Rev Esp Cardiol. 2012;65(1):4–6

Editorial

# Assessing Bleeding Risk in Acute Coronary Syndromes

## Evaluación del riesgo de hemorragia en los síndromes coronarios agudos

Guliz Erdem and Marcus Flather*

*Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Foundation Trust, and National Heart and Lung Institute, Imperial College, London, United Kingdom*

*Article history:*
Available online 6 November 2011

## INTRODUCTION

Acute coronary syndromes (ACS) are usually caused by plaque rupture, platelet activation, and thrombus formation leading to coronary occlusion and myocardial damage.[1] Understanding the pathophysiology of ACS has led to the development of highly successful antithrombotic strategies, including acetylsalicylic acid, clopidogrel, and low molecular weight heparin, which have reduced the risk of death, myocardial infarction (MI) and recurrent ischaemia.[2] Early coronary revascularization using percutaneous coronary intervention (PCI) with stent implantation has also improved the outlook for higher risk patients with ACS.[3] However, antithrombotic therapy and PCI increase the risk of bleeding and there is growing evidence that major bleeding is independently associated with a higher risk of adverse outcomes including death.[4] These observations require a review of strategies to prevent bleeding while giving the most effective treatment regimens.

## IMPORTANCE OF BLEEDING

The 20% to 30% relative increase in the risk of bleeding observed with most effective antithrombotic treatments is considered acceptable if there are similar reductions in composite rates of MI or death.[5] Clinical trials and registries indicate that bleeding rates in the first 30 days after ACS vary from 4% to 9% depending on the types of patients, treatments, and definitions of bleeding.[6–10] The OASIS-5 study showed that fondaparinux, a factor Xa inhibitor, was noninferior to low molecular weight heparin enoxaparin for the composite outcome of death, stroke, or MI in patients with non-ST-elevation ACS (NSTEACS) but had a significantly lower rate of major bleeding and reduced all-cause mortality.[11] There was a strong independent relationship between major bleeds and increased mortality and this association has been confirmed in the large registries, including CRUSADE and GRACE.[6,10] Similarly the ACUITY trial, evaluating the role of the direct thrombin inhibitor bivalirudin against heparin and/or abciximab, showed that major bleeding was an independent predictor of 30-day mortality, with a significantly elevated hazard ratio (HR) of 3.5 compared to patients with no major bleeding.[7] In a multivariate analysis of ACUITY, major bleeding and recurrent MI within 30 days appeared to have a similar adverse impact on mortality during the first 12 months after ACS but MI was associated with an increased early risk of death while major bleeding was associated with a more prolonged risk.[7] These data suggest that bleeding in ACS patients, whatever the causative factor, is an independent marker of adverse outcome.

## WHY DOES BLEEDING INCREASE THE RISK OF DEATH IN ACUTE CORONARY SYNDROME?

Mechanisms linking bleeding to increased mortality in ACS are not clear but hypotension, increased adrenergic drive, anemia, reduced oxygen delivery, platelet dysfunction, vasoconstriction, and interruption of antithrombotic treatment are all postulated.[4,7] Blood transfusions, while providing beneficial haemodynamic effects and increasing haemoglobin, may also have adverse effects. In CRUSADE the transfusion rate was about 10% in patients not undergoing coronary artery bypass grafting (CABG)[12] with higher rates in the elderly and those with renal dysfunction especially when treated with multiple antithrombotic agents. Mortality was higher in transfused patients compared to nontranfused patients even after adjustment for patient and hospital characteristics (HR=1.67; 95% confidence interval, 1.48–1.88). Again the mechanisms for adverse effects of blood transfusion are not clear but may include platelet activation, depletion of 2,3-diphosphoglycerate during blood storage, decreased nitric oxide activity, increased plasminogen activator inhibitor, and immune activation due to infusion of foreign tissue.[4,13]

## FACTORS ASSOCIATED WITH INCREASED BLEEDING

The main causes of increased bleeding are patient characteristics, pharmacological treatments, and mechanical procedures. Patient characteristics associated with bleeding complications include older age, female sex, diabetes, hypertension, low body

* Corresponding author: Clinical Trials and Evaluation Unit, Royal Brompton and Harefield NHS Foundation Trust, London SW3 6NP, United Kingdom.
*E-mail address:* M.Flather@rbht.nhs.uk (M. Flather).

1885-5857/$ – see front matter 
doi:10.1016/j.rec.2011.08.006

weight, renal impairment, prior vascular disease, and prior stroke.[5–7,10] Given the adverse effects of bleeding, it is important to use antithrombotic regimens with the most favourable profiles for efficacy and safety. For example fondaparinux is as effective as enoxaparin in reducing the thrombotic complications of ACS, with a much lower risk of bleeding and transfusion.[11] In ACUITY, bivaluridin monotherapy was associated with lower rates of bleeding compared to heparin plus a glycoprotein inhibitor (3% vs 5.7%, *P*=.001) with similar efficacy[14] and ticagrelor is more effective than clopidogrel with a similar bleeding rate.[15] The decision-making process is more complex when considering more effective treatments with higher bleeding risk like prasugrel compared to clopidogrel, especially for patients with a high baseline risk of bleeding.[16] Although PCI, CABG and other invasive procedures increase bleeding risk, use of the radial route for PCI and off-pump techniques, cell saving, and scrupulous haemostasis for CABG will also help to avoid bleeding.[17]

## PREDICTION OF BLEEDING RISK

The CRUSADE bleeding risk score, derived from more than 70 000 NSTEACS patients identified 8 baseline characteristics associated with risk of major bleeding: heart rate, systolic blood pressure, hematocrit, creatinine clearance, female sex, diabetes, congestive heart failure, and prior vascular disease.[6] The ACUITY-HORIZONS-AMI bleeding risk score includes 6 baseline variables: female sex, anemia, age, raised white cell count, serum creatinine, type of ACS (non-ST-segment elevation MI or ST-segment elevation MI), and one treatment variable (heparin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin).[7,18] The GRACE risk score, developed to predict death, also predicts the risk of bleeding and the GRACE investigators have developed other scores to predict freedom from major adverse events including bleeding.[10,19]

## WHAT CAN WE DO TO REDUCE BLEEDING RISK FOR ACUTE CORONARY SYNDROME PATIENTS?

Guidelines now recommend formal risk stratification for ACS. The GRACE risk model will predict the risk of death and bleeding, and more specific bleeding scores can be used from CRUSADE or ACUITY-HORIZONS. Patients at highest risk of bleeding are also at highest risk of ischaemic and thrombotic complications. Thus higher risk patients need a more careful treatment approach to maximize the efficacy of therapy to reduce thrombotic risk while reducing bleeding risk.[5,20] The use of effective treatments with lower risks of bleeding, eg, low dose acetylsalicylic acid, fondaparinux, bivalirudin, and ticagrelor may be the preferred choices. Use of gastrointestinal protection such as proton pump inhibitors may be helpful although not evidence based at present. Reduction of bleeding risk is also essential when invasive procedures such as PCI and pacing are carried out, and blood transfusion should be reserved for significant hypotension or life-threatening haemorrhage rather than to treat haemoglobin reduction. The prevention of CABG-related major bleeding requires the use of less invasive procedures, shorter acting antithrombotics, and careful haemostasis. In conclusion, avoidance of major bleeding, while delivering effective therapy, is a key new goal for the management of ACS, especially for elderly patients and those with renal dysfunction since these are particular markers of poor tolerance to bleeding.

## CONFLICTS OF INTEREST

None declared.

## REFERENCES


1. Viles-Gonzalez JF, Fuster V, Badimon JJ. Atherothrombosis: a widespread disease with unpredictable and life-threatening consequences. Eur Heart J. 2004;25:1197–207.
2. Erdem G, Geisler T, Flather MD. What goes into a major acute coronary syndrome trial and what will future trials look like? Curr Cardiol Rep. 2010;12:348–55.
3. Giugliano RP, Pollack Jr CV, Brogan Jr GX, Cohen M, Diercks DB, Grines CL, et al. Acute coronary syndromes: from the emergency department to the catheterization laboratory-integrating evidence from recent ACS/NSTEMI trials into clinical practice: an evidence-based review of recent clinical trial results and report on a roundtable discussion. J Interv Cardiol. 2011;24:119–36.
4. Bassand JP. Acute Coronary Syndromes and Percutaneous Coronary Interventions: impact of bleeding and blood transfusion. Hamostaseologie. 2009;29:381–7.
5. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J. 2011;32:1854–64.
6. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation. 2009;119:1873–8.
7. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J. 2009;30:1457–66.
8. 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.
9. Budaj A, Eikelboom JW, Mehta SR, Afzal R, Chrolavicius S, Bassand JP, et al.; OASIS 5 Investigators. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J. 2009;30:655–61.
10. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, Montalescot G, 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.
11. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al.; Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354:1464–76.
12. Yang X, Alexander KP, Chen AY, Roe MT, Brindis RG, Rao SV, 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.
13. Silvain J, Pena A, Cayla G, Brieger D, Bellemain-Appaix A, Chastre T, et al. Impact of red blood cell transfusion on platelet activation and aggregation in healthy volunteers: results of the TRANSFUSION study. Eur Heart J. 2010;31:2816–21.
14. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol. 2007;49:1362–8.
15. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al.; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
16. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al.; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.
17. Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med. 2004;350:21–8.

18. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55:2556–66.
19. Brieger D, Fox KA, Fitzgerald G, Eagle KA, Budaj A, Avezum A, et al.; Global Registry of Acute Coronary Events Investigators. Predicting freedom from clinical events in non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009;95:888–94.
20. Fitchett D. 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;23:663–71.