Balancing Benefit and Bleeding Risk of Antithrombotic Agents in the Individual Patient With an Acute Coronary Syndrome

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In most countries, the antithrombotic armamentarium for treating acute coronary syndrome (ACS) patients currently consists of aspirin, clopidogrel, heparin, enoxaparin, bivalirudin, and fondaparinux. A large number of new antithrombotic agents for treating ACS patients are about to enter the market or are under development: new P2Y12 inhibitors (prasugrel, ticagrelor, canegrelor), thrombin receptor (proteinase-activator receptor-1) antagonists (SCH 530348, E555), direct antithrombin (dabigatran), and anti-Xa agents (otamixaban, rivaroxaban, apixaban). For all these new agents, there is evidence of enhanced or additional antithrombotic efficacy compared with standard antithrombotic regimens. A remaining clinical challenge of major importance is the price to be paid in terms of extra bleeding complications. For example, although there is very convincing evidence that prasugrel reduces the risk of stent thrombosis compared with clopidogrel, the practicing physician might be hesitant to put a particular ACS patient undergoing percutaneous coronary intervention on prasugrel because of the increased risk of a major or even fatal bleeding complication as demonstrated in the total population treated with prasugrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON). What the practicing physician would like to know is, In which patients does the reduced risk of stent thrombosis with prasugrel by far outweigh the risk of a severe and possibly fatal bleeding?

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Risk factors for bleeding complications have been identified in several previous studies: eg, age, female gender, renal impairment, and previous bleeding. Some of these risk factors such as age, renal failure, and hypertension have been shown in large registries to also be risk factors for recurrent ischemic events and death (summarized, for instance, by Gale et al and Diez and Cohen). Thus, identifying these risk factors in a particular patient is not very helpful. In an interesting article by Pocock et al in this issue of Circulation, risk factors for myocardial (re)infarction and major (non–coronary artery bypass graft) bleeding complications are not only identified but also analyzed quantitatively using individual data from the large Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial in which 13,819 non–ST-elevation ACS patients were randomized to standard treatment with heparin and a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. In this trial, patients randomized to treatment with a GP IIb/IIIa inhibitor were also randomized between upfront administration of these agents and administration during the percutaneous coronary intervention procedure. Independent risk factors for myocardial (re)infarction and major non–coronary artery bypass graft bleeding complications were identified. Most of the risk factors identified in this analysis are similar to those found in other studies, but only 2 were common for bleeding and (re)infarction: age and, surprisingly, ST-segment deviation on the admission ECG. (Re)infarction and major non–coronary artery bypass graft bleeding complications had a similar and significant impact on long-term mortality, but the effect of (re)infarction was much more pronounced early on and became nonsignificant after 30 days, whereas the effect of major bleeding was remarkably constant and significant up to 1 year. Treatment with bivalirudin alone rather than heparin and a GP IIb/IIIa inhibitor resulted in a 50% reduction in the risk of major non–coronary artery bypass graft bleeding and a (nonsignificant) 8% increase in the risk of (re)infarction.

There are a number of remarkable findings in this analysis. The first was the finding that only 2 risk factors were common for infarction and bleeding complications: age and ST-segment deviation on the admission ECG. For example, female gender and diabetes mellitus were not retained as independent predictors for both events in this analysis. That age is a common risk factor is well known and easy to understand. The explanation for ST deviation on the admission ECG is more difficult. Obviously, ST deviations on the admission ECG, together with positive biomarkers, identify a subpopulation at higher risk of recurrent ischemic complications that therefore is treated more aggressively and hence experiences an increased risk of bleeding complications. That ST-segment deviations and not positive biomarkers were an independent risk factor for bleeding could be explained by the fact that in many cases the biomarker results are known only when antithrombotic treatment has already been started. Also difficult to understand is the striking observation that an increased incidence of bleeding complications resulting from the acute intravenous administration of an antithrombotic would lead to a persistent and more or less constant increase in death rate over the next 12 months. A reasonable expla-
nination for this long-term effect seems to be a restrictive long-term use of oral antithrombotic agents. That this is a likely explanation is supported by another recent analysis of the ACUITY trial data in patients who had a gastrointestinal bleeding in the first month after the acute event. These patients were less likely to be put on dual antiplatelet therapy at discharge from the hospital.

The imbalance between ischemic and bleeding risk in the first week after the acute event indicates that the strength of the antithrombotic treatment should be much greater in the first days after the acute event than during long-term follow-up. This is already achieved in part by the addition of an anticoagulant to the dual antiplatelet therapy with aspirin and clopidogrel in the peri- to percutaneous coronary intervention period, but apparently, this combination treatment seems to be insufficient in a significant number of patients. Giving an anticoagulant for a longer period of time could be 1 option to improve antithrombotic efficacy. This option is currently being explored in trials with oral anti-Xa and anti-IIa agents such as apixaban in the Examination of Apixaban (Factor Xa inhibitor) as Adjunctive Therapy in Patients With Recent Acute Coronary Syndrome (APPRAISE-2) trial, rivaroxaban in the Assessment of Treatment With Lisinopril And Survival (ATLAS-2) trial, and dabigatran in the Efficacy and Safety of Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Recent Myocardial Damage (ESTEEM) trial. Giving a stronger antiplatelet therapy in the acute phase might be a second option, which is supported by trials with new P2Y12 inhibitors such as the TRITON2 and Platelet Inhibition and other ACS patients undergoing a percutaneous coronary intervention compared with the standard 300/75 mg regimen. An alternative strategy to improve antiplatelet therapy is adding yet another platelet inhibitor blocking a different pathway of platelet aggregation. This is currently being explored in the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA* CER) trial with the new proteinase-activator receptor-1 (thrombin) receptor antagonist SCH 530348.

The present analysis very much focuses on the reduction in bleeding complications with bivalirudin. Although there is little doubt that bivalirudin reduces the risk of major bleeding complications compared with heparin and a GP IIb/IIIa inhibitor (other studies have also shown this), the exact amount of benefit may have been overestimated in this study. The ACUITY trial was an open-label trial; therefore, the reporting of bleeding complications, especially groin hematomas, which occur very frequently after percutaneous coronary intervention and were a component of the primary safety end point, may have been subject to bias. Nevertheless, the key finding with regard to bivalirudin in this study, namely that the reduction in bleeding risk outweighs a possible increase in infarction, is convincing and clinically relevant.

In nearly all patients with ACS, anticoagulant treatment has to be combined with antiplatelet agents in the acute phase. Thus, the benefit-to-risk ratio of an anticoagulant, eg, bivalirudin, has to be evaluated on the background of (dual) antiplatelet therapy. It is not well known how much the bleeding risk with an anticoagulant differs from that of an antiplatelet agent in ACS patients and whether the risk factors for bleeding are the same for these 2 types of agents. For example, what would be the benefit-to-risk ratio of bivalirudin compared with heparin plus a GP IIb/IIIa inhibitor in patients treated with aspirin and prasugrel, which is known to be more effective than clopidogrel but on the other hand is associated with an increased bleeding risk? It would therefore be of significant interest if analyses similar to that performed by Pocock et al were performed with the available data from large studies with P2Y12 antagonists in ACS patients (TRITON, PLATO, CHAMPION, CURRENT trials) and with upcoming data from the ongoing TRA*CER trial. The value of these analyses would be much greater if uniform definitions for major bleeding complications and myocardial infarction had been used. Unfortunately, this is not the case. Currently, several definitions for bleeding complications have been used in large-scale trials (eg, Thrombolysis in Myocardial Infarction [TIMI], Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO], CURRENT, PLATO, ACUITY, etc) as if making a new definition is an absolute requirement when designing a new study to increase its prestige and visibility. It is up to the investigators of future trials to refrain from making new bleeding definitions but to ensure that all the components of already existing and frequently used definitions such as the TIMI and the more sensitive International Society on Thrombosis and Hemostasis definitions are captured. Under these assumptions, analyses like the one made by Pocock et al may pave the way for the development of a clinically useful combined benefit-to-risk score and therefore to a more personalized antithrombotic treatment for ACS patients.

Disclosures
Dr Van de Werf reports receiving consulting and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, SanofiAventis, and The Medicines Co.

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In the editorial by Van de Werf, “Balancing Benefit and Bleeding Risk of Antithrombotic Agents in the Individual Patient With an Acute Coronary Syndrome,” which appeared in the January 5/12, 2010 issue of the journal (Circulation, 2010;121:5–7), there is an error in the second paragraph of the paper. The first sentence of the second paragraph states “Risk factors for bleeding complications have been identified in several previous studies, eg, age, female gender, renal impairment, and previous bleeding.”

The sentence should read “Risk factors for bleeding complications have been identified in several previous studies: eg, age, female gender, renal impairment, and previous bleeding.”

The change has been made to the current online version of the article. The authors regret the error.

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