrhage prior to discharge increased by about 30% per decade of age [odds ratio (OR) 1.28, 95% CI 1.21–1.37].[10] An hypothetical explanation is that with age, collagen and amyloid deposits in the ageing arterial tunica media may cause brittle, leaky vessels that are less inclined to constrict and are more prone to bleed. Women with ACS also tend to have a higher risk of bleeding than men: within the GRACE registry, women had a 43% higher likelihood of developing major bleeds in-hospital compared with men (adjusted OR 1.43, 95% CI 1.23–1.66).[10] This increased risk presumably stems from smaller body and vessel size, reduced creatinine clearance (for a given weight and serum creatinine), higher prevalence of comorbidities, higher risk of drug overdosing,[20] and, perhaps, differences in pharmacological response to antithrombotics compared with men.[21] Renal function also plays an important role in bleeding risk: in contemporary ACS registries, the estimated risk of in-hospital major bleeds increases by approximately 50% in patients with renal insufficiency (OR 1.48, 95% CI 1.19–1.84).[10] In a *post hoc* analysis of over 34 000 patients enrolled in NSTE-ACS trials and followed for up to 12 months, the adjusted OR for major bleeds was 1.4 (95% CI 1.3–16) for each 1.13 mg/dL (or 100 μmol/L) rise in baseline creatinine; indeed, serum creatinine and age were the two most powerful predictors of bleeding.[16] Patients with renal failure are more susceptible to excess dosing of antithrombotic drugs but also typically have more

Table 4 Recommended data collection and reporting of the incidence, severity, management, and sequelae of bleeding in acute coronary syndrome

Category	Recommended data point
Timing	Timing of bleeding in relation to presentation
Location	Organ system involved
Precipitating or contributing therapies	Antithrombotic and invasive therapies and the intensity of treatment where relevant (e.g. dose, INR, aPTT) immediately prior to or at time of bleed
Presentation	Whether bleed was symptomatic or not
Severity	Nadir haemoglobin (or haematocrit) Number of units of red blood cells transfused Need for inotropes Need for surgical intervention Need for hospitalization Need for medical intervention
Sequelae/outcomes[a]	Fatal bleeding Modification of antithrombotic therapy (permanently or temporary discontinuation) Use of anti-fibrinolytic and general haemostatic agents (e.g. recombinant factor VIIa) Myocardial infarction Stroke

[a]Patients should be followed for a minimum of 6 months after an episode of bleeding.

Table 5 Reasons why randomized trials may underestimate the 'real-world' incidence of clinically important bleeding in acute coronary syndrome

Characteristic	Reason
Study population	Highly selected patients at low risk of bleeding
Timing of recruitment	Convenience sampling; recruitment may be delayed until hours or days after presentation with acute coronary syndrome
Interventions	Standardized management protocol are rigorously applied in randomized trials but are not equally applied in everyday clinical practice
Bleeding outcome	Clinically important bleeding may not be captured by the definitions used for major and minor bleeding

diffuse and advanced arterial disease and therefore may be prone to higher risks of both thrombosis and bleeding.

In addition to these clinical factors, genetic factors also predispose to bleeding: among patients initiating warfarin therapy, carriers of the cytochrome P450 (CYP) 2C9 gene variants *2 and *3 and of the C1173T variant of vitamin K epoxide reductase complex subunit 1 require lower doses and develop more often an INR >4 compared with non-carriers.[22] Likewise, in clopidogrel-treated patients, the gain-function variant CYP2C19*17 resulting in higher active clopidogrel metabolite levels and increased platelet inhibition has been linked to an increase in the incidence of bleeding without improved efficacy.[23]

Prognostic implications of bleeding in acute coronary syndrome

The clinical impact of bleeding has long been downplayed due to the availability of blood transfusions and haemostatic agents, with bleeding often merely regarded as an unpleasant event, increasing the length of hospital stay and costs, but not clearly impacting survival. It was only recently recognized that major bleeding was associated with a subsequent increase in late mortality, potentially negating the long-term benefits of ACS treatment.[10,24–26]

Compared with patients without bleeding, patients who experience bleeding are more likely to die not only early in-hospital but also late after discharge.[26–28] One possibility to explain the relationship of bleeding with adverse outcomes in routine practice is that recognized predictors of bleeding have much overlap with predictors of ischaemic events; bleeding acting as a marker for increased ischaemic risk as well as contributing to death in some cases. A second possibility is that bleeding has directly harmful consequences and also set in motion a number of adaptive changes, in turn themselves leading to an adverse outcome. Consequences of bleeding include hypotension, anaemia, and reduction in oxygen delivery (*Figure 2*). Experimental data suggest that a haemoglobin level down to 7 g/dL is tolerated without myocardial ischaemia if there is no obstructive coronary artery disease (CAD).[29] Anaemia per se is associated with an increased risk of adverse

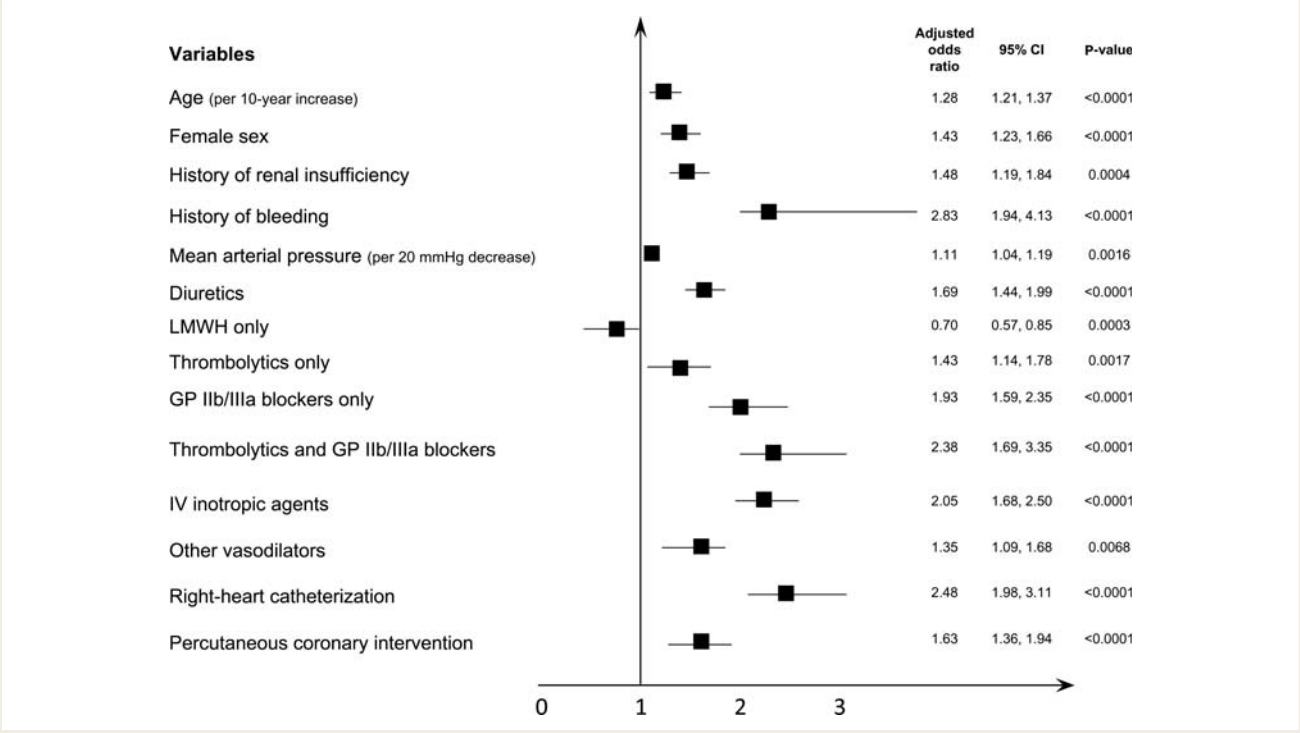

Figure 1 Predictors of bleeding in acute coronary syndrome. Adapted from Moscucci *et al.*, GRACE.[9] Referent groups male sex: UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH, neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit test *P*-value = 0.59, C-statistic = 0.75. GP, glycoprotein; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

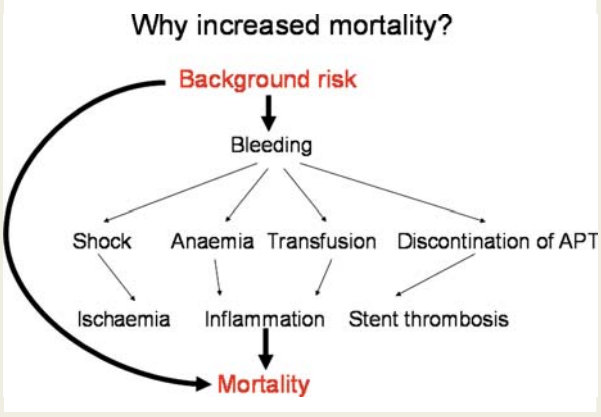

Figure 2 Schematic representations of the hypothetical mechanisms linking bleeding and mortality.

outcomes in patients with ACS, or undergoing coronary revascularization.[30–32] However, many patients with anaemia actually presented with anaemia prior to receiving any antithrombotic therapy and without overt bleeding. In these patients, pre-existing anaemia may exacerbate the consequences of subsequent bleeding, and certainly increases the probability of transfusion.

Discontinuation of antithrombotic therapy to minimize bleeding is an important trigger of ACS.[33,34] It may re-exacerbate the thrombotic risk allowing the accretion of new thrombus material. In the face of bleeding, no general guideline can be given. Clinicians need to weigh the respective risks related to ongoing bleeding, dose reduction, or temporary discontinuation of antithrombotics, whenever possible, with rapid resumption of the initial antithrombotic therapy, depending on the half life and reversibility of the effect and the possibility to treat bleeding (e.g. compressible vs. non-compressible bleeding site). Antithrombotic therapy should be, however, discontinued if bleeding leads to hypotension or if bleeding is life-threatening and uncontrolled. This should be followed by haemodynamic support with fluid repletion and vasopressor therapy as necessary. All of these actions, however, place the patient at increased risk of recurrent ischaemia and infarction.

Transfusion of whole blood or packed red blood cells might have appeared the simple and ultimate solution to manage major bleeding, as it rapidly compensates for the volume loss associated with the bleeding event, and as such is indicated when bleeding is associated with haemodynamic instability or shock. However, when bleeding is less severe and haemodynamic conditions remain stable, the effect of transfusions on mortality is at best neutral. Even in patients with cardiovascular diseases or in the elderly, transfusion have no positive impact on outcome.[29,35] Furthermore, despite major bleeding with the loss of >5 g/dL haemoglobin, blood transfusion is associated with increased mortality, and blood loss down to a nadir haematocrit as low as 25% may be well tolerated.[36] There are many potential mechanisms for the

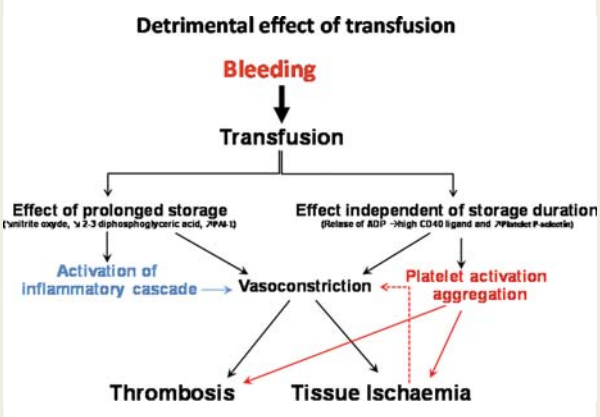

Figure 3 Potential mechanisms of the detrimental effect of blood transfusion.

detrimental effects of transfusions, including platelet activation and aggregation, impaired oxygen, and nitric oxide delivery capabilities (*Figure 3*).[37] As a matter of fact, in general, restrictive transfusion strategies are associated with trends towards decreased mortality, myocardial infarction, and heart failure.[37] Therefore, transfusion may increase rather than decrease the risk of adverse events in patients with ACS.[38] Likewise, the common[39] liberal use of blood transfusion to maintain predefined haemoglobin levels in CAD patients without overt bleeding and with haematocrit >25% or haemoglobin > 8 g/dL is not recommended.

Bleeding in percutaneous coronary intervention

In patients undergoing PCI, approximately half of the bleeding events occur at the arterial access site, and may range from clinically unimportant subcutaneous access site haematoma to fatal retroperitoneal bleeding.[40] The deleterious impact of access and non-access site bleeding on outcomes is established but the impact on mortality appears greater for non-access site bleeding.[5] One should also consider remote bleeding complications, unrelated to the procedure itself but caused by the protracted combined antiplatelet therapy required after stent placement.

Bleeding rates in patients undergoing PCI vary according to definition and to the clinical setting for PCI,[38,40] with lowest rates in elective PCI[41] and the highest rates in primary PCI for STEMI.[25] Importantly, the absolute increase in mortality caused by major bleeding in ACS is substantial, in the order of 11% (95% CI 8–14) corresponding to a number of patients 'needed to harm' of only 9.1 (95% CI 7.1–12.5), deserving careful attention from clinicians.[42] Furthermore major bleeding is also associated with increased risk of ischaemic events.

Although radial access for angiography and PCI is associated with near abolition of access site bleeding,[43,44] some infrequent complications persist, which may range from local superficial haematomas in the forearm, found in less than 5% of cases, to exceptional compartment syndrome, found in < 0.01% of cases. Use of access site closure devices does not appear to have a major impact in the prevention of severe bleeding.[45]

Although clearly not the sole consideration, prevention of bleeding is important when selecting antithrombotic strategies for PCI. There are differences in the risk of bleeding according to the type and dosing of antithrombotic therapies used for PCI.[26,41,46–49] Given the impact of drug overdosing on bleeding and its interaction with age, sex, and renal function,[20,21] attention should be devoted to appropriate dosing, particularly in patients at high risk for bleeding, identified readily on the basis of these simple clinical baseline characteristics[10,19,20,47] or using risk scores.[50]

Avoidance of bleeding in acute coronary syndrome and percutaneous coronary intervention

The role of overdosing

Overdosing is a frequent situation associated with established increased major bleeding risk and in-hospital death.[20,21] Using the minimal effective dose and adjusting the dose, when appropriate, to body weight, age, and to renal function are sensible steps to minimize the risk of bleeding.

Fondaparinux, low-molecular-weight heparins (LMWH), hirudin, argatroban, bivalirudin, and GP IIb/IIIa blocker are largely cleared by the kidneys, and should therefore not be used or need to be down-titrated in patients with severe renal failure, defined as a creatinine clearance <30 mL/min.[20,21] Unfractionated heparin remains the anticoagulant of choice in this particular situation, but does not totally protect against bleeding complications. With worsening renal function, there is a gradual increase in the risk of bleeding with UFH, similar to that seen with LMWH.[51]

Unfractionated heparin, LMWH, intravenous direct thrombin inhibitors, TNK-tPA, and GP IIb/IIIa blockers all require careful weight-adjusted dosing.[28,46,47,51,52] The use of high loading and maintenance doses of clopidogrel to speed up its efficacy and overcome high residual-on treatment platelet reactivity, especially in the setting of PCI, may be beneficial in terms of clinical outcomes, although in the CURRENT/OASIS 7 trial this was only seen in patients going on to PCI,[53] but not when the trial was analysed by intention-to-treat[54] and was achieved at the expense of increased major bleeding.

Use for the shortest possible duration

In determining the duration of antithrombotic therapy, it is important always to balance the bleeding-related risks with the antithrombotic benefits, and therefore adopt the shortest possible course of therapy. As an example, dual therapy with aspirin and clopidogrel is recommended for 1 month after bare metal stenting in stable patients, and for 6 up to 12 months after an ACS (regardless of stenting) and after implantation of drug eluting stents (regardless of clinical diagnosis). Continuation of dual antiplatelet therapy beyond these intervals should be considered an exception rather than the rule. So far, there is a single randomized study

Table 6 Ongoing randomized clinical trials comparing various durations of dual antiplatelet therapy after placement of drug-eluting stents

Study	Patients (*n*)	Randomization	Primary outcome measure	Secondary outcomes
ISAR-SAFE, NCT00661206	PCI-DES (6 000)	6 vs. 12 months	15 months: death/MI/stroke/TIMI major bleed	Individual component outcomes
ISAR-CAUTION, NCT00640679	PCI-DES (3000)	12 vs. tapered within 4 weeks after 12 months	3 months: CV death, non-fatal MI or ST, stroke, major bleeding or rehospitalization for ACS	The individual components of the primary outcome. All cause mortality
ARCTIC, NCT00827411	Elective PCI–DES (2466)	12 vs. 18–24 months	12 months: composite endpoint of death, M, stroke, Urgent revascularization, ST	Individual component outcomes
OPTIDUAL, NCT00822536	PCI-DES ($n = 1966$)	12 vs. 36–48 months	3 years: death, non-fatal myocardial infarction, non-fatal stroke, and severe bleeding	Individual component outcomes, stent thrombosis (ARC), target vessel revascularization
DAPT Study, NCT00977938	DES/BMS–PCI ($n = 20645$)	12 vs. 30 months	30 months: (1) death/MI/stroke at 33 months: (2) Def/prob ST at 33 months	GUSTO bleeding
ITALIC, NCT00780156	PCI-DES $n = 3200$)	6 vs. 36 months in aspirin good responders	12 months: death, MI urgent revasc, stroke requiring a new hospitalisation and major bleedings	Individual component outcomes, at 24 and 36 months and bleeding complications
OPTIMIZE, NCT01113372	PCI-ZES ($n = 3120$ non-STEMI)	3 vs. 12 months	1-year death/MI/stroke/ TIMI major bleed	ARC stent thrombosis
CYPRESS-phase II, NCT00954707	PCI-SES ($n = 2500$)	12 vs. 30 months	Death/MI/stroke at 12–33months	Stent thrombosis; bleeding
TAXUS study, NCT00997503	PCI-PES ($n = 4200$)	12 vs. 30 months	Death/MI at 12 months	Stent thrombosis
EASTS, NCT01233167	PCI-SES ($n = ?$)	12 vs. 24 months vs. tapered	Death/MI/TVR	Multiple individual EP
SCORE, NCT00781573	PCI-DES ($n = ?$)	12 vs. 24 months	Death/MI at 12 months	Death/MI/stroke/repeat revasc/ bleeding at 12 months

DES, drug-eluting stent; ZES, zotarolimus-eluting stent; SES, sirolimus-eluting stent.

showing no hazard of clopidogrel discontinuation 1 year after drug-eluting stent implantation.[55] There are currently 11 randomized trials ongoing comparing various duration of dual antiplatelet therapy in this setting (*Table 6*).

Choice of drugs

Antithrombotic agents shown to produce less bleeding while maintaining anti-ischaemic efficacy in randomized trials should be preferred, particularly for those for whom bleeding reduction was associated with reduced mortality or improved clinical outcomes. This is the case of fondaparinux against enoxaparin in the medical management of patients with NSTE-ACS[26] and of bivalirudin vs. UFH+GPIIb/IIIa blockers in primary PCI for ST-segment elevation myocardial infarction.[25] Agents which lower bleeding rates while achieving non-inferior efficacy are also of interest, although consideration of the individual patient risk profile for bleeding and MI becomes an important factor in the decision-making process. This is the case for bivalirudin vs. UFH + GpIIb/IIIa blockers in NSTE-ACS[28,56] and, possibly, of enoxaparin vs. UFH in patients undergoing elective or primary angioplasty.[41,57]

Reducing gastrointestinal bleeding

The risk of gastrointestinal haemorrhage increases two- to three-fold even with low-dose aspirin monotherapy compared with placebo, and all doses of aspirin are associated with an increased risk of gastrointestinal bleeding. The risk of aspirin-related ulcer complications is significantly increased in patients aged more than 60 years, patients with serious comorbidities, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, anticoagulants, or other antiplatelet agents. Overall, there is no evidence of decreased efficacy, but clear evidence of increased safety with lower doses of aspirin.[54] Proton-pump inhibitors display a high capacity to reduce recurrent gastrointestinal bleeding in patients at high risk for gastrointestinal side effects under chronic aspirin therapy, although they are not effective in preventing lower gastro-intestinal bleeding.[58] Adding a proton-pump inhibitor to reduce gastrointestinal bleeding events in patients at high risk of gastrointestinal toxicity who receive long-term treatment with low-dose aspirin is recommended.[59] On the other hand, there is a pharmacologic interaction between omeprazole and clopidogrel,[60] which is some observational cohorts appeared to be associated with higher cardiovascular event rates. However, the jury is still out regarding the clinical significance of this interaction, which did

not appear to impact clinical outcomes in one prospective, albeit somewhat underpowered, randomized trial[61] or in other large observational cohorts.[62–64] Whether proton pump inhibitors should be routinely added to the already long list of medications needed after an ACS or PCI requires testing, given the implications in terms of cost, adherence to polypharmacy, and cost-effectiveness, and is not at the moment recommended. Instead, a recent consensus document on the concomitant use of proton pump inhibitors and thienopyridines highlights that proton pump inhibitors are appropriate in patients with risk factors for gastrointestinal bleeding who require antiplatelet therapy,[65] such as patients with prior history of upper gastro-intestinal tract bleeding, advanced age; concomitant use of warfarin, steroids, or NSAIDs; or *H. pylori* infection.

Preventing access site bleeding

Numerous devices have been developed to obtain efficient arterial closure immediately at the end of a PCI procedure performed with the femoral approach, but have failed to abolish major access site bleeds or improve clinical outcomes.[45] Consistent results indicate that a reduced arterial sheath size, timely sheath removal, and the use of radial (instead of femoral) artery access for PCI are associated with a frank reduction in peri-PCI bleeding rates. Using a radial approach, as opposed to femoral access for angiography and PCI appears remarkably effective in preventing access site bleeding[43,44]: pooled results from 17 randomized studies indicate a 78% reduction in entry site complications when a radial approach is used, with a number need to treat of only 39 patients.[43] Whether using radial access for PCI in ACS patients can improve clinical outcomes is being tested in the 7000 patient RIVAL randomized trial.[66] In the interim, a large observational database analysis has suggested that in patients at higher risk for bleeding, use of vascular closure devices and bivalirudin for PCI were associated with lower bleeding rates.[67]

Patients on chronic oral anticoagulation

Given the concerns with increased bleeding risk in patients receiving protracted triple antithrombotic therapy with oral anticoagulants (atrial fibrillation, venous thrombosis, pulmonary embolism, mechanical prosthetic valves),[68] aspirin, and thienopyridines, it makes sense to minimize the overlap between these agents, and therefore to prefer bare metal stents over drug-eluting stents in order to allow safe early discontinuation of clopidogrel. The selection of a post-PCI antithrombotic strategy in this context should probably be based on individual patient characteristics, as retrospective analyses suggest that triple therapy provides the best benefit-risk ratio, provided that clopidogrel co-treatment is kept as short as possible.[63] In general, if the patient is at high risk of thromboembolic events requiring oral anticoagulants (e.g. because of a prosthetic mitral valve, recent venous thrombosis or pulmonary embolism, or atrial fibrillation with a $CHADS_2$ score$>$1), triple oral antithrombotic therapy (aspirin + clopidogrel + oral anticoagulants) should be used until clopidogrel can be safely discontinued. Once the risk of stent thrombosis is lower, consideration should be given to oral anticoagulants alone,[69] although contemporary studies on this important topic are lacking. This is, in fact, an incentive to use bare metal stents during PCI procedures in these patients in order to discontinue clopidogrel after 4 weeks. In patients with a lower thromboembolic risk in whom oral anticoagulation is optional (e.g. atrial fibrillation with $CHADS_2$ score 0–1)—especially if they have an increased bleeding risk (e.g. age $>$75 years, severe renal dysfunction, recent gastrointestinal bleeding, prior stroke, uncontrolled hypertension)—physicians may consider using dual antiplatelet therapy for several weeks before resuming oral anticoagulants and discontinuing one oral antiplatelet agent or maintaining dual antiplatelet therapy in the long term as it has a better efficacy profile than aspirin alone at least in patients with atrial fibrillation considered unsuitable for vitamin K antagonists (*Figure 3*).[69] For long-term use, after the need of clopidogrel has waned, we concur with the recent ESC Atrial Fibrillation guidelines in recommending VKA alone rather than the combination of VKA + aspirin.[69,70] For patients who develop ACS while being on chronic oral anticoagulation, adding antiplatelet therapy to oral anticoagulation should be considered, but the optimal duration of 'triple' antithrombotic therapy in these patients is unknown and should probably be minimized, particularly in patients who do not undergo placement of a stent, in order to minimize bleeding risks.

Management of bleeding in acute coronary syndrome

As indicated by the ESC Guidelines,[71] bleeding can be managed with simple means. Sometimes antithrombotic therapy must be partially or completely discontinued and even antagonized by specific drugs and measures. In patients who have undergone stenting and in whom dual antiplatelet therapy is indicated, withholding one or both antiplatelet agents should always be considered putting the patient at substantial risk of stent thrombosis; therefore, the benefits of treatment interruption need to be weighed against the risks of stent thrombosis and treatment interruption should always be considered as a temporary measure. Guidelines for the perioperative management of antiplatelet agents[72] provide a useful algorithm (*Table 7*). As often as possible, oral antiplatelet therapy must be restarted after the bleeding event is resolved.

General management of bleeding

Patients with ACS may experience bleeding due to procedures or as a side effect of antithrombotic treatment. Minor bleeding usually does not need medical attention during the acute phase. There is, however, evidence that, after discharge, minor or nuisance bleeding may lead patients to discontinue antiplatelet therapy, which may lead to recurrent ischaemic events.[12,73–75] Patients experiencing significant or major bleeding during an ACS should be closely monitored, preferably in an intensive or coronary care unit, and transfusions should be considered in haemodynamically unstable patients (including patients with ongoing severe bleeding) and should not be underdosed. Antithrombotic treatment interruption may be associated with recurrent ischaemic events. Proton pump inhibitors should be the preferred agents for the therapy and prophylaxis of ASA-associated gastro-intestinal injury.[59,65,75] This and additional local endoscopic treatment may control gastrointestinal bleeding and avoid interruption of antiplatelet therapy, a decision to be made on a strictly individual basis.[59]

Table 7 Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Anesthesiology and Intensive Care Task Force[72]

	Haemorrhagic risk of the invasive or surgical procedure (to be evaluated with the physician or the surgeon)		
	Major	**Intermediate**	**Minor**
Risk of stent thrombosis (to be evaluated with the cardiologist)			
Major	Postpone intervention 6 months to 1 year after stenting. If impossible: Stop aspirin-clopidogrel 5 days or stop aspirin-clopidogrel 10 days max and substitute	Postpone intervention 6 months to 1 year after stenting. If impossible: maintain aspirin stop clopidogrel 5 days	Maintain aspirin and clopidogrel
Moderate	Stop aspirin-clopidogrel 5 days or stop aspirin-clopidogrel 10 days max and substitute	Maintain aspirin stop clopidogrel 5 days	Maintain aspirin and clopidogrel or maintain aspirin stop clopidogrel 5 days

Haemorrhagic risk: major: intervention cannot proceed on APA; moderate: intervention can proceed on ASA alone; minor: intervention can proceed on ASA and clopidogrel.
Risk of DES thrombosis: major: in place less than 6 months to 1 year or patient requiring ASA and clopidogrel or patient with risk factor; moderate: in place more than 6 months to 1 year.
APA, antiplatelet agents; ASA, aspirin.

Management of bleeding according to specific situations

The management of bleeding complications in special situations can be summarized as follows:

- Minor bleeding should preferably be managed without interruption of active treatments (grade I, level of evidence C).
- Major bleeding requires interruption and/or neutralization of both anticoagulant and antiplatelet therapy, unless bleeding can be adequately controlled by specific haemostatic interventions (grade I, level of evidence C).
- Blood transfusions may have deleterious effects on outcome and should therefore be considered individually, but withheld in haemodynamically stable patients without overt bleeding with haematocrit >25% or haemoglobin level >8 g/dL (grade I, level of evidence C).

Clinical research implications

Measuring and reporting bleeding in trials

With the use of invasive methods for diagnosis and treatment, particularly PCI with femoral arterial access and with the increasing antithrombotic armamentarium used to avoid thrombotic complications, the importance of bleeding complications as a mechanism contributing to mortality has recently emerged.

In addition to the mere reporting of bleeding according to accepted definitions, risk factors for major bleeding in patients with ACS should be collected and analysed to identify subgroups of patients that need special care with regard to antithrombotic treatment in ACS, and current guidelines should take them into consideration. To build-up a base of evidence for the handling of this balance in clinical practice, definitions of bleeding should be internationally uniform and relevant to the clinical situation, for comparison across geographic regions, ethnicities, and other relevant population differences, looking for valid risk factors and optimal treatment of the delicate haemostatic/thrombotic balance in various phases of the disease. Bleeding should be reported using more than one bleeding scale,[14] one of which should be the BARC bleeding definition.[15]

Bleeding as an outcome measure in trials

Bleeding is an important predefined endpoint of all trials and registries of ACS and PCI, possibly of equal importance to events related to ischaemia and thrombosis. Bleeding is significantly associated with short-term mortality and, remarkably, a similar significant difference between patients with major bleeding and those without bleeding is noted also for thrombotic events such as myocardial infarction and stroke.[16,17] In addition, interruption of antithrombotic therapy related to bleeding episodes is independently associated with increased mortality.[73] These observations suggest that increased haemostatic activation induced by the disease state itself, interruption of antithrombotic therapy, and possibly blood transfusions all contribute importantly to poor outcomes.

In addition to reporting bleeding events in ACS studies, the 'number needed to harm' (NNH) should be reported on to balance the 'number needed to treat' (NNT) as an efficacy measure. This should help analyse the contribution to efficacy and safety by the various elements of the 'therapeutic package' as defined in *Table 4*. This table proposed an 'ideal set' of data pertaining to antithrombotic drugs or bleeding to be collected in future studies.

Bleeding as a subject for future research

Among the many remaining questions regarding bleeding, the most pressing ones are the following:

- Is bleeding truly causal in subsequent mortality or is it merely a marker of increased risk related to worse baseline characteristics?
- To what extent and during what time frame is there an increased risk of mortality related to bleeding?
- Is spontaneous bleeding different from bleeding induced by percutaneous or surgical revascularization procedures?

- Which laboratory tests are clinically most suitable to assess the haemostatic balance during the active treatment period?
- What are the basic changes in the haemostatic balance that take place during the disease process in ACS and the various therapeutic interventions (including stopping of treatment and blood transfusion), as explanation for the thromboembolic and bleeding complications?
- Are there individual explanations, genetically or by coexisting disease states, for the appearance of thromboembolic and/or bleeding complications?
- Is transfusion really deleterious? What should be the optimal transfusion strategy for patients with ACS?
- How should we address and treat anaemia in patients with ACS, particularly in the perioperative period?
- Should more 'tailored' antithrombotic strategies, involving shorter use of potent antithrombotic combinations and, possibly, reduced regimens of antithrombotic therapies, be used for managing patients with ACS?
- In which ACS patient subsets should single, dual, triple, or quadruple treatment (thrombolytic; single, dual, or triple antiplatelet; anticoagulant) be administered? In which doses and for how long, to avoid thromboembolic complications while minimizing bleeding (using the NNT/NNH measures)?

Conclusions

Modern ACS management involves a mix of antithrombotic therapy and invasive procedures. Guidelines for ACS management give several agents their highest recommendation based on the available trial data. However, all these therapies carry, to a varying degree, a risk for bleeding. Bleeding complications are important clinical events, associated with subsequent mortality. Although reducing bleeding risk has become a clinical priority, there remains gaps in knowledge regarding the incidence of bleeding and the underlying mechanisms that explain the negative associations. Moreover, the varying definitions of bleeding used in clinical studies to date have made it difficult to compare the safety of available agents. The recent Bleeding Academic Research Consortium standardized approach to capturing bleeding information represents a first step in closing the knowledge gap, which will need prospective validation in future studies. The recent confirmation of a decline in the rate of bleeding together with large variations in bleeding frequency from hospital to hospital also suggests that change in local practice patterns impacts bleeding and calls for reinforced attention from clinicians towards prevention and treatment of bleeding.

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