Major Bleeding and Adverse Outcome following Percutaneous Coronary Intervention

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Abstract

Advances in anti-thrombotic and anti-platelet therapies have improved outcomes in patients undergoing percutaneous coronary interventions (PCIs) through a reduction in ischaemic events, at the expense of peri-procedural bleeding complications. These may occur through either the access site through which the PCI was performed or through non-access-related sites. There are currently over 10 definitions of major bleeding events consisting of clinical events, changes in laboratory parameters and clinical outcomes, where different definitions will differentially influence the reported incidence of major bleeding events. Use of different major bleeding definitions has been shown to change the reported outcome of a number of therapeutic strategies in randomised controlled trials but as yet a universal bleeding definition has not gained widespread adoption in assessing the efficacy of such therapeutic interventions. Major bleeding complications are independently associated with adverse mortality and major adverse cardiovascular event (MACE) outcomes, irrespective of the definition of major bleeding used, with the worst outcomes associate with non-access-site related bleeds. We consider the mechanisms through which bleeding complications may affect longer-term outcomes and discuss bleeding avoidance strategies, including access site choice, pharmacological considerations and formal bleeding risk assessment to minimise such bleeding events.

Keywords

Percutaneous coronary intervention (PCI), haemorrhage, peri-procedural bleeding complications, mortality, adverse outcomes

Disclosure: The authors have no conflicts of interest to declare.
Received: 26 November 2014 **Accepted:** 29 January 2015 **Citation:** *Interventional Cardiology Review*, 2015;10(1):22–5
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Major bleeding or haemorrhage following a percutaneous coronary intervention (PCI) is not a benign event. There is now convincing evidence that it independently predicts increased mortality and adverse outcomes in patients.[1,2] The adverse outcomes associated with a bleeding event are not just as a direct result of the haemorrhagic event, such as whether or not a patient survives their gastrointestinal (GI) or intracranial haemorrhage, but are seen in the subsequent progress of the patient up to at least one year after the event. Herein, we discuss the recent data on post-PCI bleeding and the difficulties in comparing different studies with different methodologies and definitions of major haemorrhage. We then consider the mechanisms through which bleeding complications may affect longer-term outcomes and discuss bleeding avoidance strategies to minimise such bleeding events.

Importance of Definition

Major bleeding rates in modern PCI practice are highly variable in the published literature. They range from less than 1 % to nearly 10 % in PCI for ST-elevation myocardial infarction (STEMI). This is dependent on a number of procedural factors but also importantly on the definition of major haemorrhage the study uses.[3–7] Definitions are based on a combination of laboratory and clinical factors to indicate severity (see *Table 1*).[8–15] The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria have been used for over 25 years. They were developed to classify major and minor haemorrhage following thrombolysis of STEMI and relied predominantly on laboratory measures, such as haemoglobin. Over time the TIMI definition has evolved to encompass more bleeding complications to reflect modern practice and require clinical, or radiographic, evidence of actual blood loss.[8,9] However, the TIMI definition is still biased to identify acute and very severe bleeds and there can be uncertainty about when peak and trough haemoglobin level should be measured. Other criticisms include the nomenclature. A TIMI 'minor' bleed can have a haemoglobin drop of 3–5g/l, which is not minor and indeed could have life-threatening consequences. Recent consensus statements by the Bleeding Academic Research Consortium (BARC) have tried to standardise bleeding definitions, but the success of this endeavour will only be judged in time.[15]

The definition of peri-procedural major bleed used can eliminate the effect of a given therapeutic intervention and thereby influence the outcome of a study. The RIVAL trial,[16] a landmark, multicentre trial comparing radial and femoral PCI, did not demonstrate a significant difference in non-coronary artery bypass grafting (CABG) related major bleeding, as defined by the study. RIVAL defined major bleeding as either: fatal, requiring transfusion of 2 or more units, causing hypotension requiring inotropes, requiring surgery, leading to disability, intracranial bleeding or a drop of >50 g/l of haemoglobin. However, using a broader definition of major bleeding, such as the

ACUITY definition,[11] which includes bleeds causing large haemotomas or pseudoaneurysms requiring intervention, then radial access was associated with a significant reduction in major bleeding (odds ratio [OR] 0.43; p<0.00001) and thus the overall impact of the trial is different. It is therefore important to consider the definition of haemorrhage used in any trial related to PCI outcomes, particularly if comparison is being made between trials with different methodology. This may have a profound influence on a day-to-day practice for the clinical cardiologist and, indeed, may help influence a decision to switch from femoral to radial practice or use glycoprotein IIb/IIIa inhibitors (GPIs), based on the 'headline' message of a trial.

Impact of Major Bleeding Post-percutaneous Coronary Intervention

Major bleeding events following a PCI are associated with adverse outcomes such as increased mortality and major adverse cardiovascular events (MACE).[17–19] Major bleeding complications account for 12.1 % of all in-hospital mortality after PCI in the National Cardiovascular Data Registry.[20]

The risk of bleeding following PCI in a patient is increased if the patient is older, has a more acute presentation, has renal failure, heart failure or is haemodynamically compromised.[21,22] These factors all predict a poorer outcome in themselves. Does bleeding post-PCI independently predict poor outcome or is it a marker for other comorbidity? Previous studies, which did not account for the higher incidence of these comorbidities in patients who bled, could over-estimate the impact of bleeding in the future. Indeed, following an analysis of the Global Registry of Acute Coronary Events (GRACE) data, which took account of the comorbidity, then eliminated the significance of the effect of bleeding, the authors concluded that the comorbidities associated with major bleeding accounted for the higher mortality observed.[23] Our recent meta-analysis[1] of 42 studies including over 500,000 patients, reported that studies that did not adjust for the incidence of confounding comorbidity in patients that bled demonstrated that major bleeding conferred a sixfold increased risk of death, which reduced to threefold once baseline covariates were adjusted for. It is therefore important to consider the confounding influence of comorbidities on the long-term impact of peri-procedural bleeding.

Different definitions of major bleeding will also have a differential impact on mortality and MACE outcomes, for example the REPLACE-2 (OR 6.69, 95 % confidence interval [CI] 2.26–19.81), STEEPLE (OR 6.59, 95 % CI 3.89–11.16) and BARC (OR 5.40, 95 % CI 1.74–16.74) had the worst prognostic impacts on mortality while HORIZONS-AMI (OR 1.51, 95 % CI 1.11–2.05) had the least impact in a recent meta-analysis.[1]

Mechanism of Effect

Why does bleeding have such a profound effect on outcome following PCI? Clearly in the acute setting, a GI or intracranial haemorrhage can cause fatal blood loss. Blood loss can occur from the access site, e.g. the femoral artery, or away from the access site, such as intra-cranially or in the contralateral retroperitoneal space. GI haemorrhage after PCI for acute myocardial infarction is associated independently with a prolonged hospital stay and greater mortality in-hospital and at 6-month mortality.[24] Access-site-related bleeding, such as major femoral bleeding complications requiring transfusion, are also independently associated with increased 30-day mortality.[25] When we compare non-access site, or systemic, bleeding with such access site bleeding, both are associated with increased 1-year mortality, although non-access site bleeding confers poorer prognosis and is associated with a twofold greater impact on 1-year mortality compared with access-site-related bleeding.[26]

Table 1: Definitions of Major and Minor Haemorrhage Used to Classify the Severity of Bleeding following Percutaneous Coronary Intervention

	Major Bleeding	Minor Bleeding
TIMI[8,9]	Any intracranial bleeding Clinically overt haemorrhage associated with a drop in haemoglobin of 5 g/dl Fatal bleeding (results in death <7 days)	Mild bleeding that does not meet severe/moderate criteria
GUSTO[10]	Severe or life-threatening Intracerebral haemorrhage Resulting in substantial hemodynamic compromise requiring treatment Moderate Requiring blood transfusion but not resulting in haemodynamic compromise	
ACUITY[11] HORIZONS[12]	Intracranial or intraocular haemorrhage Access site haemorrhage requiring intervention >5 cm haematoma Retroperitoneal Reduction in haemoglobin concentration of >4 g/dl without an overt source of bleeding Reduction in haemoglobin concentration of >3 g/dl with an overt source of bleeding Reoperation for bleeding Use of any blood product transfusion	
GRACE[13,14]	Requiring a transfusion of >2 units blood Resulting in a decrease in haematocrit of >10 % Intracerebral haemorrhage Resulting in stroke or death	
BARC[15]	**Type 0**: No bleeding **Type 1**: Bleeding that is not actionable **Type 2**: Any actionable sign of haemorrhage not type 3, 4 or 5 but at least one of: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalisation or increased level of care, or (3) prompting evaluation **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 Bleeding requiring intravenous vasoactive agents **Type 3c**: Intracranial haemorrhage Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision **Type 4**: Coronary artery bypass graft -related bleeding **Type 5**: Fatal bleeding	

Peri-procedural mortality directly due to the acute haemorrhage does not explain why the adverse outcomes are observed up to a year after the PCI. Bleeding complications may affect the long-term prognosis via several distinct mechanisms. The premature discontinuation of anti-platelet medications may increase the risk of stent thrombosis, itself an independent predictor of long-term outcome.[27] Erythropoietin production is stimulated in an anaemic state following blood loss. This could contribute to a pro-thrombotic state beyond the acute phase through platelet activation and induction of plasminogen activator inhibitor-1 (PAI-1) and thus worsen prognosis.[28–30] Treatment with erythropoietin in patients following STEMI has been shown to increase the composite end point of death, MI, stroke and stent thrombosis.[31] Blood transfusions themselves have an adverse impact on mortality. This has been demonstrated independently of the bleeding and haematocrit 30 days after the event[32,33] and with use of other blood products, such as plasma or platelets, which may be necessary following a major haemorrhage.[34] For example, our recent meta-analysis of 2,258,711 patients undergoing PCI with 54,000 transfusion events demonstrated that blood transfusion was independently associated with an increase in mortality (OR 3.02, 95 % CI 2.16–4.21) and MACE (OR 3.15, 95 % CI 2.59–3.82) with similar observations recorded in studies that adjusted for baseline hematocrit, anaemia and bleeding.[35] Potential mechanisms through which the long-term adverse outcome of transfusion may be mediated are thought to include, the prothrombotic effects of CD40 ligand released by platelets and inhibition of endogenous fibrinolytic systems.[28,36] Furthermore, during storage, significant changes in the deformability of red blood cells, as well as changes in their shape, may predispose to 'plugging' of transfused cells at the microvascular level, leading to tissue ischaemia. Therefore, the adverse outcomes associated with a bleeding event are likely to relate to the site of the bleed and the acute haemorrhagic event itself, as well as the therapeutic interventions undertaken following the bleeding event, such as discontinuation of anti-platelet therapy, reversal of anti-coagulants and receipt of blood transfusions.

Bleeding Avoidance Strategies

Peri-procedural major bleeding complications independently predict higher mortality and poorer outcomes. The importance of avoiding such complications is increasingly apparent and strategies to achieve this need to be a fundamental part interventional practice. The radial artery should be the preferred access route for PCI to avoid access site-related bleeding events although there may be circumstances, where this may not be possible or femoral devices, such as intra-aortic balloon pumps, may be required. There is evidence that the change in practice from femoral to radial access has influenced outcome. Analysis of the UK national PCI database, comparing primary PCI outcome for STEMI, demonstrated significantly fewer access-site related bleeding complications via the radial approach, which was independently associated with a 30 % reduction in 30-day mortality whose magnitude was similar to that observed following a move from thrombolysis to primary PCI in the management of STEMI.[37] Similarly, a meta-analysis of randomised controlled trials of STEMI patients receiving primary PCI demonstrates a reduction in mortality and MACEs, driven by a reduction in major bleeding in patients who had their procedure via the radial rather than femoral route.[38]

The magnitude of the mortality benefit seen by pursuing a default radial strategy is related to the baseline bleeding risk of an individual patient.[39] Patients with the highest risk of bleeding, assessed in this way, gained most from a transradial route for their PCI, with a greater mortality benefit than those at a lower risk of bleeding. Paradoxically, perhaps, patients assessed as having a higher risk of bleeding were unfortunately less likely to receive a transradial PCI in this retrospective study.

Adjuvant pharmacological agents also help determine the likelihood of major bleeding following PCI and therefore outcome. GPIs are potent antiplatelet agents effective in improving ischaemia-related outcomes in PCI,[40–42] measured as reduction of a composite clinical end point (death, reinfarction or repeat revascularisation) at the price of an increased risk of major haemorrhage. An initial rise in popularity, due to this evidence, has been followed by a fall in GPI use due to their cost, the bleeding complications and data, such as the HORIZONS-AMI trial.[12] HORIZONS-AMI demonstrated less major bleeding and a mortality benefit for using bivalirudin (a direct thrombin inhibitor) versus heparin and GPI. More recently, the HEAT trial[43] did not show a mortality benefit or reduced major bleeding for bivalirudin and, indeed, unfractionated heparin alone had a comparable outcome to bivalirudin. The HEAT trial employed much more contemporary practice than HORIZONS-AMI; well deployed, third-generation drug-eluting stents were used via a radial approach (80 %), with high use (90 %) of newer P2Y12 agents (prasugrel and ticagrelor). The newer P2Y12 agents also improve outcomes following the percutaneous treatment of acute coronary syndrome (ACS) compared with clopidogrel, at the expense of increased bleeding risk.[44,45] Fondaparinux given instead of enoxaparin to ACS patients reduces major bleeding and improves long-term mortality.[46]

We should tailor our procedural practices and pharmacological therapies used in PCI procedures undertaken on an individual patient basis, balancing risk of ischaemia or failure of the procedure with the risk of bleeding. Pre-procedural assessment of a patient's bleeding risk should be part of our routine assessment of a patient. Analysis of over a million PCIs recorded in the US CathPCI registry was used to develop and validate a PCI bleeding risk prediction score and simplified bedside tool. Entering only 10 variables, such as age, sex, body mass index (BMI), renal function and pre-procedural haemoglobin level, yields a score and a percentage bleeding risk on which a clinician can act.[47] Other bleeding risk scores have also been developed to predict non-CABG–related TIMI major bleeding in patients undergoing PCI in the elective and acute setting, such as the Mehran score, through a patient-level pooled analysis of the REPLACE-2, ACUITY and HORIZONS-AMI trials.[21] The risk score consists of seven variables: serum creatinine level, age, sex, presentation, white blood cell count, cigarette smoking and anticoagulant agent use. While many of these scores may identify patients at risk of bleeding complications the requirement of laboratory results such as creatinine, haemoglobin levels and white blood cell count for their calculation means that they cannot be used in the highest-risk patients, such as primary, PCI or other emergent cases where such lab results may not be available at the time of the PCI. Nevertheless, a high bleeding risk score should encourage bleeding avoidance strategies, such as a transradial approach and avoidance of high bleeding risk pharmacological agents, such as GPIs. Similarly, if the femoral route is required for arterial access, care should be taken using micro-puncture techniques and ultrasound guidance and vascular closure devices considered.[48]

Conclusion

PCI represents a delicate balance between minimising thrombotic complications without significantly increasing haemorrhagic event rates. PCI necessitates the use of highly potent antithrombotic and anticoagulant drugs, as well as requiring arterial access and instrumentation. Bleeding complications are therefore an inevitable consequence of PCI. Awareness of the predictors and importance of major peri-procedural bleeding as well as the judicious use of efficacious bleeding avoidance strategies will optimise ouctomes of PCI procedures undertaken. ■

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