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BALANCING HEMOSTASIS AND THROMBOSIS IN INTERVENTIONAL VASCULAR MEDICINE AND SURGERY

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Abstract

Antithrombotic therapy and revascularization are critical factors in managing patients presenting with acute coronary syndromes and are described in multiple guidelines documents. In addition to preventing intravascular thrombosis, they increase the risk of bleeding, which has been implicated as a risk factor in short- and long-term mortality. Randomized controlled trials provide useful aggregate information comparing the risks and benefits of various therapies. In this paper, we will use a case-based format to discuss optimal individualized antithrombotic treatments.

Commonly Used Antithrombotic Drugs

Aspirin is a mainstay of therapy in patients with acute coronary syndromes (ACS). Compared with placebo, it decreases mortality by approximately 50% while only mildly increasing bleeding in a dose-dependent manner.[1, 2] Aspirin works by irreversibly inhibiting intraplatelet cyclooxygenase, and its effect is present until complete turnover of the platelet pool occurs (usually 10–14 days). Given its excellent therapeutic window, aspirin should be administered to ACS patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant.[3] In the event of a life-threatening hemorrhage, its effect can be reversed by administration of platelets since the circulating plasma half-life of aspirin is less than 1 hour.

Clopidogrel is a thienopyridine that blocks the P2Y12 adenosine diphosphate (ADP) receptor on platelets. Unlike aspirin, it requires metabolic transformation in the liver to be active. In addition to aspirin, clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) has been shown to reduce a composite of death, myocardial infarction, and severe recurrent ischemia by 20% in patients with ACS.[4] Clopidogrel increases the risk of bleeding in patients undergoing coronary artery bypass graft (CABG) surgery and hence should be withheld for several days preoperatively in patients who become stable.

Prasugrel is the latest thienopyridine that has been approved by the FDA for use in ACS. Compared with clopidogrel, it produces greater inhibition of ADP-dependent platelet aggregation with less inter-patient variability; it has also been shown to reduce the likelihood of a recurrent ischemic event or of stent thrombosis in patients with ACS who undergo percutaneous coronary intervention (PCI). However, it also increases the risk of major bleeding, particularly in patients undergoing CABG. Subgroups with less clinical efficacy and greater risk of bleeding include those older than 75 years of age, a body weight less than 60 kg, and those with prior stroke or transient ischemic attack.[5] These patient groups are the subject of an FDA-boxed warning.

Heparin, either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), is also frequently used. Heparin binds antithrombin, a circulating serpin, resulting in a complex that irreversibly inhibits thrombin and factor Xa. Its benefit in acute coronary syndromes is established.[6, 7] Nonspecific binding to plasma proteins and nonlinear rates of hepatic metabolism, however, make the level of antithrombotic effect variable. In the event of hemorrhage, most of the effects of heparin can be reversed with protamine. LMWHs produce a more consistent level of anticoagulation than heparin, are generally regarded as not requiring monitoring, and are at least as effective as heparin. However, since the clearance of its anti-Xa activity occurs through renal mechanisms, the dose must be modified in patients with creatinine clearance (CrCl) <30 mL/min. In addition, protamine produces only partial reversal of its effect. Switching therapies from LMWH to UFH at the time of PCI can be problematic as it may create periods of over- or under-anticoagulation, which can result in ischemic or hemorrhagic events, respectfully.[8] Thus, in patients who are initially treated with enoxaparin and then undergo PCI, enoxaparin therapy should be continued.

Bivalirudin is a direct thrombin inhibitor that has several mechanistic advantages over heparin. Unlike heparin, it inhibits clot-bound thrombin efficiently, is unaffected by plasma protein binding, and does not activate platelets. In comparison to a routine strategy of heparin and a glycoprotein IIb/IIIa receptor blocker, the use of bivalirudin plus a provisional glycoprotein IIb/IIIa receptor blocker in patients with ACS was shown to be as effective in reducing an ischemic endpoint and to produce less bleeding.[9] As a result, bivalirudin use has become more widespread. The 2007 ACC/AHA guidelines for managing ACS recommend that bivalirudin be used when an early invasive strategy is planned and clopidogrel (at least 300 mg) is given at least 6 hours earlier. In patients scheduled for CABG, bivalirudin should be discontinued at least 3 hours in advance.

Glycoprotein IIb/IIIa receptor blockers inhibit the final common pathway of platelet aggregation. When combined with heparin, eptifibatide given to patients with an ACS reduces the composite risk of death or recurrent myocardial infarction. This effect appears to be most pronounced in patients who undergo revascularization procedures. Its use today in conjunction with heparin is less common than several years ago. Although useful in patients undergoing PCI, abciximab was found not to be useful in upstream management of patients with ACS. Since eptifibatide is excreted by the kidney, its dose must be adjusted in patients with impaired CrCl. The half-life is 90 minutes in patients with normal kidney function. Managing bleeding in patients treated with eptifibatide requires transfusion of platelets. Since the

diffusion coefficient of eptifibatide is high, there is considerable excess of the drug in the circulation, leading to occupancy of IIb/IIIa on newly transfused platelets. Therefore, large quantities of transfused platelets are required and are able to reverse the drug's antiplatelet activity only partially. On the other hand, support of renal perfusion is likely to increase the excretion of eptifibatide. Combining eptifibatide with clopidogrel in the medical phase of ACS management is recommended, but the relative contribution of each of these antiplatelet drugs is uncertain. While "upstream" use of eptifibatide is still a class I recommendation in ACS, it has received a class IIa recommendation when used with clopidogrel.[3] In addition, their dose needs to be appropriately adjusted for renal function. Overdosing of eptifibatide is relatively common. Studies suggest that there is a significant reduction in major bleeding and mortality using CrCl rather than creatinine alone.[10-12]

Adverse Events

Overdosing of anticoagulants is common and results in excess bleeding. In a prospective observational study involving more than 30,000 ACS patients and 350 hospitals, an excess dose was administered to 32.8% of patients treated with UFH, 13.8% treated with LMWH, and 26.8% of patients treated with glycoprotein IIb/IIIa inhibitors.[12] Bleeding increased relative to the number of agents administered in excess and to the degree of dose excess. Patients who received excessive doses had higher risks of major bleeding, higher lengths of stay, and higher mortality. The authors estimated that 15% of major bleeding was due to excessive dosing. However, patients who received the recommended doses had the lowest risks of bleeding, which suggested that clinical trial safety endpoints are attainable.

Several additional studies have further supported the association of bleeding and adverse events. Eikelboon et al. examined the association between bleeding and death or ischemic events in more than 30,000 patients with ACS. Using Cox proportional hazards modeling, they found that patients with major bleeding experienced a 5-fold higher incidence of death during the first 30 days (Figure 1) and a 1.5-fold higher risk of death between 30 days and 6 months (Figure 2).[13] Manoukian et al. noted a similar 6-fold increase in mortality among patients with severe bleeding.[14] In addition, bleeding was noted to be a greater independent predictor of mortality than several traditional predictors, including age (Figure 3). While the degree of causality is uncertain, the strength of the association is clear. Patients at risk to develop bleeding are often at risk to die of other etiologies, and while a small minority of patients die of hypovolemic shock as a result of bleeding, the question of whether or not relatively minor episodes of bleeding are actually responsible for later mortality is controversial. Several causal mechanisms have been postulated. First, major bleeding may result in cessation of antithrombotic drugs. Second, bleeding may result in platelet activation or reduce oxygen delivery to tissues. Third, patients with bleeding complications have a longer length of stay and require more invasive monitoring and treatment, all of which might increase the risk of death. Fourth, transfusion itself may result in impairment of oxygen delivery.[15]

Several mechanisms may link blood transfusion with mortality. First, stored RBCs are low in 2, 3-diphosphoglyceric acid, resulting in increased oxygen affinity and decreased delivery to tissues.[15] Second, they are depleted in nitric oxide and act as

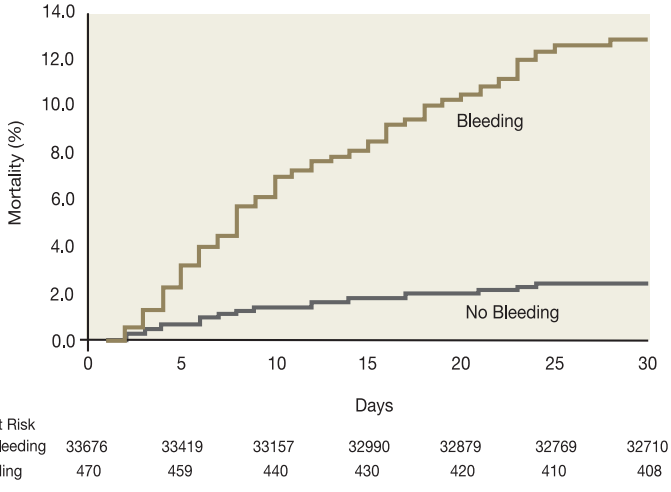

Figure 1. Kaplan-Meier estimates of mortality during the first 30 days among patients who developed and did not develop major bleeding.

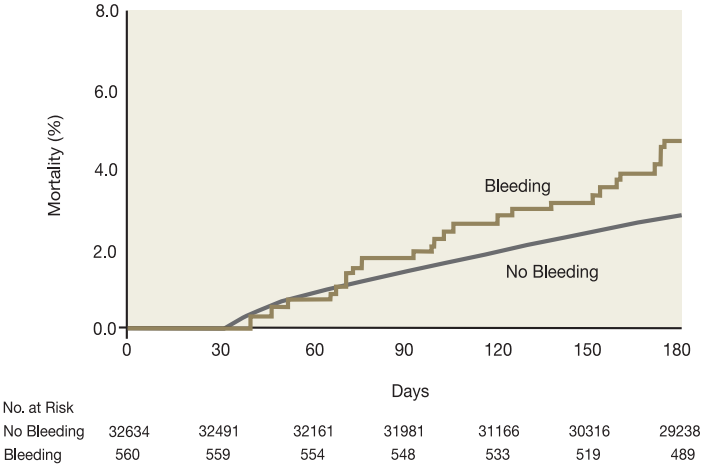

Figure 2. Kaplan-Meier estimates of mortality between 30 days and 6 months among patients who developed and did not develop major bleeding, excluding deaths that occurred during the first 30 days or within 30 days of a major bleed.

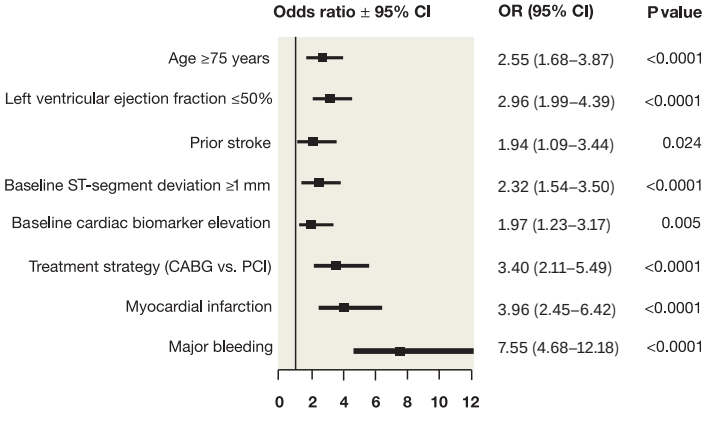

Figure 3. Independent predictors of mortality. CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention.

nitric oxide "sinks" that can potentially cause platelet activation and vasoconstriction.[16] Third, they may activate markers of inflammation, including interleukin-6.[17]

To better quantify bleeding risk, bleeding scores have been developed.[18, 19] Studies by Subherwal et al. and Nikolsky et al. showed that female sex, reduced CrCl, and baseline anemia were independent predictors of bleeding.[18, 19] In the CRUSADE database, these and other predictors were assigned a risk score (Table 1), and higher scores were associated with a higher rate of bleeding (Figure 4).[18] The incidence of major bleeding is variable, but risk factors associated with increased bleeding include advanced age, female sex, and renal insufficiency.

There has been a great deal of variability in the bleeding definitions used in clinical trials. Recently, the Bleeding Academic Research Consortium developed standardized endpoint definitions for patients receiving antithrombotic therapy. Adoption of these standardized endpoints will allow for interpretation of the relative safety of various antithrombotic strategies across different clinical trials and registries.[20]

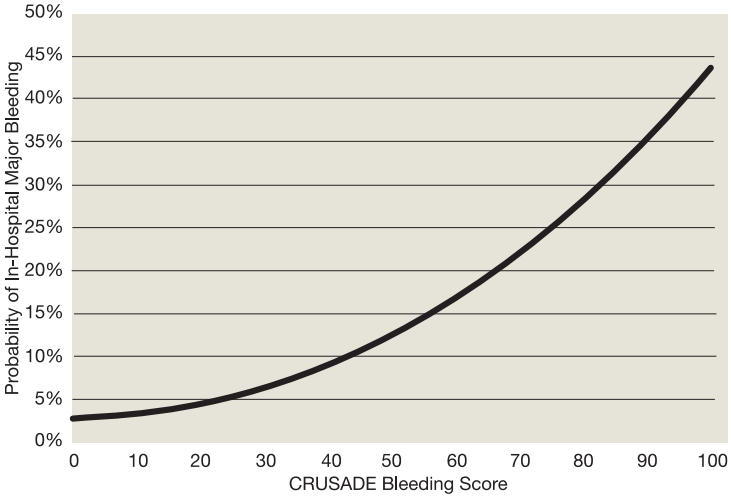

Figure 4. Predicted probability of in-hospital major bleeding across the spectrum of CRUSADE bleeding score in the derivation cohort.

Cases

Case 1

A 72-year-old woman (60 kg) with coronary artery disease (CAD), insulin-dependent diabetes, hypertension (HTN), tobacco use, and chronic kidney disease (CrCl 30 mL/min) presents to the emergency room with several episodes of chest pain within the last 24 hours, all relieved with nitroglycerin. Her EKG is remarkable, showing 2 mm ST depression in the anterolateral leads. In addition, she has a troponin level of 5 ng/mL and a hematocrit of 30 g/dL. She denies any prior history of coronary artery disease or bleeding.

Discussion

This patient is at high risk for recurrent ischemia and infarction. She has a TIMI risk score of 7 (one point each for age >65, >3 or more risk factors for CAD, known CAD, aspirin use within 7 days, severe angina, ST changes >0.5 mm, and positive troponin), which

Table 1. Algorithm used to determine the risk score of CRUSADE in-hospital major bleeding. CHF: congestive heart failure.

Predictor	Score
Baseline hematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,* mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (bpm)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11

Predictor	Score
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease†	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

*Creatinine clearance was estimated with the Cockcroft-Gault formula.
†Prior vascular disease was defined as history of peripheral artery disease or prior stroke.

puts her at a 41% risk of death, MI, or severe ischemia requiring urgent revascularization over the next 14 days.[21] Based on the ACC/AHA guidelines for treating unstable angina and non-ST-segment elevation myocardial infarction, Class I agents include aspirin, heparin, clopidogrel or glycoprotein IIb/IIIa (both have a IIa indication). However, she has multiple risk factors for bleeding including baseline anemia, female sex, and reduced CrCl. Using the available information and the CRUSADE algorithm, she would have a score of 58, which would place her risk of major hemorrhage at 15%. An attractive option based on data from the ACUITY study would be to use bivalirudin with provisional glycoprotein IIb/IIIa use in conjunction with aspirin and clopidogrel. Patients with moderate renal impairment (30–59 mL/min) should receive the same bolus but a lower infusion rate.

Case 2

A 30-year-old man with a history of ulcers presents with atypical chest and epigastric burning, normal levels of cardiac biomarkers, a normal EKG, and a hematocrit of 28. He does not have diabetes, HTN, dyslipidemia, tobacco use, or a family history of heart disease.

Discussion

The lack of risk factors, atypical presentation, history of ulcers, and baseline anemia should alert the clinician that he likely has an active ulcer rather than acute coronary syndromes. In this case, all antithrombotics should be avoided until a diagnosis is established.

Case 3

A 50-year-old man (80 kg) with insulin-dependent diabetes mellitus who had previously refused CABG for multi-vessel CAD develops classic exertional chest pressure (relieved with nitroglycerin) and a troponin of 10 ng/mL. On examination, he has a blood pressure of 135/80, a heart rate of 76, an S3 gallop, and bibasilar rales, with a normal hematocrit and renal function. His EKG has diffuse ST depression. On echocardiography, he has an EF of 35% with a normal-sized left ventricle, normal valves, and elevated filling pressures. He now is agreeable to CABG.

Discussion

This patient has multi-vessel CAD, and CABG is planned. The CRUSADE score is 13, which would place his risk of major hemorrhage at 4%. In addition to aspirin and heparin, a glycoprotein IIb/IIIa such as eptifibatide might be considered in place of clopidogrel, as the former may be discontinued a few hours prior to CABG, whereas the latter would increase the risk of bleeding unless stopped 5 days prior to surgery.

Conclusion

Patients presenting with acute coronary syndrome experience mortality from ischemic as well as hemorrhagic events. Careful assessment of clinical clues and patient risk factors of hemorrhage allows customization of antithrombotic therapy.

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