



Evaluating the need for a practical risk score to predict major bleeding in acute coronary syndromes

"...it is of great importance to balance the risk of hemorrhagic complications against the risk of ischemic complications when determining the optimal treatment for individual [acute coronary syndrome] patients."

KEYWORDS: acute coronary syndrome ■ bleeding ■ risk score

The incidence of recurrent adverse ischemic events and death after acute coronary syndromes (ACS): unstable angina, ST-segment elevation myocardial infarction [STEMI] and non-STEMI [NSTEMI]) has been significantly reduced by advances in antithrombotic therapy and invasive treatment strategies [1–4]. However, the use of multiple antiplatelet agents (i.e., aspirin, P2Y12 inhibitors, and glycoprotein IIb/IIIa inhibitors [GPIs]) and antithrombotic therapies (i.e., unfractionated heparin [UFH], low-molecular weight heparin, factor-Xa inhibitors and direct thrombin inhibitors), in combination with an early invasive approach has increased the risk of bleeding. The incidence of hemorrhagic complications after treatment of ACS ranges from 1 to 10%, depending on differences in patient characteristics, antithrombotic therapies, timing of event reporting and bleeding definitions [5–8]. Despite this heterogeneity, numerous studies have demonstrated that bleeding is associated with an increased risk for both short- and long-term adverse outcomes [5,7–12]. Although the exact mechanisms causing this increased risk after bleeding complications are not fully understood, a number of factors are likely to contribute, such as the cessation of evidence-based therapies (i.e., antiplatelet agents, β -blockers and statins) in patients who bleed, adverse effects of blood transfusion, detrimental effects of acute anemia and a greater prevalence of comorbidities in patients who bleed.

In contemporary practice, cardiologists have a wide variety of antiplatelet and antithrombin agents from which to choose. Each individual drug has a different profile of clinical efficacy (suppression of ischemic complications from the ACS event itself, or from the treatments subsequently required, most commonly percutaneous coronary intervention [PCI]) versus complications (principally bleeding). Large

randomized clinical trials have demonstrated that treatment strategies that reduce bleeding while effectively suppressing ischemia are associated with improved survival in patients with ACS. The Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial randomized 20,078 patients with non-ST-elevation ACS to the low-molecular weight heparin enoxaparin or the factor-Xa inhibitor fondaparinux [13]. Fondaparinux was noninferior to enoxaparin in terms of the primary end points of death, myocardial infarction or refractory ischemia at 9 days. Moreover, fondaparinux was associated with significantly reduced rates of major bleeding at 9 days (2.2 vs 4.1%; $p < 0.01$) and significantly reduced rates of mortality at 30 days (2.9 vs 3.5%; $p = 0.02$) and 6 months (5.8 vs 6.5%; $p = 0.05$). The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 STEMI patients undergoing primary PCI to treatment with either UFH plus a GPI or the direct thrombin inhibitor bivalirudin. In HORIZONS-AMI, bivalirudin compared with UFH plus a GPI was associated with significantly reduced major bleeding (4.9 vs 8.3%; $p < 0.01$) at 30-day follow-up, and mortality at 30 days (2.1 vs 3.1%; $p = 0.047$) and 1 year (3.5 vs 4.8%; $p = 0.04$) [14,15].

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Therefore, it is of great importance to balance the risk of hemorrhagic complications against the risk of ischemic complications when determining the optimal treatment for



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individual ACS patients. We recently conducted a pooled analysis of the HORIZONS-AMI and the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trials to develop a practical risk score to predict the risk of noncoronary artery bypass graft surgery (CABG)-related major bleeding in ACS [7]. The ACUITY trial randomized 13,819 patients with non-ST-segment elevation ACS undergoing an invasive strategy within 72 h of presentation to one of three antithrombotic regimens: heparin (UFH or enoxaparin) plus a GPI; bivalirudin plus a GPI; or bivalirudin monotherapy [16]. The resulting risk score model incorporates seven readily available variables; gender, age, serum creatinine, white blood cell count, anemia, type of ACS (unstable angina, NSTEMI or STEMI) and antithrombotic medications (UFH plus a GPI, or bivalirudin). For each variable, a patient's risk score increases by an integer amount for each level above the lowest category. If a patient received bivalirudin monotherapy, five is subtracted from the integer score. Subsequently, we defined four categories of bleeding risk, low (integer score <10, with a 30-day major bleeding risk 0.9–2.8%), moderate (integer score 10–14, with a 30-day major bleeding risk 2.8–4.7%), high (integer score 15–19, bleeding risk 4.7–7.9%) and very high (integer score \geq 20, bleeding risk >7.9%). A website is currently under construction to assist with calculating an individual patient's preprocedural bleeding risk, facilitating selection of the optimal pharmacologic for the patient with ACS undergoing an early invasive strategy.

In addition to choosing an antithrombotic agent associated with reduced bleeding, a patient undergoing a percutaneous invasive strategy might also benefit from a radial access approach rather than a femoral access approach. Several studies suggest that the radial approach is associated with reduced rates of bleeding and vascular complications, with similar rates of procedural success [17,18]. Moreover, a large observational study reported radial access halved the rate of blood transfusion after PCI, and was independently associated with reduced 30-day and 1-year mortality [19]. However, patients undergoing radial artery access still have hemorrhagic complications from nonvascular access sites (accounting for 40–60% of all bleeding in ACS after PCI), and thus still would benefit from a pharmacologic regimen that minimizes iatrogenic bleeding complications. The currently ongoing International Randomized Trial of Transradial Versus Transfemoral PCI

Access Site Approach in Patients with Unstable Angina or Myocardial Infarction Managed with an Invasive Strategy (RIVAL) trial aims to enroll 7000 patients and is designed to investigate whether a reduction in ischemic events accompanies a reduction in access site bleeding.

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In conclusion, the use of a practical risk score model enables physicians to estimate an individual patient's risk of bleeding after invasive management for ACS. Considering the risk of ischemia versus bleeding for each pharmacologic regimen according to an individual patient's profile [20] allows physicians to identify those patients who might benefit the most from treatment strategies to reduce bleeding.

Future perspective

The contemporary treatment of ACS with multiple antiplatelet agents and antithrombotic therapies in combination with an early invasive approach has effectively reduced the incidence of recurrent adverse ischemic events and death, but has also increased the risk of bleeding. Patients with ACS who develop bleeding complications are at an increased risk for subsequent adverse events. A recently developed practical risk score consisting of six baseline variables (female sex, advanced age, serum creatinin, white blood cell count, anemia and type of ACS [with or without ST-segment elevation]) and one treatment variable (use of heparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin monotherapy) can be useful to calculate an individual patient's bleeding risk and tailor the appropriate treatment strategy. The clinical implementation of this risk score can potentially facilitate clinical decision-making for patients with ACS.

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