Hemorrhage in Patients With Acute Coronary Syndrome: From Annoying Observation to Major Challenge

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Introduction

Treatment strategies for acute coronary syndrome (ACS) involve the use of anticoagulants, antiplatelet therapies, and invasive risk stratification in high-risk patients.[1] While this combination has led to a steady decline in adverse outcomes, bleeding complications remain an important risk.[2] Bleeding in patients with ACS or those undergoing percutaneous coronary intervention (PCI) has taken on significance because of studies indicating a relationship between hemorrhagic complications and medication noncompliance, recurrent ischemic events, and mortality.[3] The purpose of this article is to review the incidence of bleeding complications in patients with ACS and those undergoing PCI, review the relationship between bleeding and adverse outcomes, summarize the potential mechanisms underlying this relationship, and provide recommendations on reducing bleeding risk.

Bleeding Definitions and Incidence

Because treatment strategies for ACS include the early initiation of antithrombin and antiplatelet therapy followed by long-term use of aspirin and thienopyridines,[1] hemorrhagic complications can occur acutely or chronically. Quantifying the risk of bleeding is difficult because the definition of bleeding can influence its reported incidence. For example, the Superior Yield of the new Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial compared enoxaparin and unfractionated heparin (UFH) in ACS, and found a difference in bleeding risk between the 2 agents that was based on the definition used. The incidence of Thrombolysis in Myocardial Infarction (TIMI) major bleeding was 9.1% in the enoxaparin arm and 7.6% in the UFH arm, a significant difference with a *P* value of .008. The rate of severe bleeding in Global Use of Strategies to Open Occluded Arteries (GUSTO), however, was 2.7% in the enoxaparin arm and 2.2% in the UFH arm, a nonsignificant difference.[4] Other trials have demonstrated similar disparities in bleeding incidence based on definition.[5] In addition, the reported rates of bleeding can be influenced by the data source (clinical trials vs registries) and use of concomitant therapies, including invasive procedures. Given these potential confounders, the data suggest that the rate of "major" or "severe" bleeding is 1%-10% during the treatment of ACS.[3]

Determining bleeding incidence with long-term antithrombotic therapy is difficult because bleeding complications tend to be "front-loaded" or concentrated in the early phase of treatment. Over time, the attrition of patients who cannot tolerate the bleeding associated with antiplatelet or anticoagulant therapies leads to a cohort that is at relatively lower risk for long-term bleeding. However, it is important to note that patients who are prescribed chronic dual antiplatelet therapy with aspirin and clopidogrel can experience minor levels of bleeding. Roy et al examined 2360 unselected patients who underwent placement of a drug-eluting coronary stent and found that the incidence of bleeding over long-term follow-up was 32.7%; approximately 85.7% of these reports were "nuisance" bleeding events (defined as bruising, petechiae, or ecchymoses).[6]

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Association Between Bleeding and Adverse Outcomes

Several studies have demonstrated an association between bleeding and adverse outcomes including myocardial infarction (MI), stroke, stent thrombosis, and death.[2,3,7] This risk appears to be "dose-related", with a stepwise increase in the risk of morbidity and mortality as bleeding severity worsens. For example, a study examining 4 large ACS trials showed that, compared with no bleeding, the hazard ratios for the risk of 30-day mortality associated with GUSTO mild, moderate, and severe bleeding were 1.6, 2.7, and 10.6, respectively.[8] In addition to mortality, Eikelboom et al found an association between major bleeding and an increased risk of stroke at 30 days.[2] This relationship between hemorrhagic complications and adverse outcomes has been demonstrated for a number of bleeding definitions, including TIMI, GUSTO, the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, and the Organization to Assess Strategies in Ischemic Syndromes (OASIS) trial.[3]

Potential Mechanisms Underlying the Bleeding-Outcome Relationship

The relationships described in the above-cited studies are associations and have not proved causality. At the extremes, eg, bleeding leading to hemodynamic compromise or intracranial hemorrhage, the event may cause death; however, milder bleeding events are unlikely to be directly linked to mortality. Potential mechanisms that underlie the relationship between less severe bleeding and adverse outcomes include cessation of evidence-based antithrombotic therapy and red blood cell transfusion.

Spencer et al examined the 40 087 patients with ACS in the Global Registry of Acute Coronary Events (GRACE) to determine the incidence and outcomes related to in-hospital major bleeding and the patterns of medication use after a bleeding event.[9] The incidence of in-hospital major bleeding (defined according to the GRACE criteria) was 2.8%, and patients who suffered a bleeding event accounted for 10% of hospital deaths. In addition, discontinuation of aspiring, thienopyridines, and low molecular weight heparins was higher among these patients and was also associated with increased in-hospital mortality. These data were corroborated by a study by Wang et al, who examined 2498 ACS patients enrolled in the Prospective Registry Evaluating Outcomes After Myocardial Infarction: Events and Recovery Quality Improvement (PREMIER) and found that the use of aspirin and thienopyridines

at hospital discharge and at 6-month follow-up was lower among patients who suffered an in-hospital major bleed.[10] Relatively minor levels of bleeding are also associated with discontinuation of evidence-based therapy. In the study by Roy et al, 11.1% of patients with drug-eluting stents who developed nuisance bleeding discontinued thienopyridines during follow-up.[6] This may explain the association between major bleeding and increased stent thrombosis.[7]

Aside from discontinuation of therapy, which may be appropriate in the setting of acute bleeding, patients who develop hemorrhagic complications often receive blood transfusion. In the setting of minor or mild bleeding, this is ostensibly to increase oxygen delivery by raising the hemoglobin. While there are no prospective randomized trials evaluating the appropriate transfusion strategy in patients with ischemic heart disease, every observational study has found an association between aggressive transfusion and increased mortality.[3] It is unclear why this paradox (increased hemoglobin but decreased survival) exists, but it may be due to the properties of stored red cells, which are depleted of nitric oxide and hence do not provide sufficient vasodilation to improve tissue oxygenation.[11]

Strategies to Reduce Bleeding Risk

Given that bleeding is common and associated with worse short- and long-term outcomes, implementation of strategies to reduce bleeding risk is warranted. In addition, red cell transfusion should be used judiciously until further randomized data are available. Appropriate dosing of antithrombotic agents, use of antithrombins that are associated with reduced bleeding risk, and performing PCI via the transradial rather than the transfemoral approach are strategies that can minimize hemorrhagic complications.

Data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC and AHA Guidelines) registry have demonstrated that antithrombin agents and glycoprotein IIb/IIIa inhibitors are frequently overdosed in elderly patients and in women with ACS.[12] This overdosing is in turn associated with increased bleeding. Bivalirudin and fondaparinux are anticoagulants that are associated with less bleeding compared with unfractionated heparin and enoxaparin with or without glycoprotein IIb/IIIa inhibitors, and are noninferior with respect to ischemic outcomes when used for the management of ACS.[1] Fondaparinux is associated with improved survival in non ST-segment elevation ACS[13] and bivalirudin is associated with improved survival

when used for primary PCI.[14] With respect to antiplatelet therapy, use of higher dose aspirin (325 mg) does not appear to be associated with increased bleeding risk in the short term[15]; however, for long-term therapy, doses <100 mg are associated with lower bleeding risk without compromising efficacy.[16] Cessation of clopidogrel 5 days before coronary artery bypass surgery also can reduce hemorrhage related to surgery[1]; the interval between stopping prasugrel and surgery may need to be longer due to its more potent effect.[17] For ACS patients who undergo PCI as a revascularization strategy, a significant proportion of bleeding events is related to the vascular access site. Utilizing the radial artery instead of the femoral artery for PCI is associated with a 50%-60% reduction in bleeding complications without significantly compromising procedure success.[18] Whether this leads to improved survival is unclear.

Summary

The temporal improvement in mortality from ACS has been achieved through the implementation of evidence-based antithrombotic therapy and invasive risk stratification in high-risk patients. This has come at the price of increased bleeding risk. Studies indicate that bleeding complications are associated with worse outcomes including MI, stroke, stent thrombosis, and death. Patients who develop bleeding complications are at risk for discontinuation of anticoagulant and antiplatelet therapy, which may explain, in part, the worse outcomes in these patients. Prevention of bleeding is a clinical priority and several therapeutic strategies are available. Careful attention to dosing, use of bivalirudin or fondaparinux, and performing percutaneous procedures via the transradial route all are associated with reducing bleeding risk. While some of these strategies have been shown to improve survival, others require study in prospective randomized trials.

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