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Bleeding Complications in Acute Coronary Syndromes and Percutaneous Coronary Intervention: Predictors, Prognostic Significance, and Paradigms for Reducing Risk

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Summary

In clinical trials up to 30% of patients with acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI) experience bleeding complications, and even higher rates have been reported in contemporary practice. A growing body of data suggests a strong correlation between bleeding and both short- and long-term adverse outcomes, including mortality, which is independent of baseline characteristics and remains evident in most trials, despite variations in the definition of major bleeding. Although the value of antithrombin and antiplatelet therapy in reducing the risk of ischemic events is well established, the mechanisms of action that confer the benefits of these therapies have an inherent tendency to increase the risk of bleeding complications. As a result, characterization of baseline hemorrhagic risk is critical and must be accomplished before selecting an antithrombotic therapy. Risk factors for bleeding may be divided into two categories: nonmodifiable (including age, gender, race, weight, renal insufficiency, anemia, and acuity of presentation) and modifiable (including choice of antithrombotic therapy and PCI procedural characteristics). Of these predictive factors, the choice, dosage, and duration of the antithrombin and/or antiplatelet regimen are perhaps the most readily modifiable, especially in patients with an increased risk of bleeding. This review explores the nature of the association between bleeding and adverse outcomes, including mortality; evaluates risk factors for bleeding; and examines mechanisms for reducing bleeding complications through the selection of appropriate antithrombotic therapy.

Key words: bleeding complications, percutaneous coronary intervention, acute coronary syndromes, risk factors, heparin, bivalirudin, glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, hemorrhage, transfusion

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Introduction

Patients with acute coronary syndromes (ACS) are typically managed using an early invasive approach in which cardiac catheterization is performed, generally within 24 h of hospital admission.[1] Most patients with ACS undergo revascularization, usually with percutaneous coronary intervention (PCI) or, less commonly, with coronary artery bypass graft (CABG) surgery. Patients with ACS and those undergoing PCI, in both the urgent and elective settings, have a significant risk of ischemic complications. As a result, antithrombotic therapy targeting inhibition of the coagulation cascade and platelets is commonly employed to reduce the frequency of these adverse outcomes.

Although the combined use of antithrombin therapy, antiplatelet therapy, and invasive coronary procedures reduces the risk of ischemic events, it also increases the risk of bleeding complications. Rates of bleeding in ACS and PCI trials vary widely and have been reported to occur in up to 30% of patients.[2–7] Outside the carefully controlled milieu of clinical trials, even higher bleeding rates have been reported in contemporary practice.[8]

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These complications are independently associated with an increased risk of short- and long-term adverse outcomes, including death, myocardial infarction (MI) and other ischemic outcomes, as well as increased hospital stays and associated costs.[7,9]

A growing body of data reveals that bleeding complications in ACS and PCI (i) continue to occur with relative frequency; (ii) often exceed the frequency of ischemic complications such as MI; (iii) independently predict adverse outcomes, including death; and (iv) can be reduced using effective and safe antithrombotic regimens. Furthermore, since recent data imply that patients without bleeding complications have superior outcomes, including survival, antithrombotic therapy should be carefully selected to minimize the risk of both ischemic events and bleeding complications.

This review explores the nature of the association between bleeding complications and adverse events, evaluates risk factors for bleeding, and explores methods for reducing bleeding and optimizing outcomes through selection of appropriate antithrombotic therapy in patients with ACS and those undergoing PCI.

What are the Risk Factors for Bleeding?

Risk factors for bleeding complications can be divided into two categories: nonmodifiable and modifiable (Table 1). Techniques to minimize bleeding complications in ACS and PCI include assessment of baseline hemorrhagic risk, selection of an appropriate antithrombotic regimen, procedural modifications, and careful postprocedural observation, all of which are crucial in patients at high risk.

Eikelboom and colleagues[10] assessed bleeding complications in a meta-analysis of 34,146 patients with ACS from the OASIS (Organization to Assess Ischemic Syndromes) registry, OASIS-2, and CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) studies. Using a propensity model, the authors found that age, serum creatinine, and prior stroke were significant baseline predictors of major bleeding; additionally, increased systolic blood pressure (BP) was a significant negative predictor of major bleeding (Table 2).

Manoukian and colleagues[7] extended these findings in a recent analysis of 13,819 patients with ACS managed with an early invasive strategy in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. In addition to age and renal insufficiency, independent baseline predictors of major bleeding included female gender, hypertension, anemia, baseline ST-segment deviation, and baseline cardiac biomarker elevation (Fig. 1).

Nonmodifiable Risk Factors

Age: Age is directly correlated with an increased risk of bleeding. In addition to the above analyses, a retrospective study by Kinnaird and colleagues[11] of the incidence, predictors, and prognostic impact of periprocedural bleeding and transfusion in 10,974 patients undergoing PCI found that age was among the strongest predictors of major bleeding. Patients with major bleeding (as assessed using Thrombolysis in Myocardial Infarction [TIMI] criteria) were older than patients with minor or no bleeding (aged 67.8 vs. 65.9 years, respectively, $p<0.0001$). Compared with patients less than 50 years old, those 70–80 years old and more than 80 years old were at 1.6-fold and 1.9-fold increased risk of major bleeding, respectively ($p<0.0001$ for both comparisons). Advanced age was also significantly associated with an increased risk of transfusion.

Nelson and colleagues[12] performed an analysis of over 800 elderly patients (defined as patients >75 years old) undergoing PCI in the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2) trial. They found that elderly patients (13.4% of the overall REPLACE-2 trial population) had an increased risk of major bleeding and blood transfusion compared with younger patients (6.7% vs. 2.7% [$p<0.0001$] and 5.0% vs. 1.7% [$p<0.0001$], respectively). Furthermore, elderly patients with major bleeding had higher 30-day and 1-year mortality rates than did those without major bleeding (13.0% vs. 0.4%

TABLE 1 Risk factors for bleeding in ACS and PCI

Nonmodifiable	Modifiable
• Age	• Procedural characteristics
• Gender	• Choice of antithrombotic therapy
• Race	• Dosage of antithrombotic therapy
• Weight	• Duration of antithrombotic therapy
• Renal insufficiency	
• Anemia	
• ST-segment deviation	
• Cardiac biomarker elevation	
• Diabetes	
• Hypertension	

TABLE 2 Independent baseline predictors of major bleeding in patients with ACS enrolled in OASIS-1, OASIS-2, CURE

Variable	Odds ratio	p-Value
Age per 1-year increase	1.038	<0.0001
Systolic BP per 1-mmHg increase	0.995	0.005
Creatinine per 1-μmol/L increase	1.004	0.0001
Prior stroke	1.36	0.04

Adapted from Eikelboom *et al.*[10]
Abbreviations: ACS = acute coronary syndromes, CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events, OASIS = Organization to Assess Ischemic Syndromes.

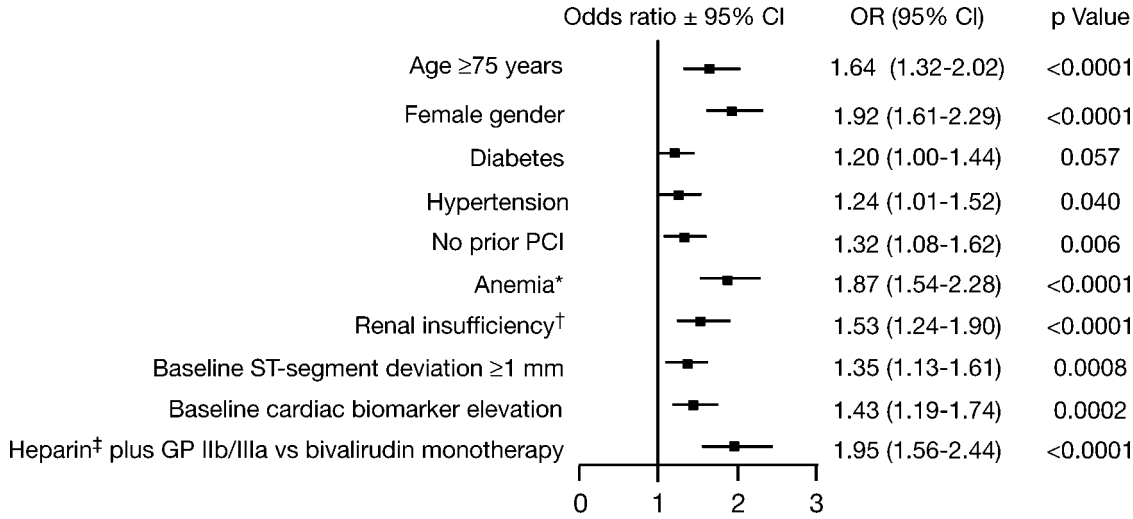


FIG. 1 Independent predictors of major bleeding in patients with ACS in the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. Reproduced with permission from Manoukian *et al.*[7] *Anemia was defined as baseline hemoglobin <13 g/dL in men and <12 g/dL in women. †Renal insufficiency was defined as a creatinine clearance <60 mL/min as calculated by the Cockcroft-Gault equation. ‡Unfractionated heparin or enoxaparin. *Abbreviations:* ACS = acute coronary syndromes, CI = confidence interval, GP = glycoprotein, OR = odds ratio, PCI = percutaneous coronary intervention.

[p<0.0001] and 16.7% vs. 4.5% [p = 0.0001] respectively).

Renal Insufficiency: Renal impairment is consistently associated with a high risk of bleeding and ischemic events.[13–16] An analysis of the REPLACE-2 trial by Chew and colleagues found that renal impairment (defined as creatinine clearance <60 mL/min) was associated with a 1.72-fold increased risk of bleeding complications (p = 0.028, as well as significant increases in the risks for ischemic events and 1-year mortality.[13] Similarly, a history of renal insufficiency (defined as any documented history of renal compromise) was associated with a significant 1.48-fold increased risk of bleeding (p = 0.0004) among 24,045 patients with ACS from the GRACE (Global Registry of Acute Coronary Events) registry.[15]

The impact of renal impairment on bleeding risk is at least partly confounded by the fact that patients with renal impairment tend to be older, female, and have comorbid conditions such as hypertension, peripheral vascular disease, cerebrovascular disease, and heart failure.[14] Additionally, elderly patients may have near-normal serum creatinine levels but still have impaired renal function.[8] As a result, patients with impaired renal function, particularly the elderly, are at increased risk of excessive dosing of unfractionated heparin (UFH) and glycoprotein (GP) IIb/IIIa inhibitors.[8] Furthermore, data from PROTECT-TIMI-30 (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia among Antiplatelet and Antithrombotic Agents—Thrombolysis in Myocardial Infarction 30) suggested that among patients with reduced creatinine clearance who received eptifibatide, failure to adjust the infusion for low creatinine clearance was associated with a very high rate of bleeding.[16] However, although excess dosing increases the risk of bleeding, certain antithrombotic agents intrinsically carry a high risk of bleeding, even when dosed appropriately. In an analysis of patients undergoing PCI in the REPLACE-2 trial, McDaniel and colleagues[17] demonstrated that even in patients with normal renal function (defined as creatinine clearance >90 mL/min), in whom excess dosing would be less likely, the use of eptifibatide compared with bivalirudin resulted in significantly higher rates of major (2.9% vs. 1.0%, p = 0.0056) and minor (23.7% vs. 11.0%, p<0.0001) bleeding. Therefore, the selection of agents with an intrinsically lower risk of excess dosing and bleeding is warranted, especially in patients with impaired renal function.

The above subanalysis of the REPLACE-2 trial by Chew and colleagues[13] also examined the efficacy and safety of bivalirudin vs. UFH plus GP IIb/IIIa inhibition among patients with renal impairment undergoing PCI. Renal function was assessed using creatinine clearance, with the threshold for impaired renal function defined as <60 mL/min. As noted previously, among the patients who met this criteria for renal impairment, there was a 1.45-fold increased risk of ischemic events (p = 0.004), a 1.72-fold increased risk of bleeding complications (p = 0.028), and significantly excessive 12-month mortality. Bleeding risk was reduced among patients receiving bivalirudin compared with those receiving UFH plus a GP IIb/IIIa inhibitor, regardless of whether baseline creatinine clearance was ⩾60 mL/min (1.6% vs. 3.1%,

$p = 0.001$) or <60 mL/min (3.2% vs. 7.1%, $p = 0.009$). In absolute terms, the risk reduction among patients with renal impairment who received bivalirudin translated into the prevention of one TIMI major or minor bleeding event for every 26 patients.[13]

Anemia: The impact of anemia in ACS and PCI has been recently reviewed by Voeltz and colleagues.[18] Anemia is common in ACS and PCI—occurring in more than 40% of patients in some studies—and is a major risk factor for bleeding, transfusion, cardiovascular (CV) events, and mortality, as well as prolonged hospitalization and high hospitalization costs.

In an analysis by Voeltz and colleagues[19] from the REPLACE-2 trial, anemia was present in 23% of patients. Major bleeding was significantly more common in anemic patients than in their nonanemic counterparts (4.9% vs. 2.8%, $p = 0.0001$). Furthermore, 1-year mortality was nearly 3-fold higher in anemic patients than in nonanemic patients (4.3% vs. 1.5%, $p<0.0001$), although short-term rates of ischemic complications were similar. Importantly, the use of bivalirudin in anemic patients resulted in a lower risk of major bleeding compared with the use of GP IIb/IIIa inhibitors plus heparin (3.5% vs. 6.2%, $p = 0.0221$).

In a meta-analysis of 39,922 patients in clinical trials of ACS, Sabatine and colleagues[20] found anemia was a powerful independent predictor of major adverse CV events in both ST-segment-elevation MI (STEMI) and non–ST-segment-elevation MI (NSTEMI). Their cohort analysis of 16 TIMI trials found that as hemoglobin levels dropped below 14 g/dL, rates of CV mortality and heart failure increased in patients with STEMI. However, in NSTEMI patients, the risk of CV death, MI, or recurrent ischemia did not increase until the baseline hemoglobin level fell below 11 g/dL.[20]

Other Factors: Gender and Body Weight, Presentation Variables, Others?: In addition to the baseline variables mentioned above, a number of other nonmodifiable factors may increase the risk of bleeding, but data are inconsistent. In the analysis by Manoukian and colleagues[7] from the ACUITY trial, female gender (odds ratio [OR] 1.92, 95% confidence interval [CI] 1.61–2.29, $p<0.0001$), hypertension (OR 1.24, 95% CI 1.01–1.52, $p = 0.040$), diabetes (OR 1.20, 95% CI 1.00–1.44, $p = 0.057$), and having no prior history of PCI (OR 1.32, 95% CI 1.08–1.62, $p = 0.006$) were independent predictors of major bleeding in patients with ACS. Although data are inconsistent, female gender may be associated with an increased risk for major bleeding compared with male gender.[10,11] Blacks have also been shown to be associated with a higher risk of major bleeding compared with whites, in some studies.[21] Data on the impact of body weight on risk are ambiguous; some studies suggest that low weight is a significant risk factor, whereas others have not found a significant association between weight and outcomes.[11,22] Beyond these baseline variables, certain clinical presentation features appear to increase the risk of bleeding. In the ACUITY analysis by Manoukian and colleagues,[7] independent predictors of major bleeding also included ST-segment deviation $\geqslant 1$ mm (OR 1.35, 95% CI 1.13–1.61, $p = 0.0008$) or cardiac biomarker elevation (OR 1.43, 95% CI 1.19–1.74, $p = 0.0002$), indicating that patients who present with increased ischemic risk also have increased bleeding risk.

Modifiable Risk Factors

Dosing of Antiplatelet/Antithrombotic Medications: The anti-ischemic benefits of various antithrombotic and antiplatelet agents are well known. However, the same mechanisms that confer these benefits are also responsible for increasing the risk of bleeding. As shown below, certain agents carry a higher intrinsic risk of bleeding complications than others, even when dosed appropriately.

In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of American College of Cardiology/American Heart Association guidelines) registry, relative to patients who were not administered excess doses, patients given excess doses of UFH (adjusted OR 1.08; 95% CI 0.94–1.26), low-molecular-weight heparin (LMWH) (adjusted OR 1.39; 95% CI 1.11–1.74), and GP IIb/IIIa inhibitors (adjusted OR 1.36; 95% CI 1.10–1.68) tended to have higher risks for major bleeding.[8] Increased mortality was also noted among patients receiving excess doses of GP IIb/IIIa inhibitors, and hospital stays were longer among patients receiving excess doses of LMWH or GP IIb/IIIa inhibitors.[8]

These data reinforce that excessive dosing is common and has important clinical consequences, and suggest that appropriate dosing and refinement of certain antithrombin and antiplatelet agents to attenuate the risk of bleeding remains a major unmet need.[8]

Procedural Characteristics: Duration of the procedure and use of certain devices may contribute to increased bleeding risk. An analysis of the EPIC (Evaluation of c7E3 Fab in Preventing Ischemic Complications of High-Risk Angioplasty) trial found an increased risk of bleeding among patients undergoing longer PCI (defined as >100 min; OR 1.10, 95% CI 1.07–1.14, $p<0.001$), repeat PCI (OR 3.06, 95% CI 1.69–5.53, $p<0.004$), and unsuccessful PCI.[22] In another analysis of EPIC by Blankenship and associates,[23] the size of the vascular sheath was found to be an independent predictor of vascular-site bleeding or surgery. Use of an intra-aortic balloon pump has also been associated with a significantly increased risk of bleeding events.[11]

Although procedural characteristics are driven largely by clinical need, these data suggest that every effort should be made to identify patients at high risk of bleeding complications and employ a minimally invasive approach to PCI when feasible. Such an approach would

ideally include some or all of the following: minimal catheter size, use of the radial access site, low-bleeding-risk antithrombotic strategies, low-viscosity contrast media, direct stenting, avoidance of closure devices, early ambulation, short postprocedure observation times, and early (perhaps even same-day) discharge.[24,25]

Is there an Association between Bleeding and Outcomes?

A strong, consistent relationship exists across trials between bleeding complications and short- and long-term adverse outcomes, including mortality, in patients with ACS and those undergoing PCI (Table 3). This relationship is independent of baseline patient characteristics, comorbidities, and treatments. Furthermore, the association between bleeding and mortality is a graded response, beginning with mild bleeding and becoming more powerful for moderate and severe bleeding.

The relationship among bleeding, ischemic events, and death in patients with ACS was examined in the meta-analysis by Eikelboom and colleagues.[10] Major bleeding was defined as that which was significantly disabling, required transfusion of $\geqslant$2 units of packed cells, or was life-threatening (fatal or intracranial bleeds, hemoglobin drop $\geqslant$5 g/dL, and bleeds causing substantial hypotension, surgical intervention, or transfusion of $\geqslant$4 units of blood). All other bleeding was defined as minor. The primary outcome was death during the first 30 days.[10]

In this meta-analysis, major bleeding was associated with a broad range of baseline characteristics, including age, diabetes, history of stroke, baseline systolic and diastolic BP, serum creatinine levels, and ST-segment changes.[10] Before adjustment for baseline characteristics, major bleeding was associated with a 5-fold higher incidence of death during the first 30 days ($p<0.001$) and a 1.5-fold higher incidence between 30 days and 6 months ($p=0.002$). After adjustment, major bleeding was strongly and independently associated with a 5.37-fold increased risk of death during the first 30 days ($p<0.001$) and weakly, but significantly, associated with a 1.54-fold increased risk of death after 30 days ($p=0.047$). When analyzed by bleeding vs. no bleeding, risk of death was strongly correlated with major bleeding (p for trend = 0.009; Fig. 2). Analysis by subgroup, including patients with a high baseline propensity for bleeding, showed that the association between bleeding and risk of death was independent of baseline characteristics and co-interventions. Major bleeding was also strongly correlated with the risk of MI or stroke within 30 days, but was not significantly related to the risk of either endpoint between 30 days and 6 months.[10]

More recently, Manoukian and colleagues[7] evaluated the impact of major bleeding on 30-day outcomes using

TABLE 3 Summary of impact of bleeding and transfusion on outcomes in major analyses

Study	Measure	Comparison	Hazard ratio
Manoukian 2007[7]	30-Day mortality	Major vs no major bleeding	7.55*
	30-Day MI	Major vs no bleeding	3.96*
Eikelboom 2006[10]	30-Day adjusted hazard of death	Major vs no bleeding	5.37
	Death between 30 days and 6 months	Major vs no bleeding	1.54
	Ml within 30 days	Major vs no bleeding	4.44
	MI between 30 days and 6 months	Major vs no bleeding	1.14
	Stroke within 30 days	Major vs no bleeding	6.46
	Stroke between 30 days and 6 months	Major vs no bleeding	1.30
Rao 2005[27]	30-Day adjusted hazard of death	Severe vs no bleeding	10.6
	30-Day adjusted hazard of death or MI	Severe vs no bleeding	5.6
	6-Month adjusted hazard of death	Severe vs no bleeding	7.5
Attubato 2004[26]	30-Day adjusted mortality	Major vs no bleeding	3.53*
Rao 2004[28] (transfusion)	30-Day adjusted hazard of death	Transfusion vs no transfusion	3.94
	30-Day adjusted hazard of death or MI	Transfusion vs no transfusion	2.92

* Odds ratio.

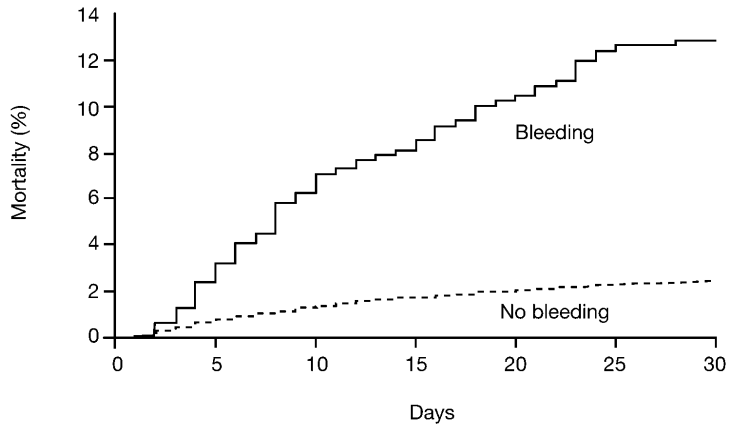


FIG. 2 Kaplan-Meier estimates of mortality among patients enrolled in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, by severity of bleeding. Reproduced with permission from Eikelboom *et al.*[10]

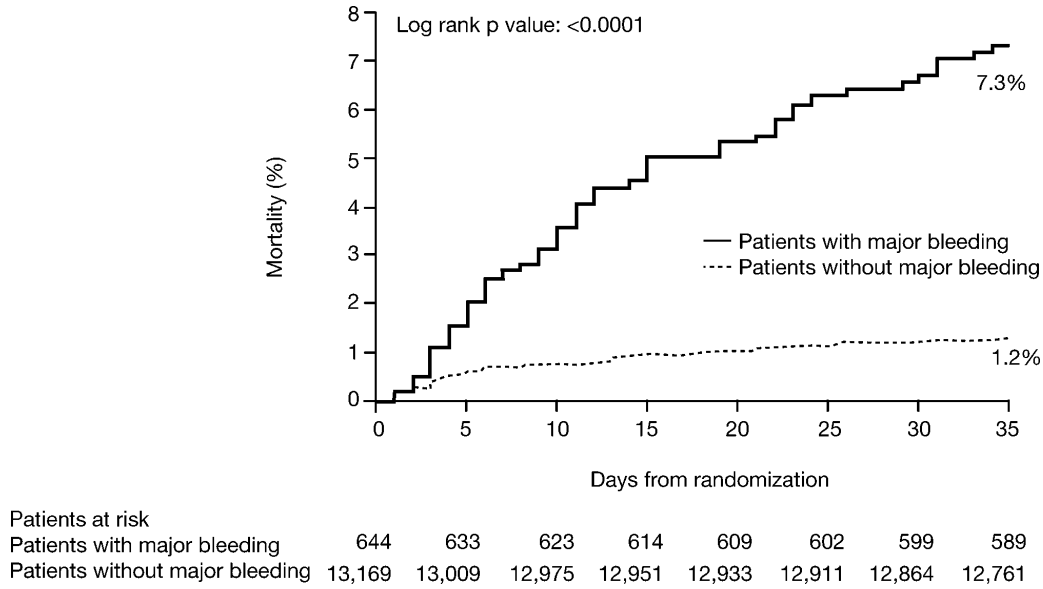


FIG. 3 Kaplan-Meier estimates of mortality in patients with acute coronary syndromes in the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. Reproduced with permission from Manoukian *et al.*[7]

data from 13,819 patients with moderate- and high-risk ACS undergoing an invasive strategy in the ACUITY trial. Major bleeding was defined as intracranial or intraocular, access-site bleeding requiring intervention, $\geqslant$5-cm-diameter hematoma, hemoglobin drop $\geqslant$4 g/dL without or $\geqslant$3 g/dL with an overt source, reoperation for bleeding, or blood product transfusion. Patients with major bleeding had elevated rates of 30-day mortality (7.3% vs. 1.2%, $p<0.0001$; [Fig. 3]), composite ischemia (23.1% vs. 6.8%, $p<0.0001$), and (importantly) stent thrombosis (3.4% vs. 0.6%, $p<0.0001$), compared with patients without major bleeding (Table 4). Furthermore, in a multivariable analysis, major bleeding was found to be the most powerful independent predictor of 30-day mortality (OR 7.55, 95% CI 4.68–12.18, $p<0.0001$), interestingly numerically higher than MI (Fig. 4).[7]

Similar results were observed in the 6,010 patients undergoing elective or urgent PCI in the REPLACE-2 trial, which compared bivalirudin plus provisional GP IIb/IIIa inhibition with UFH plus planned GP IIb/IIIa inhibition.[26] Major bleeding was defined as clinically significant bleeding (intracranial, intraocular, or retroperitoneal), overt blood loss resulting in a hemoglobin drop >3 g/dL, any hemoglobin drop >4 g/dL, or transfusion of $\geqslant$2 units of blood products. Despite the use of

a less-stringent major bleeding definition than the TIMI and GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) criteria, the unadjusted 30-day mortality was significantly higher in patients with than without major bleeding (10/195 [5.2%] vs. 9/5,806 [0.2%], $p<0.001$). Furthermore, major bleeding was a powerful independent predictor of 1-year mortality (OR 3.53, 95% CI 1.9–6.53, $p<0.0001$), validating the REPLACE-2 major bleeding definition as clinically important.[26]

Rao and colleagues[27] evaluated the impact of bleeding severity in a pooled analysis of 25,452 patients with ACS from four multicenter, randomized trials. Bleeding was defined using GUSTO criteria. Among patients with a bleeding episode (27.6%), stepwise increases in the risk of 30-day and 6-month mortality were observed as bleeding severity increased; these associations remained significant after adjustment for a wide range of confounders, including (but not limited to) age, gender, body weight, diabetes, and treatment assignment.[27]

The relationship between blood transfusion and clinical outcomes was evaluated in a meta-analysis of 2,401 patients with ACS by Rao and colleagues.[28] Patients who underwent transfusion were generally older and had more comorbid illnesses at presentation than those not receiving transfusion; patients receiving transfusion also had significantly higher unadjusted rates of death at 30 days (8.0% vs. 3.1%, $p<0.001$), MI (25.2% vs. 10.0%, $p<0.001$), and death or MI (29.4% vs 10.0%, $p<0.001$). After adjustment, transfusion was associated with a 3.94-fold increased risk of 30-day death and a 2.92-fold increase in 30-day death and MI. Notably, the predicted probability of 30-day death was higher among patients receiving transfusion at nadir hematocrit values >25%, suggesting that routine use of blood transfusion to maintain arbitrary hematocrit values should be considered with caution.[28]

How Can Bleeding Risk Be Reduced?

The combined use of antithrombin agents, antiplatelet agents, and invasive coronary procedures reduces the risk of periprocedural ischemic events but also increases the risk of bleeding in patients undergoing PCI and in those with ACS. Close attention should be paid to the use and dosing of UFH, LMWH, GP IIb/IIIa inhibitors, thienopyridines (i.e. clopidogrel), and direct thrombin inhibitors. Selection and dosing of appropriate periprocedural pharmacologic therapy can optimize the balance between reducing the risk of ischemic events and reducing the risk of bleeding.

Unfractionated Heparin

The bleeding risk associated with UFH is well known and may be related, in part, to its narrow therapeutic window and wide interpatient variations in anticoagulant effect. A meta-analysis of 4 trials of UFH in PCI evaluated the relationship between activated clotting time (ACT) and ischemic or bleeding complications in 9,974 patients.[29] Although the incidence of the composite of death, MI, or revascularization was similar across ACT quartiles, higher doses of UFH (>5,000 U, or up to 90 U/kg) were independently associated with higher rates of bleeding events. The incidence of major or minor bleeding within 48 h of the procedure increased with increasing ACT quartile ($p=0.04$ for trend). Notably, there was a linear increase in the incidence of bleeding that peaked as ACT approached 365 s ($p=0.01$), which did not increase beyond that value. Weight-indexed dosing was independently associated with higher bleeding rates for each 10 U/kg (OR 1.04, 95% CI 1.02–1.17, $p=0.001$).[29]

Low-Molecular-Weight Heparins

LMWHs were developed in an attempt to overcome some of the disadvantages of UFH, including increased risk of bleeding and relative unpredictability. Among the most important recent trials of these agents are the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors)[6] and OASIS-5[5] trials.

SYNERGY evaluated outcomes in high-risk patients with NSTEMI who received either enoxaparin or UFH.[6] Disappointingly, there was no difference between enoxaparin and UFH in the 30-day composite primary outcome of all-cause death or nonfatal MI (14.0% vs. 14.5%, respectively, p = ns), and rates of major bleeding were significantly higher for enoxaparin than for UFH using TIMI criteria (9.1% vs. 7.6%, $p=0.008$). Major bleeding was also numerically higher for enoxaparin using GUSTO criteria, although this difference was not statistically significant (2.7% vs. 2.2%, $p=0.08$).

Fondaparinux

Bleeding was also an important focus of the OASIS-5 trial, which compared enoxaparin with fondaparinux in over 20,000 patients with unstable angina and NSTEMI.[5] Although rates of ischemic events were similar for enoxaparin and fondaparinux (5.7% vs. 5.8%, respectively, p = ns), bleeding was significantly more frequent with enoxaparin than with fondaparinux (4.1% vs. 2.2%, $p<0.001$). At 6 months, the composite efficacy and safety endpoint (which included both ischemic outcomes plus major bleeding) occurred significantly more frequently in the enoxaparin arm. This result was driven by the substantial lower rates of major bleeding among patients who received fondaparinux. There were, however, significant thrombotic issues related to the use of fondaparinux in the catheterization laboratory, most notably a greater incidence of catheter thrombus, compared with enoxaparin, which required the use of significant doses of UFH during PCI. This finding implies that fondaparinux

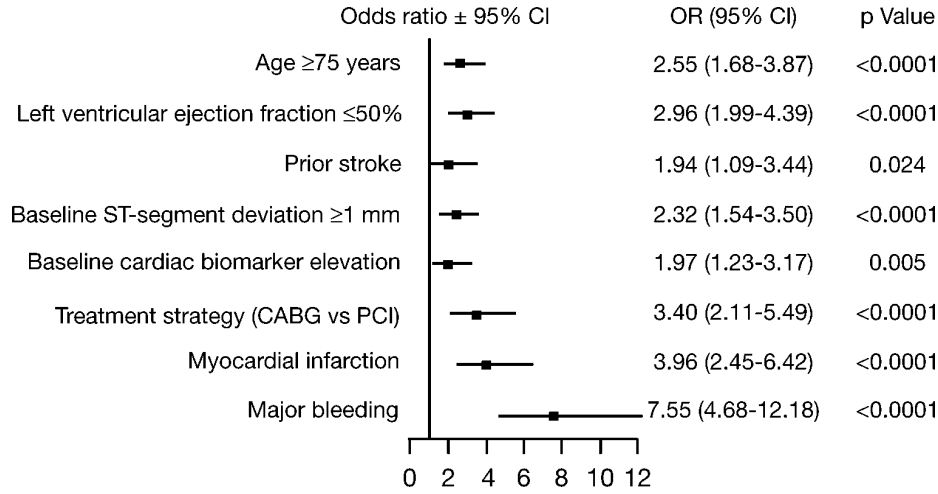


FIG. 4 Independent predictors of 30-day mortality in patients with ACS in the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. Reproduced with permission from Manoukian *et al.*[7] *Abbreviations:* ACS = acute coronary syndromes, CABG = coronary artery bypass graft surgery, CI = confidence interval, OR = odds ratio, PCI = percutaneous coronary intervention.

may not be suited for patients with ACS undergoing an invasive management strategy, unless a supplemental antithrombin is also administered during PCI.[5]

Glycoprotein IIb/IIIa Inhibitors

Although the GP IIb/IIIa inhibitors have demonstrated considerable efficacy in reducing the risk of adverse ischemic events compared to UFH, these agents can be associated with substantial bleeding risk. A study by Aguirre and colleagues[22] examined bleeding complications in high-risk patients who received abciximab against a background of aspirin and UFH. In this study, major bleeding complications unrelated to CABG occurred in 3.3% of patients who received placebo, 8.6% of patients who received bolus abciximab, and 10.6% of patients who received bolus and infusional abciximab ($p<0.001$). Furthermore, transfusion was required in 7.5% in the placebo group compared with 16.8% in the group receiving bolus and infusional abciximab ($p<0.001$).[22]

The risk of bleeding complications associated with GP IIb/IIIa inhibitors may be attenuated by lower doses of UFH (compared to standard-dose UFH), as shown in the EPILOG (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade) study. EPILOG compared the efficacy and safety of placebo plus standard-dose UFH, abciximab plus

TABLE 4 Clinical outcomes in patients with and without major bleeding

	Major bleeding n=644 (4.7%)	No major bleeding n=13,175 (95.3%)	p value
Composite ischemia	149 (23.1)	901 (6.8)	<0.0001
Death from any cause	47 (7.3)	159 (1.2)	<0.0001
Myocardial infarction	94 (14.6)	610 (4.6)	<0.0001
Q-wave	27 (4.2)	117 (0.9)	<0.0001
Non-Q-wave	68 (10.6)	495 (3.8)	<0.0001
Unplanned revascularization for ischemia	49 (7.6)	289 (2.2)	<0.0001
PCI	43 (6.7)	221 (1.7)	<0.0001
Coronary artery bypass surgery	10 (1 .6)	73 (0.6)	0.001
Stent thrombosis	22 (3.4)	82 (0.6)	<0.0001
Thrombocytopenia (acquired)*	136 (21.1)	1329 (10.1)	<0.0001

* Platelet count <150,000 cells/mm^3 in patients without baseline thrombocytopenia.
Abbreviations: PCI = percutaneous coronary intervention.

standard-dose UFH and abciximab plus low-dose UFH in 2,792 patients undergoing urgent or elective PCI.[2] Although major bleeding rates were not significantly different between the three groups; minor bleeding was significantly higher for abciximab plus standard-dose UFH compared to placebo plus standard-dose UFH (7.4% vs. 3.7%, $p < 0.001$), but not for abciximab plus low-dose UFH compared to placebo plus standard-dose UFH (4.0% vs. 3.7%, p = ns).[2] Close attention should therefore be paid to appropriate weight-based dosing and monitoring of UFH, especially in patients who receive concomitant GP IIb/IIIa inhibitors.

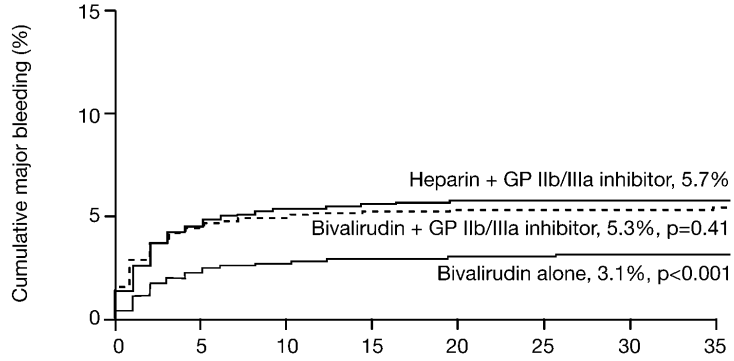
Direct Thrombin Inhibitors

Clinical trials, including REPLACE-2[30] and the recent ACUITY trial,[31] indicate that the direct thrombin inhibitor bivalirudin is associated with considerably less risk of bleeding complications than UFH or a GP IIb/IIIa inhibitor plus UFH, while maintaining similar protection from ischemic events in patients undergoing PCI or patients with ACS.

In the REPLACE-2 trial, over 6,000 patients undergoing elective or urgent PCI were randomly assigned to bivalirudin (0.75 mg/kg bolus and 1.75 mg/kg/h infusion) with provisional GP IIb/IIIa inhibition or combination UFH (65 IU/kg bolus) plus planned GP IIb/IIIa inhibition.[30] The use of bivalirudin resulted in similar rates of the 30-day ischemic composite (death, MI, or urgent repeat revascularization) compared with UFH plus GP IIb/IIIa inhibition (9.2% vs. 10.1%, p = 0.32) and a significantly lower rate of major (2.4% vs. 4.1%, p<0.001) and minor (13.4% vs. 25.7%, p<0.001) bleeding. Furthermore, rates of transfusion were also significantly lower in patients receiving bivalirudin than in those receiving UFH plus planned GP IIb/IIIa inhibition (1.7% vs. 2.5%, p<0.02).[30]

In the ACUITY trial, 13,819 patients with moderate- and high-risk ACS undergoing an early invasive strategy were randomly assigned to one of three antithrombotic regimens: combination therapy with UFH or enoxaparin plus a GP IIb/IIIa inhibitor, combination therapy bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin monotherapy (with provisional use of a GP IIb/IIIa inhibitor).[31] Although rates of 30-day composite ischemia were similar for the three regimens (7.3, 7.7, and 7.8%, respectively, p=ns), major bleeding (3.0% vs 5.7%, p<0.001) and net clinical outcome (10.1% vs. 11.7%, p = 0.001) were significantly lower for bivalirudin monotherapy than for UFH or enoxaparin plus a GP IIb/IIIa inhibitor. Moreover, significant reductions in the risk of bleeding from any cause, minor bleeding, major and minor bleeding according to the TIMI scale, and blood transfusion were observed in patients receiving bivalirudin monotherapy (Fig. 5).[31] At 1 year, the rate of the composite ischemic endpoint remained similar in each of the three groups, and mortality was numerically (although not statistically) lowest in patients receiving bivalirudin monotherapy compared to UFH or enoxaparin plus a GP IIb/IIIa inhibitor or bivalirudin plus a GP IIb/IIIa inhibitor (3.8% vs. 4.4% vs 4.2%, p = ns). Furthermore, in a multivariable analysis of predictors of 1-year mortality, the hazard ratio (HR) for major bleeding was numerically higher (2.89, 95% CI 2.24–3.72, p = <0.0001) than the HR for MI (2.47, 95% CI 1.87–3.27, p = <0.0001).[32]

In a subanalysis of patients from the ACUITY trial who underwent PCI (n = 7,789), major bleeding occurred significantly less frequently in patients receiving bivalirudin monotherapy than in those receiving UFH plus a GP IIb/IIIa inhibitor (4% vs. 7%,



Number at risk								
Heparin + GP IIb/IIIa inhibitor	4603	4336	4282	4258	4240	4208	3729	2575
Bivalirudin + GP IIb/IIIa inhibitor	4604	4329	4286	4266	4250	4222	3761	2625
Bivalirudin alone	4612	4423	4389	4366	4352	4312	3846	2633

FIG. 5 Comparison of bleeding rates among moderate- and high-risk patients enrolled in the Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial. Reproduced with permission from Stone *et al.*[31]

$p<0.001$).[32] This dramatic reduction in the relative risk of bleeding—combined with comparable protection from ischemic events—represents a substantial advantage of bivalirudin over usual care consisting of a GP IIb/IIIa inhibitor plus UFH.[32]

A recent multivariable analysis by Manoukian and colleagues of major bleeding and 30-day outcomes from ACUITY found that the use of UFH plus a GP IIb/IIIa inhibitor was an independent predictor of major bleeding compared with bivalirudin monotherapy. Furthermore, major bleeding was the most powerful predictor of 30-day mortality in this analysis.[7] In aggregate, these results suggest that the direct thrombin inhibitor bivalirudin is associated with significantly and substantially reduced bleeding risk compared with regimens containing a GP IIb/IIIa inhibitor. Together with trials indicating that bivalirudin is at least noninferior to UFH plus GP IIb/IIIa inhibitors in low-, moderate-, and high-risk patients undergoing PCI, these data indicate that bivalirudin is an effective and safe antithrombotic therapy, particularly in patients with an increased risk of bleeding.

Conclusions

An abundance of data supports the relationship between bleeding complications and an increased risk of adverse outcomes, including mortality and ischemic events. Bleeding complications may be reduced by assessing hemorrhagic risk (e.g., baseline clinical and demographic factors, procedural characteristics) and selecting effective antithrombotic regimens with low bleeding risk. Of the risk factors for bleeding, perhaps the most easily modifiable is the periprocedural antithrombin and antiplatelet regimen. The benefit of antithrombin and antiplatelet therapy in reducing risk of ischemic events must be balanced carefully against a particular regimen's propensity to cause bleeding complications. In light of the available data suggesting a direct link between bleeding risk and short- and long-term mortality and ischemic events—it is possible, indeed likely, that appropriate selection of antiplatelet and antithrombotic regimens may indirectly reduce mortality and ischemic events through a reduction in risk of bleeding.

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