The impact of bleeding in patients with acute coronary syndromes: How to optimize the benefits of treatment and minimize the risk

David Fitchett MD

D Fitchett. The impact of bleeding in patients with acute coronary syndromes: How to optimize the benefits of treatment and minimize the risk. *Can J Cardiol* 2007;23(8):663-671.

Recurrent ischemic events after an acute coronary syndrome (ACS) remain common. Antithrombotic therapy with coronary revascularization reduces the frequency of such life-threatening events. However, with the greater use of antithrombotic medications and early revascularization, bleeding has become an increasingly important problem. Not only does bleeding result in an immediate threat, but it is also associated with increased coronary artery disease mortality and reinfarction, both in the short and long term. Older patients and women, as well as patients with anemia, renal dysfunction, high-risk ACS, diabetes, hypertension and those undergoing invasive procedures, are at especially high risk for bleeding. Major bleeding is associated with a 60% increased risk of in-hospital death, and a fivefold increase in one-year mortality and reinfarction. However, the causal link between bleeding and increased coronary artery disease events is unproven.

Although there is no proof that reducing bleeding events improves outcomes, the current paradigm for the management of ACS is a strategy to minimize recurrent ischemic events but also to minimize the risk of bleeding. Such a strategy includes matching the ACS risk to the most appropriate treatment, assessing the bleeding risk, using vascular access techniques to minimize bleeding, selecting the antithrombotic agent that is best for the patient, minimizing the duration of exposure to antithrombotic agents, using the correct dose of medications, recognizing the early signs of bleeding and using gastro-protective agents to minimize upper gastrointestinal bleeding.

Key Words: *Acute coronary syndromes; Bleeding; Transfusion*

Thrombosis, recognized as the cause of coronary arterial occlusion in patients with acute coronary syndromes (ACS), has led to treatment strategies with fibrinolytics, and antiplatelet and antithrombotic therapy (antithrombotic agents act on the coagulation cascade, and include heparins, fondaparinux and direct thrombin inhibitors such as bivalirudin). Preventing thrombosis has had an important impact by reducing mortality and recurrent ischemic events. Over the past 30 years, new agents have been added to the current treatment, usually providing an incremental benefit and, at the same time, increasing the danger from bleeding. This was an acceptable hazard, provided that the bleeding risk was small and that the treatment reduced ischemic outcomes. Recent studies (1,2) with newer antithrombotic agents have

Les conséquences des hémorragies chez les patients atteints de syndromes coronariens aigus : Comme optimiser les bienfaits du traitement et réduire les risques au minimum

Les événements ischémiques récurrents après un syndrome coronarien aigu (SCA) sont courants. Le traitement antithrombotique accompagné d'une revascularisation coronaire réduit la fréquence de ces événements qui mettent en jeu le pronostic vital. Cependant, avec le plus grand usage des antithrombotiques et la revascularisation rapide, les hémorragies deviennent de plus en plus problématiques. Non seulement l'hémorragie constitue-t-elle une menace immédiate, mais elle s'associe également à une augmentation de la mortalité causée par la coronaropathie et à une récurrence d'infarctus, à court et à long terme. Les patients plus âgés et les femmes, ainsi que les patients anémiques, atteints d'un dysfonctionnement rénal, très vulnérables à un SCA, diabétiques, hypertendus ou qui subissent une intervention envahissante courent un risque particulièrement élevé d'hémorragie. L'hémorragie majeure s'associe à une augmentation de 60 % du risque de décès à l'hôpital et de cinq fois le taux de mortalité et de récurrence d'infarctus au bout d'un an. Cependant, le lien causal entre l'hémorragie et l'augmentation des événements coronaropathiques n'est pas démontré.

Il n'existe pas de preuve probante pour étayer que la diminution du nombre d'événements hémorragiques améliore les issues, mais le paradigme actuel de prise en charge du SCA prend la forme d'une stratégie pour réduire au minimum les événements ischémiques récurrents et aussi le risque d'hémorragie. Cette stratégie comprend le jumelage du risque de SCA avec le traitement le plus pertinent, l'évaluation du risque d'hémorragie, le recours à des techniques d'accès vasculaire pour enrayer l'hémorragie, le choix du meilleur antithrombotique pour le patient, la réduction maximale de la durée d'exposition aux antithrombotiques au moyen de la bonne dose de médicaments, le dépistage des signes précurseurs d'hémorragie et le recours aux agents gastroprotecteurs pour limiter les saignements gastro-intestinaux.

failed to show incremental benefits, but indicate that the same benefits can be achieved as the previous standard of care with a lower risk of bleeding. In addition, it is now recognized that both bleeding and the need for blood transfusions are associated with a major risk for recurrent ischemic coronary events and death, independent of the immediate consequence of blood loss. There is also new evidence indicating that a reduction in bleeding events and a restricted transfusion strategy results in improved long-term outcomes.

The present review considers strategies to maintain the benefits of antithrombotic and antiplatelet therapy, and to minimize the risk for hemorrhage in an era in which high-risk ACS patients undergo early cardiac catheterization and revascularization.

St Michael's Hospital, Toronto, Ontario

Correspondence: Dr David Fitchett, St Michael's Hospital, 30 Bond Street, Toronto, Ontario M3B 1W8. Telephone 416-864-5627,

fax 416-864-5159, e-mail fitchettd@smh.toronto.on.ca

Received for publication January 10, 2007. Accepted March 15, 2007

TABLE 1
Definitions of major or severe bleeding

Source (reference)	Definition
• GUSTO (5)	Bleeding resulting in hemodynamic compromise or intracranial hemorrhage
• OASIS (60)	Need for blood transfusion of 2 units or more, or disabling bleeding leading to death, surgery or intracranial bleeding
• TIMI (definition A) (ACUTE-II [61] and A to Z [62])	Hemoglobin drop of 50 g/L or more, or intracranial bleeding or noncoronary artery bypass graft-related bleeding causing pericardial tamponade
• TIMI (definition B) (TIMI 11B [19] and INTERACT [20])	Overt bleeding leading to death; retroperitoneal, intracranial, intraocular bleeding; hemoglobin drop of 30 g/L; or blood transfusion of 2 units or more
• TIMI (definition C) (PURSUIT [17] and SYNERGY [7])	Hemoglobin drop of more than 50 g/L, or a greater than 15% absolute decrease in hematocrit or intracranial hemorrhage
• ISTH definition (8)	Fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing hemoglobin drop of 20 g/L or more, and/or blood transfusion of 2 units or more

ACUTE Antithrombotic Combination Using Tirofiban and Enoxaparin; A to Z Aggrastat to Zocor; GUSTO Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; INTERACT INtegrilin and Enoxaparin Randomized assessment of Acute Coronary syndrome Treatment; ISTH International Society on Thrombosis and Haemostasis; OASIS Organization to Assess Strategies for Ischemic Syndromes; PURSUIT Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; SYNERGY Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors; TIMI Thrombolysis In Myocardial Infarction

Incidence and risk of bleeding

Major bleeding and/or the need for blood transfusion is the most common serious adverse outcome for patients admitted to hospital with an ACS. In a recent report from the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry (3) of patients with ACS, the non-coronary artery bypass graft-related transfusion rate was 9.9%, compared with other in-hospital outcomes of death (4.3%), reinfarction (2.5%), heart failure (8%), cardiogenic shock (2.6%) and stroke (0.8%). The incidence of major hemorrhage and transfusion surpasses the frequency of recurrent myocardial infarction, stroke and cardiovascular mortality, and is associated with reduced long-term survival.

The reported incidence of bleeding in studies of patients with ACS varies widely. It is largely determined by the study design (randomized trial or community registry), the definition of bleeding severity, patient factors that include demographics (eg, age and sex), comorbidities (diabetes, hypertension, renal and hepatic impairment, and hemostatic disorders), as well as treatment factors that include concomitant therapy (antiplatelet, anticoagulant and fibrinolytic medication), invasive procedures (percutaneous coronary intervention [PCI] and coronary artery bypass graft), and the timing of the drug administration related to procedures and surgery (4).

The definitions of major bleeding used in various clinical trials are shown in Table 1. The Global Utilization of

Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) trial (5) defined severe clinical bleeding as that resulting in potentially life-threatening complications such as hemodynamic compromise or intracranial hemorrhage. In contrast, the Thrombolysis In Myocardial Infarction (TIMI) trial bleeding end points (TIMI definitions and references are shown in Table 1) were attained by a drop in hemoglobin without any clinically life-threatening event. Although the GUSTO and TIMI trial definitions of major bleeding identified patients at risk for future adverse events, an analysis of both definitions suggests that outcomes are more accurately predicted by bleeding as assessed by clinical criteria (GUSTO) than by definitions that are largely assessed by laboratory criteria (6).

The variety of definitions complicates the comparison of clinical trials, because minor bleeding in one study may be defined as major bleeding in another trial, and different definitions can result in up to a threefold variation in the reported frequency of major bleeding (7). Consequently, the International Society on Thrombosis and Haemostasis (8) has proposed a standard definition (Table 1) of major bleeding that may be used in future clinical trials.

The incidence of major bleeding observed in major clinical trials of antithrombotic medications for the early management of ACS ranges from 1% to 9%. (Table 2). A combined analysis of the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry (9), the OASIS-2 registry and the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial using the OASIS definition of major bleeding found that 2.0% to 2.3% of patients developed major bleeding during the study follow-up period or within six months. Bleeding was related to age, female sex, systolic blood pressure, creatinine level and prior stroke, as well as to management with antithrombin agents, glycoprotein (GP) IIb/IIIa inhibitors, and invasive or operative procedures. Predictors of bleeding in the recently reported Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial (10) were age of 75 years or older, presence of anemia, renal dysfunction (creatinine clearance of less than 60 mL/min), diabetes, female sex, high-risk ACS, hypertension, no prior PCI and prior use of antithrombotic therapy.

The Global Registry of Acute Coronary Events (GRACE) (11) of 24,045 patients found major bleeding in 3.9% of patients with ACS. Major bleeding was defined as life-threatening bleeding requiring transfusion of more than two units of blood, a hematocrit decrease of 10% or more, or bleeding resulting in death or cerebral or subdural hematoma. A multivariate model identified age, renal insufficiency, history of bleeding, use of diuretics, GP IIb/IIIa inhibitors, intravenous inotropes, right heart catheterization and PCI as independent predictors of major bleeding. A recent Canadian registry (12) using a similar definition reported major bleeding in 79 of 5482 patients (1.4%). Patients with bleeding complications were older (75 years versus 66 years), had higher baseline creatinine levels, and had an increased incidence of diabetes, hypertension, prior stroke, Killip class greater than II and ST-segment depression on admission.

Bleeding associated with antithrombotic and antiplatelet agents (Table 2)

Clinical trials of antithrombotic and antiplatelet agents for the management of ACS have evaluated the outcomes resulting from either adding the study agent (usually an antiplatelet

TABLE 2**Incidence of noncoronary artery bypass graft (CABG)-related bleeding in clinical trials of antithrombotic medications for patients with acute coronary syndromes**

Source (reference)	Bleeding definition	Treatment duration	Concomitant medication	Major non-CABG-related bleeding rates		Other severe bleeding
				Active medication	Comparator	(Active/comparator)
Cairns et al (63)		2 years	None	ASA approximately 2%	Placebo <1% (P NA)	
CURE (13)	CURE*	9 months	ASA, heparin	Clopidogrel 3.7%	Placebo 2.6% (P=0.001)	Life-threatening 2.2%/1.8% (P = NS)
PURSUIT (17)	TIMI (C) [†]	72 h	ASA, heparin	Eptifibatide 3.0%	Placebo 1.3% (P<0.001)	GUSTO [‡] severe 1.1%/0.3% (P<0.001)
PRISM-PLUS (16,14)	TIMI [§]	48 h	ASA, heparin	Tirofiban 1.4%	Placebo 0.8% (P = NS)	Transfusion 4.0%/2.8% (P = NS)
CAPTURE (64)	CAPTURE	18 h – 24 h	ASA, heparin	Abciximab 3.8%	Placebo 1.9% (P=0.043)	Transfusion 7.1%/3.4% (P=0.005)
ESSENCE (18)	ESSENCE**	2 – 8 days	ASA	Enoxaparin 6.5%	UF heparin 7.0% (P = NS)	
FRISC (65)	FRISC ^{††}	6 days	ASA	Dalteparin 0.8%	Placebo 0.5% (P = NS)	
INTERACT (20)	TIMI (B) ^{‡‡}	48 h	ASA, eptifibatide	Enoxaparin 2.9%	UF heparin 5.7% (P=0.03)	Transfusion 4.2%/5.2% (P = NS)
SYNERGY (66)	TIMI (C) [†]	36 h	ASA	Enoxaparin 9.1%	UF heparin 7.6% (P=0.008)	GUSTO [‡] major 2.7%/2.2% (P = NS) Transfusion 17% vs 16% (P = NS)
OASIS-5 (1)	OASIS ^{§§}	Up to 8 days	ASA, clopidogrel	Fondaparinux 2.2%	Enoxaparin 4.1% (P=0.001)	Transfusion 1.6% vs 2.8% (P<0.001)
ACUITY (2)	ACUITY ^{¶¶}	Up to 72 h	ASA, clopidogrel	Heparin + GP IIb/IIIa 5.7%	Bivalirudin 3.0% (P<0.001)	Transfusion 1.6% vs 2.7%/2.6% (P<0.001)
CLARITY (39)	TIMI [§]	8 days	ASA, heparin, thrombolysis	Clopidogrel 1.3%	Placebo 1.1% (P = NS)	30-day major bleeding 1.9% vs 1.7% (P = NS)
COMMIT (40)	COMMIT***	Mean 15 days	ASA, thrombolysis	Clopidogrel 0.58%	Placebo 0.55% (P = NS)	
EXTRACT (67)	TIMI [†]	Minimum 48 h	ASA, thrombolysis	Enoxaparin 2.1%	UF heparin 1.4% (P<0.001)	Intracranial hemorrhage 0.8% vs 0.7% (P = NS)
OASIS-6 (38)	OASIS ^{§§}	Fondaparinux 8 days, heparin 24 h – 48 h	ASA, thrombolysis	Fondaparinux 1.8%	Heparin 2.1% (P = NS)	Modified TIMI ^{†††} 1.0% vs 1.3% (P = NS)

*Major bleeding was defined as substantially disabling bleeding, intraocular bleeding leading to vision loss or bleeding necessitating the transfusion of at least 2 units of blood. Life-threatening bleeding was defined as bleeding that was fatal, or that which led to a reduction of hemoglobin of at least 50 g/L, substantial hypotension requiring the use of intravenous inotropic agents, surgical intervention, symptomatic intracranial bleeding, or that which necessitates the transfusion of 4 units of blood or more; [†]A hemoglobin drop of more than 50 g/L, or a greater than 15% absolute decrease in hematocrit or intracranial hemorrhage; [‡]Bleeding resulting in hemodynamic compromise or intracranial hemorrhage; [§]A hemoglobin drop of 50 g/L or more, or intracranial bleeding or non-CABG-related bleeding causing pericardial tamponade; ^{||}Intracranial bleeding or a hemoglobin drop of less than 50 g/L; ^{**}Bleeding resulting in death, transfusion of at least 2 units of blood, a drop in hemoglobin of 30 g/L or more, or retroperitoneal, intracranial or intraocular hemorrhage; ^{††}A drop in hemoglobin of more than 20 g/L associated with corresponding signs or symptoms, intracranial bleeding, or bleeding leading to transfusion, interruption of treatment or death; ^{‡‡}Overt bleeding leading to death; retroperitoneal, intracranial or intraocular bleeding; hemoglobin drop of 30 g/L; or blood transfusion of 2 units or more; ^{§§}Need for blood transfusion of 2 units or more, or disabling bleeding leading to death, surgery or intracranial bleeding; ^{¶¶}Intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, a reduction in hemoglobin level of at least 40 g/L without an overt bleeding source or at least 30 g/L with such a source, reoperation for bleeding, or transfusion of a blood product; ^{***}Hemorrhagic stroke and major noncerebral bleeding was defined as bleeding that required transfusion or was fatal; ^{†††}Fatal hemorrhage, cardiac tamponade or clinically significant hemorrhage with decrease in hemoglobin of less than 50 g/L. ACUITY Acute Catheterization and Urgent Intervention Triage strategy; ASA Acetylsalicylic acid; CAPTURE c7E3 fab AntiPlatelet Therapy in Unstable REfractory angina; CLARITY CLopidogrel as Adjunctive Reperfusion Therapy; COMMIT Clopidogrel and Metoprolol in Myocardial Infarction Trial; CURE Clopidogrel in Unstable angina to prevent Recurrent Events; ESSENCE Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events; EXTRACT Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment; FRISC FRagmin in unstable Coronary Artery Disease; GP Glycoprotein; GUSTO Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; INTERACT INtegrilin and Enoxaparin Randomized assessment of Acute Coronary Syndrome Treatment; NA Not available; NS Not significant; OASIS Organization to Assess Strategies for Ischemic Syndromes; PRISM PLUS Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PURSUIT Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; SYNERGY Superior Yield of the New Strategy of enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors; TIMI Thrombolysis In Myocardial Infarction; UF Unfractionated

agent) to the existing treatment or comparing the study drug (usually an antithrombotic agent) with a standard medication. Adding clopidogrel to acetylsalicylic acid (ASA) in the CURE trial (13) reduced adverse outcomes (RR 0.8, 95% CI 0.72 to 0.90) over the nine-month duration of the trial. Major bleeding was increased by an absolute 1%, but there was no increase in life-threatening bleeding. Most of the bleeding occurred during the first month of treatment and was related to the ASA dose more than to the combined treatment.

Intravenous GP IIb/IIIa inhibitors (either tirofiban or eptifibatide) are recommended by the American College of Cardiology and the American Heart Association guidelines (14) for the early treatment of high-risk patients with non-ST-segment elevation ACS if cardiac catheterization or PCI is planned.

Tirofiban (15,16) and eptifibatide (17) infusions for periods of up to 96 h reduced early fatal and nonfatal myocardial

infarction when used as the initial medical management in patients with non-ST-segment elevation ACS and high-risk features. In the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial (17), the bleeding rate was two to three times greater in patients receiving eptifibatide, with most of the bleeding complications related to the femoral catheterization access site. In the Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) study (15), in which most patients underwent early angiography, there was a trend toward a twofold increase in TIMI major bleeding for patients receiving tirofiban (heparin 0.8%, heparin plus tirofiban 1.4%, P not significant).

Low-molecular-weight heparin is at least as effective as unfractionated heparin in reducing recurrent ischemic events; however, low-molecular-weight heparin is easier to administer

and results in reliable levels of anticoagulation. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) (18) and TIMI 11B (19) trials showed enoxaparin to be superior to unfractionated heparin, without an increase in major bleeding (major bleeding RR [95% hazard ratio (HR)]: ESSENCE 0.90 [0.63 to 1.27], TIMI 11B 1.52 [0.85 to 2.70]). The INTEgrilin and Enoxaparin Randomized assessment of Acute Coronary syndrome Treatment (INTERACT) trial (20) compared enoxaparin with unfractionated heparin in high-risk patients receiving the GP IIb/IIIa inhibitor eptifibatide. In the enoxaparin-treated patients, recurrent ischemic events were less frequent, and the 30-day rate of death or myocardial infarction was reduced. The incidence of major bleeding was 53% lower in the patients receiving enoxaparin (RR 0.47, 95% CI 0.63 to 1.27). The Superior Yield of the New strategy of Enoxaparin, Revascularization and GLYcoprotein IIb/IIIa inhibitors (SYNERGY) trial (7) examined the use of enoxaparin in aggressively managed, high-risk non-ST-segment elevation ACS patients who underwent coronary angiography a median of 22 h from presentation. The study failed to demonstrate an efficacy superiority of enoxaparin compared with unfractionated heparin, and enoxaparin was associated with increased TIMI major bleeding (9.1% versus 7.6%, $P=0.008$) but no difference in transfusion requirements (17% versus 16%). When patients received no heparin before random assignment or had consistent treatment, enoxaparin reduced fatal and nonfatal outcomes, but bleeding rates were significantly higher in patients receiving enoxaparin.

The OASIS-5 study (1) showed the factor Xa inhibitor fondaparinux to be noninferior to enoxaparin (HR 1.01, 95% CI 0.9 to 1.13) nine days after random assignment. However, major bleeding rates were 50% lower in the fondaparinux-treated patients. At 30 days and after six months, mortality was significantly reduced in patients who received fondaparinux. Major bleeding was associated with a mortality rate five times higher than in patients without bleeding, and largely accounted for the difference in mortality rates observed between the fondaparinux- and enoxaparin-treated patients. The ACUITY trial (2) examined the use of the direct thrombin inhibitor bivalirudin in a strategy that compared bivalirudin with either bivalirudin and a GP IIb/IIIa inhibitor or heparin and a GP IIb/IIIa inhibitor. The ischemic end point was achieved in a similar number of patients in all three arms of the study. However, major bleeding was significantly lower in patients receiving bivalirudin alone (3%) than either bivalirudin plus a GP IIb/IIIa inhibitor (5.3%) or heparin plus a GP IIb/IIIa inhibitor (5.7%).

Management strategy and bleeding

The management of patients with ACS has evolved over the past 30 years with the use of more effective and powerful antithrombotic agents, as well as more frequent and earlier cardiac catheterization and revascularization. With these developments, recurrent ischemic complications have been substantially reduced (21,22) and long-term survival has improved (23). However, the improved outcomes came with an increased risk of major hemorrhage. Furthermore, the benefits and safety of medications, demonstrated during an era in which invasive management was used less frequently and at a later time, may not be present with today's aggressive, early invasive strategy. A comparison of the clinical trials comparing enoxaparin with unfractionated heparin illustrates this point.

Earlier trials (ESSENCE [24], TIMI 11B [19] and INTERACT [25]) showed that enoxaparin resulted in improved clinical outcomes, with no increase or even a reduction in bleeding (25). In contrast, the recent SYNERGY trial (7) showed no benefit, but rather a 17% increase in major bleeding, in patients receiving enoxaparin. Aggressive, early invasive management in the SYNERGY trial patients, 92% of whom underwent cardiac catheterization at a median of 22 h, appeared to have removed the advantage of enoxaparin and increased bleeding risk. The cause of increased bleeding risk is unclear but may relate to swapping from one antithrombin to another.

Excessive dosing of unfractionated heparin, low-molecular-weight heparin and GP IIb/IIIa inhibitors was observed in almost one-third of patients with non-ST-segment elevation ACS in the CRUSADE registry (26). Patients most likely to have received excessive doses were elderly patients, and those with low body weight, congestive heart failure, diabetes and reduced renal function. Patients who received excessive doses of the antiplatelet or antithrombin agents had an 8% to 36% increased risk of bleeding. If both heparin and a GP IIb/IIIa inhibitor were given at an excessive dose, the absolute risk of bleeding was 22.2%, compared with 6.6% if the doses of both agents were appropriate. Alexander et al (26) estimated that approximately 15% of major bleeding in patients with ACS may be attributed to excessive dosing of antithrombotic agents. Clearly, optimal dosing is a therapeutic target to reduce bleeding risk. A further analysis of the CRUSADE registry indicated that the lowest in-hospital mortality was achieved in the hospitals that were adherent to guideline-recommended treatments and that used the correct doses of heparin and GPIIb/IIIa inhibitors (unpublished data).

The CURE trial (27) showed a 20% reduction in major coronary events with clopidogrel and ASA compared with ASA alone, with an absolute 1% greater incidence of major bleeding in patients who received dual antiplatelet therapy. However, bleeding rates appeared to be related to the ASA dose more than to the ASA and clopidogrel combination. Bleeding was more frequent with ASA 325 mg alone than with ASA 70 mg to 100 mg combined with clopidogrel.

Bleeding sites

A high proportion of patients with ACS undergo PCI during the index hospitalization. In these patients, the most common bleeding location is at the femoral artery vascular access site. The GRACE (11) registry reported that the most common bleeding sites for all patients were gastrointestinal in 31.5% patients, retroperitoneal in 6.0% patients, genitourinary (4.8%) and at the vascular access site (23.8%). Following PCI, major hemorrhage occurred in 5.4% of patients (28) (gastrointestinal [11%], retroperitoneal [5%], hemorrhagic stroke [2.5%] and at the vascular access site [63%]), requiring transfusion in 5.4% of patients.

Intracranial hemorrhage and thrombolysis

Although primary PCI is the preferred management for patients with an ST-segment elevation ACS, the geographical distribution of the population in Canada limits timely access to a catheterization laboratory. Consequently, thrombolysis remains the most frequently used reperfusion strategy among these patients. In the most recent clinical trials, the incidence of intracranial hemorrhage associated with thrombolysis was 0.64% to 0.94% (29), with an associated mortality of

Figure 1) Relationship between the severity of bleeding, as measured by the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO) scale, and 30-day mortality (A) and six-month mortality (B)

approximately 60%. An increased risk of intracranial hemorrhage after thrombolysis is associated with older age, female sex, low body weight, presence of hypertension, excessive anticoagulation with warfarin and the use of a tissue plasminogen activator compared with streptokinase (30–32).

It is apparent that heparin dosage and monitoring play important roles in intracranial hemorrhage (33). Excessive anticoagulation with heparin resulting in activated partial thromboplastin time levels above the therapeutic range is not only associated with increased bleeding, but also with an excess of recurrent ischemic events (34). The use of enoxaparin in older patients in the ASsessment of the Safety and Efficacy of a New Thrombolytic regimen (ASSENT)-3 trial (35) was associated with increased intracranial hemorrhage, but the Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment (ExTRACT) trial (36) showed a reduced-dosage regimen of enoxaparin to be safe in elderly patients (37). The OASIS-6 trial (38) evaluated the use of fondaparinux in patients with ST-segment elevation myocardial infarction. Fondaparinux reduced death and reinfarction with no increase in hemorrhagic complications.

The early administration of clopidogrel to patients with ST-segment elevation who received thrombolysis resulted in increased arterial patency (ClopidoGrel as Adjunctive Reperfusion Therapy [CLARITY] trial [39]) and better clinical outcomes (CLARITY [39] and the CloPidoGrel and Metoprolol in Myocardial Infarction Trial [COMMIT, 40]). Both studies indicated that the addition of clopidogrel to thrombolysis was not associated with an increased risk of bleeding.

Impact of bleeding on prognosis of patients with ACS

For patients with ACS, there is a strong relationship between bleeding, mortality and recurrent myocardial infarction. Registries of patients with ACS have shown that major bleeding is associated with a 60% increase in in-hospital death (11,12) and a fivefold increase in one-year mortality (35.9% versus 7.4% in patients without major bleeding) (12). One-year myocardial infarction rates were also almost five times higher in the patients with major bleeding (12).

An analysis of 34,000 patients in the OASIS studies (9) demonstrated that patients with major bleeding have 30-day mortality rates five times higher than those with no bleeding, but the increased risk of death over the succeeding six months was lower (HR 1.54, 95% CI 1.10 to 2.36). In a combined

TABLE 3
Biologically plausible factors linking bleeding with adverse cardiovascular outcomes

• Reduced myocardial oxygen delivery
Hypotension
Anemia
• Premature discontinuation of antithrombotic drugs
• Platelet activation and increased thrombotic risk
• Deleterious effects of blood transfusion
Reduced oxygen delivery of transfused blood
Nitric oxide sink
Effect of cytokines in transfused plasma
Platelet aggregation
Vasoconstriction
Inflammation

analysis of the PURSUIT and Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) trials (41), 30-day and six-month mortality relate to the severity of bleeding as measured by the GUSTO scale (Figure 1). In the recent ACUITY trial (42), major bleeding occurred in 5.9% of patients, and was associated with more deaths than in those who had no major bleeding (5.4% versus 0.8%), myocardial infarction (17.1% versus 5.5%) and the need for unplanned revascularization (9.3% versus 3.0%).

Bleeding in patients with ACS has a number of immediate consequences, including the cessation and reversal of anti-thrombotic therapy, hypotension and blood transfusion.

Blood transfusion in patients with ACS is associated with higher mortality. From a combined analysis (3) of the GUSTO IIb, PURSUIT and PARAGON B trials, 10% of patients required a blood transfusion. Patients requiring blood transfusions were older and had more comorbidities. Transfusion was associated with an increased adjusted HR for 30-day death (HR 3.94, 95% CI 3.26 to 4.75), and 30-day death or myocardial infarction (HR 2.92, 95% CI 2.55 to 3.35). A Cochrane systematic review (43) indicated that a restrictive transfusion practice was associated with a 20% lower mortality rate, a 56% reduced myocardial infarction rate and a 51% lower heart failure rate. However, in elderly patients with acute myocardial infarction who presented with anemia and a hematocrit level of lower than 30%, transfusion was associated with a lower short-term mortality rate (44).

Is there a causal link between hemorrhage and adverse outcomes?

Although bleeding is independently predictive of adverse outcomes after ACS, there is no established causal link between bleeding and adverse ischemic outcomes; however, there is a strong and consistent relationship between bleeding and adverse ischemic events. Furthermore, more serious bleeding relative to minor bleeding is associated with worse outcomes, regardless of baseline characteristics and management strategies (41). Biologically plausible mechanisms linking hemorrhage and adverse outcomes are shown in Table 3. It is also possible that patients who bleed have the same or similar risk factors for bleeding as for late mortality (45). However, recent clinical trials (1,46) that compared antithrombotic agents suggested that agents associated with a lower incidence of bleeding also reduce mortality and recurrent ischemic events. Most

TABLE 4
Increased bleeding risk for patients with acute coronary syndromes

• General risk factors
Elderly
Renal insufficiency
Hepatic dysfunction
Female sex
Low body weight
Anemia
Hemostatic disorders
Current use of antithrombotic or antiplatelet medication
Recent invasive procedure
• Invasive procedures
Obesity
Peripheral vascular disease
Recent femoral puncture (especially with persistent hematoma)
Femoral artery versus radial access
• Gastrointestinal bleeding
History of gastrointestinal bleeding
Active gastrointestinal peptic ulcer or inflammatory disease
Prior peptic ulcer (especially with ulcer complication)
Known intestinal polyps or malignancy
• Intracranial bleeding
Prior history of cerebrovascular hemorrhage
Hypertension

importantly, the difference in mortality and ischemic events between the agents is closely related to the difference in bleeding rates. A comparison of a standard clinical practice with a management strategy that uses multiple techniques to minimize bleeding is necessary to show that reducing bleeding events is directly associated with improved outcomes.

Reducing bleeding complications in patients with ACS

Although there is no direct proof that reducing bleeding decreases ischemic events and cardiovascular mortality, there is no question that reducing bleeding favourably impacts morbidity and health care costs. The current paradigm for the management of patients with ACS is to use antithrombotic drugs and revascularization to minimize recurrent ischemic events, and, at the same time, minimize the opportunity for major hemorrhage that may negate the benefits of the antithrombotic and antiplatelet drugs.

There are currently no guidelines that incorporate a bleeding risk assessment and the appropriate response when a higher bleeding risk is identified. There often is a fine balance between benefit and risk, but in a patient at high risk for recurrent potentially fatal ischemic cardiac adverse events, a higher risk of bleeding may be acceptable when using agents with proven benefit of improved outcomes. Optimizing benefit and minimizing bleeding risk includes the following strategies.

Selecting a treatment strategy based on risk stratification:

The choice of management strategy for a patient with a proven or suspected ACS is based on a risk assessment for an adverse outcomes and the application of an evidence-based strategy. An early invasive management strategy, clopidogrel, heparin (including low-molecular-weight heparin) and GP IIb/IIIa inhibitors have proven to be beneficial in patients with high-risk features and non-ST-segment elevation ACS. The benefit of such an aggressive strategy in patients with no high-risk

features is either small or unproven, but is associated with an important bleeding hazard. A suggested risk-oriented management algorithm was recently published by a Canadian working group (47). This algorithm recommended an invasive strategy for higher-risk patients and avoids exposing lower-risk patients to unnecessary and potentially hazardous treatment.

Assessing bleeding risk and considering management modification: The risk for bleeding should be assessed before initiating a management strategy. Table 4 indicates situations in which bleeding risk is increased. In patients at increased risk for hemorrhagic complications, consideration should be given to possible means of reducing bleeding, such as by choice of radial access for coronary intervention, reduced dosage of anti-coagulants, shortened exposure to multiple antithrombotic agents and the use of gastroprotective medication.

When considering thrombolysis, absolute and relative contraindications to treatment should be evaluated. Patients with an absolute contraindication for thrombolysis should be considered for primary angioplasty, despite the inherent delay in treatment due to interhospital transfer. Weighing the benefits of thrombolysis and assessing bleeding risk are required to determine whether thrombolysis is acceptable in patients with relative contraindications to thrombolysis. Patients with two or more risk factors (age older than 65 years, systolic BP higher than 170 mmHg, and low body weight [less than 70 kg in men and 65 kg in women]) of intracranial hemorrhage have a greater than 2% risk (31) and should be considered for primary angioplasty.

Using vascular access techniques to minimize bleeding:

Vascular access techniques can reduce the risk of major bleeding. Using a smaller-sized catheter and removing the arterial sheath at the earliest opportunity reduces the risk of bleeding. Avoiding antithrombin treatment after sheath removal reduces bleeding risk and the development of false aneurysms. Access through the radial artery for coronary angiography with or without PCI is associated with lower major bleeding rates. Vascular closure devices may reduce the risk of major hemorrhage. However, whether closure devices reduce vascular complications remains controversial.

Coronary angioplasty, with the administration of large doses of heparin and GP IIb/IIIa inhibitors after a recent femoral puncture for diagnostic catheterization, can result in severe hemorrhage at the original access site, especially if there is a persistent hematoma or false aneurysm. If there is a firm and tender hematoma, ultrasound vascular imaging should be performed to rule out the presence of a false aneurysm. A false aneurysm should be treated by compression or thrombin injection before proceeding to further invasive procedures that use antithrombin or antiplatelet medications at the same or at a different vascular access site.

Selecting an anticoagulant agent: The choice of antithrombin and antiplatelet agent should be made according to the management strategy. If the usual practice is to take high-risk non-ST-segment elevation ACS patients to the catheterization laboratory within the first 24 h, unfractionated heparin, bivalirudin or fondaparinux appear to offer similar protection from ischemic events, but with a reduced risk of bleeding. On the other hand, if patients do not usually have cardiac catheterization performed within the first 24 h to 36 h, enoxaparin reduces ischemic events compared with unfractionated heparin and is associated with no increase or even a reduced incidence of bleeding (48). Fondaparinux (1) is also an excellent antithrombotic agent with similar protection from early

myocardial ischemic events to enoxaparin, but with improved long-term outcomes that are probably the result of reduced major bleeding. More information is needed to confirm the safety of added heparin to prevent catheter thrombosis in patients undergoing PCI.

Minimizing exposure to antithrombotic agents: In a patient at high risk for a bleeding complication, it is important to minimize the duration of the exposure to antithrombotic treatment. For patients with high-risk ACS features, a delay in reaching the cardiac catheterization laboratory has few advantages and may potentially increase bleeding risk. The Intracoronary Stenting with Antithrombotic Regimen COOLing-off (ISAR-COOL) trial (49) suggested that there was no benefit from a period of medical treatment with a GP IIb/IIIa inhibitor and heparin before coronary angioplasty in patients with ACS. Despite medical treatment aimed to stabilize the ruptured plaque, more coronary events occurred in patients receiving percutaneous treatment than in those who had a very early procedure. In this relatively small trial, there was no difference in bleeding events between the two groups. However, in patients at high-risk of bleeding, more prolonged antithrombotic treatment before catheterization likely increases the bleeding hazard.

Dosing antithrombotic drugs appropriately: In patients with ACS, excessive dosing of thrombolytic, antiplatelet and antithrombotic medications is an important cause of potentially avoidable bleeding. A recent registry (26) reported that 42% of patients with ACS received at least one antithrombotic drug in excess. Excessive dosing increases mortality and morbidity, and prolongs the duration of hospital stay (26). The same study showed the safety of antithrombotic medications when dosed appropriately. Older patients and women, as well as patients with low body weight, diabetes mellitus and heart failure, were most likely to receive excessive doses of unfractionated heparin, low-molecular-weight heparin or intravenous GP IIb/IIIa inhibitors (26). It was estimated that as much as 15% of major bleeding in patients with ACS may be attributed to excessive dosing of antithrombotic medications (26).

Individualized dosing based on weight and renal function for heparins and GP IIb/IIIa inhibitors has been shown to minimize the bleeding risk and maintain therapeutic benefit (50). However, the therapeutic window for both fibrinolytic and antithrombotic drugs is narrow, with too low a dose providing no benefit but a modest excess in dose resulting in adverse outcomes. Dosing errors most frequently occur when adjustments are not correctly made for renal function and body weight.

To avoid dosing errors, the patient should be weighed (or, at least for the first dose, the patient should be asked his or her weight), because approximations are often wrong. The estimated creatinine clearance rates (eCrCl) should also be determined, because serum creatinine levels are a poor estimate of renal function. The doses of enoxaparin and intravenous GP IIb/IIIa inhibitors should be adjusted according to the eCrCl. For enoxaparin, the recommended dose adjustment is to administer enoxaparin 1 mg/kg daily for patients with an eCrCl of less than 30 mL/min. Adjusted doses of enoxaparin may reduce the risk of bleeding. However, a recent evaluation (51) of low-molecular-weight heparin in patients with renal insufficiency determined that it was not possible to conclude that empirically dose-adjusted enoxaparin was not associated with increased risks for major bleeding events. Fondaparinux should also be avoided in patients with severe renal impairment

(52). For patients with an eCrCl of less than 30 mL/min and an increased bleeding risk assessment, unfractionated heparin should be chosen until the safety of reduced-dose enoxaparin or fondaparinux in this population is shown.

Using gastroprotective measures to prevent upper gastrointestinal bleeding: Although estimates vary widely, the long-term use of ASA at vasculoprotective doses approximately doubles the risk of gastrointestinal hemorrhage (53,54), with an absolute risk of approximately 2%. The risk of bleeding is greater with larger doses, so that the greatest benefit with the smallest risk is achieved with a dose of ASA of between 75 mg and 150 mg daily (55). Although the upper gastrointestinal bleeding risk from the combination of ASA and clopidogrel is increased (54), the risk is minimized by using low-dose ASA (81 mg). At this dose, in combination with clopidogrel, the bleeding rates were similar to those observed with ASA monotherapy at a dose of 325 mg (13).

The risk of gastrointestinal hemorrhage is increased in patients with a prior history of peptic ulceration, particularly if the ulcer was complicated by bleeding or perforation (56). At higher risk are elderly patients, those with comorbid conditions such as heart failure or rheumatoid arthritis, and patients with the concomitant use of corticosteroids, anti-coagulants, ethanol and nonsteroidal anti-inflammatory medications (56). Unfortunately, the enteric coating of ASA only lowers the likelihood of erosive gastritis, not the frequency of associated peptic ulceration (57). Among the available strategies to lower the risk of peptic ulceration in patients at high risk of bleeding, the concomitant use of proton pump inhibitors is the most attractive, even leading to healing of ulcers despite continued treatment with ASA (58). In addition, eradicating *Helicobacter pylori* may also lower the risk of ASA-induced peptic ulceration and associated complications (59).

Recognizing and correcting the bleeding early: The early detection of bleeding may lead to action that limits the severity of the hemorrhage. Reducing antithrombotic medication at the earliest opportunity in a patient with significant bleeding may be the difference between a minor bleed and a life-threatening hemorrhage. The development of a false aneurysm and retroperitoneal bleeding are often heralded by localized or referred pain.

CONCLUSIONS

Antithrombotic, antiplatelet and thrombolytic medications have proven to be beneficial in patients with ACS. Major bleeding is the most common noncardiac complication in patients with ACS and occurs in 1% to 10% of patients. However, the appropriate choice of medication and dosage results in optimal benefit and minimizes the risk of bleeding. Recognizing patients who are at high risk of hemorrhage allows a choice of strategies to minimize the risk and maintain the benefits of the treatment.

ACKNOWLEDGEMENTS: The author thanks Dr Gabor Kandel for help in writing the section on the prevention of gastrointestinal hemorrhage.

CONFLICTS OF INTEREST: Dr D Fitchett has participated in continuing medical education on behalf of, and acted as a consultant to, Roche, Merck, Schering, Bristol-Myers Squibb, sanofi-aventis and GlaxoSmithKline.

REFERENCES

1. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators; Yusuf S, Mehta SR, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006;354:1464-76.
2. Stone GW, McLaurin BT, Cox DA, et al; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203-16.
3. Yang X, Alexander KP, Chen AY, et al; CRUSADE Investigators. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005;46:1490-5.
4. Eikelboom J, Hirsh J. Bleeding and management of bleeding. *Eur Heart J* 2006;8(Suppl G):G38-45.
5. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med* 1993;329:673-82.
6. Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006;47:809-16.
7. Ferguson JJ, Califf RM, Antman EM, et al; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45-54.
8. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
9. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;114:774-82.
10. Manoukian SV, Voeltz MD, Felt F, et al. Major bleeding is associated with increased 30-day mortality and ischemic complications in patients with non-ST elevation acute coronary syndromes undergoing percutaneous coronary intervention: The ACUITY trial. *Am J Cardiol* 2006;98(Suppl 8):45M.
11. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: The Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;24:1815-23.
12. Segev A, Strauss BH, Tan M, et al; Canadian Acute Coronary Syndromes Registries Investigators. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: Insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J* 2005;150:690-4.
13. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502. (Errata in 2001;345:1716, 2001;345:1506).
14. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina) <www.acc.org/qualityandscience/clinical/guidelines/unstable/incorporated/index.htm> (Version current at April 2, 2007).
15. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. *N Engl J Med* 1998;338:1488-97. (Erratum in 1998;339:415).
16. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;338:1498-505.
17. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression using Integrilin Therapy. *N Engl J Med* 1998;339:436-43.
18. Cohen M, Demers C, Gurfinkel E, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447-52.
19. Antman EM, McCabe CH, Gurfinkel E, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
20. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A; Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) Trial Investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation* 2003;107:238-44.
21. Bavy AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: A meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol* 2006;48:1319-25.
22. Mehta SR, Cannon CP, Fox KAA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: A collaborative meta-analysis of randomized trials. *JAMA* 2005;293:2908-17.
23. Fox KAA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: The British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
24. Cohen M, Demers C, Gurfinkel EP, et al. Low-molecular-weight heparins in non-ST-segment elevation ischemia: The ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in Non-Q-wave Coronary Events. *Am J Cardiol* 1998;82:19L-24L.
25. Goodman SG, Fitchett D, Armstrong PW, Tan M, Langer A; Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) Trial Investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation* 2003;107:238-44.
26. Alexander KP, Chen AY, Roe MT, et al; CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA* 2005;294:3108-16. (Erratum in 2006;295:628).
27. Peters RJ, Mehta SR, Fox KA, et al; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. *Circulation* 2003;108:1682-7.
28. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol* 2003;92:930-5.
29. Van de Werf F, Barron HV, Armstrong PW, et al; ASSENT-2 Investigators. Assessment of the Safety and Efficacy of a New Thrombolytic. Incidence and predictors of bleeding events after fibrinolytic therapy with fibrin-specific agents: A comparison of TNK-tPA and rt-PA. *Eur Heart J* 2001;22:2253-61.
30. Huyhn T, Cox JL, Massel D, et al. Predictors of intracranial hemorrhage with fibrinolytic therapy in unselected community patients: A report from the FASTRAK II project. *Am Heart J* 2004;148:86-91.
31. Simoons ML, Maggioni AP, Knatterud G, et al. Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993;342:1523-8.
32. Brass LM, Lichtman JH, Wang Y, Gurwitz JH, Radford MJ, Krumholz HM. Intracranial hemorrhage associated with thrombolytic therapy for elderly patients with acute myocardial infarction: Results from the Cooperative Cardiovascular Project. *Stroke* 2000;31:1802-11.
33. Giugliano RP, McCabe CH, Antman EM, et al; Thrombolysis in Myocardial Infarction (TIMI) Investigators. Lower-dose heparin with

- fibrinolysis is associated with lower rates of intracranial hemorrhage. *Am Heart J* 2001;141:742-50.
34. Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: Results from the GUSTO-I trial. *Circulation* 1996;93:870-8.
 35. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: The ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001;358:605-13.
 36. Antman EM, Morrow DA, McCabe CH, et al; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). *Am Heart J* 2005;149:217-26.
 37. White HD, Braunwald E, Murphy SA, et al. Enoxaparin vs. unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction in elderly and younger patients: Results from ExTRACT-TIMI 25. *Eur Heart J* 2007;28:1066-71.
 38. Yusuf S, Mehta SR, Chrolavicius S, et al; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: The OASIS-6 randomized trial. *JAMA* 2006;295:1519-30.
 39. Sabatine MS, Cannon CP, Gibson CM, et al; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-89.
 40. Chen ZM, Jiang LX, Chen YP, et al; COMMIT (ClopIdogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet* 2005;366:1607-21.
 41. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005;96:1200-6.
 42. Stone GW, McLaurin BT, Cox DA, et al; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;355:2203-16.
 43. Hill SR, Carless PA, Henry DA, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2002;(2):CD002042.
 44. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230-6.
 45. Cohen M. Predictors of bleeding risk and long-term mortality in patients with acute coronary syndromes. *Curr Med Res Opin* 2005;21:439-45.
 46. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: Study design and rationale. *Am Heart J* 2004;148:764-75.
 47. Fitchett DH, Borgundvaag B, Cantor W, et al; Renewal of Non STE ACS Algorithm Group. Non ST segment elevation acute coronary syndromes: A simplified risk-orientated algorithm. *Can J Cardiol* 2006;22:663-77.
 48. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: A systematic overview. *JAMA* 2004;292:89-96.
 49. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: A randomized controlled trial. *JAMA* 2003;290:1593-9.
 50. Freedman JE, Becker RC, Adams JE, et al; American Heart Association. Council on Clinical Cardiology Subcommittee on Acute Cardiac Care, Council on Cardiopulmonary and Critical Care, Council on Cardiovascular Nursing, and Council on Stroke. Medication errors in acute cardiac care: An American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Acute Cardiac Care, Council on Cardiopulmonary and Critical Care, Council on Cardiovascular Nursing, and Council on Stroke. *Circulation* 2002;106:2623-9.
 51. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: A meta-analysis of the randomized trials. *Circulation* 2005;112:3855-67.
 52. Grand'Maison A, Charest AF, Geerts WH. Anticoagulant use in patients with chronic renal impairment. *Am J Cardiovasc Drugs* 2005;5:291-305.
 53. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: Meta-analysis. *BMJ* 2000;321:1183-7.
 54. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: Population based case-control study. *BMJ* 2006;333:726-8.
 55. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. (Erratum in 2002;324:141).
 56. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120:594-606.
 57. Kelly JP, Kaufman DW, Jurgelson JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet* 1996;348:1413-6.
 58. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. *N Engl J Med* 1998;338:719-26.
 59. Chan FK. Management of high-risk patients on non-steroidal anti-inflammatory drugs or aspirin. *Drugs* 2006;66(Suppl 1):23-28.
 60. MICHELANGELO OASIS-5 Steering Committee; Mehta SR, Yusuf S, Granger CB, et al. Design and rationale of the MICHELANGELO Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial program evaluating fondaparinux, a synthetic factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J* 2005;150:1107.
 61. Cohen M, Theroux P, White HD. Anti-thrombotic combination using tirofiban and enoxaparin: The ACUTE II study. *Circulation* 2000;102:II-826.
 62. Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: A randomized controlled trial. *JAMA* 2004;292:55-64. (Erratum in 2004;292:1178).
 63. Cairns J, Gent M, Singer J, et al. Aspirin, sulfipyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369-75.
 64. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: The CAPTURE Study. *Lancet* 1997;349:1429-35. (Erratum in 1997;350:744).
 65. Low-molecular-weight heparin during instability in coronary artery disease, Fragmin during Instability in Coronary Artery Disease (FRISC) study group. *Lancet* 1996;347:561-8.
 66. Ferguson JJ, Califf RM, Antman EM, et al; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45-54.
 67. Antman EM, Morrow DA, McCabe CH, et al; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006;354:1477-88.