

Non-ST-segment elevation acute coronary syndromes: do the benefits of modern antithrombotic treatments outweigh the risk of major bleeding?

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Iatrogenic major bleeding occurs in 4% of non-ST-segment elevation acute coronary syndromes (NSTE-ACS), causing increased in-hospital mortality. Prevention requires risk stratification based on advanced age, female sex, a history of bleeding, and renal failure (plasma creatinine, creatinine clearance). Particular caution is required in securing vascular access for percutaneous coronary interventions in high-risk patients. Use of the radial approach and of vascular sealing or suturing devices when performing a femoral approach markedly reduce the incidence of complications. Doses of heparin should be significantly reduced when combined with glycoprotein IIb/IIIa receptor inhibitors, and aspirin should be reduced to 75 to 150 mg/day when combined with clopidogrel. Such precautions should largely eliminate major bleeds in NSTE-ACS.

Keywords: acute coronary syndrome; anti-thrombotic treatment; hemorrhage; percutaneous coronary intervention; glycoprotein IIb/IIIa receptor inhibitor

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Over the last 15 years, the initial clinical presentation of coronary atherosclerosis has markedly changed. Acute coronary syndromes (ACS) are now the most frequent clinical presentation of these patients. The EuroHeart Survey¹ conducted in 2000 reported that, in 55% of cases, the baseline ECG showed non-ST-segment elevation changes (ST-segment depression, T-wave inversion, atypical changes,

and even a normal tracing). Thus, this clinical condition (non-ST-segment elevation ACS [NSTE-ACS]), which was initially called unstable angina or non-Q-wave myocardial infarction (MI), is very frequent and is related to plaque rupture, subocclusive superimposed thrombosis, and distal embolization. New advances in antithrombotic treatment and revascularization procedures have markedly reduced the risk of major cardiac events (death, large

SELECTED ABBREVIATIONS AND ACRONYMS

ACS	acute coronary syndrome
ACUTE II	Antithrombotic Combination Using Tirofiban and Enoxaparin-II
A-to-Z	Aggrastat to Zocor [trial]
CURE	Clopidogrel in Unstable angina to prevent Recurrent ischemic Events [trial]
ESSENCE	Efficacy Safety Subcutaneous Enoxaparin in Non-Q-wave Coronary Events [study]
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Use of Strategies to Open occluded coronary arteries [trial]
INTERACT	INTegrelin and Enoxaparin Randomized assessment of Acute Coronary syndromes Treatment [trial]
LMWH	low-molecular-weight heparin
MI	myocardial infarction
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
NSTE-MI	non-ST-segment elevation myocardial infarction
SYNERGY	Superior Yield of the New strategy of Enoxaparin, Revascularization and GLYcoprotein IIb/IIIa inhibitors [trial]
TIMI	Thrombolysis In Myocardial Infarction
UFH	unfractionated heparin

myocardial infarction compromising left ventricular [LV] function). However, today's powerful antithrombotic therapy is accompanied by an increased incidence of hemorrhagic complications.

The aim of this paper is to describe the magnitude of the problem, to identify patients at risk of major bleeding, and suggest an approach to risk stratification.

LIMITATIONS OF STUDIES OF MAJOR BLEEDINGS IN NSTE-ACS

Modern antithrombotic treatments used in NSTE-ACS include direct or indirect antithrombin inhibitors and antiplatelet agents. A number of multicenter, randomized clinical trials have been implemented in this setting, but information concerning bleeding complications is conflicting, due at least to two factors:

- Most of the clinical randomized trials were performed in selected populations: For example, patients at high risk of bleeding complications, like elderly patients, were in most of the cases excluded from these trials.
- The definitions of bleeding complications in these trials differ to a certain extent, even within the same study, which can lead to conflicting interpretations. For example, in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial,² there was an excess of major bleeding in the clopidogrel group in comparison with the placebo group (3.7% vs 2.7%; relative risk [RR]=1.38 [95% confidence interval (CI) 1.13-1.67]; $P=0.001$). However, using the Thrombolysis In Myocardial Infarction (TIMI) definition for bleeding (Table I), no difference was found between the two groups (RR=0.94 [95% CI: 0.68-1.30]; $P=0.70$). The same observation can be made if one uses the Global Use of Strategies to Open occluded coronary arteries (GUSTO) definition (Table I) in this trial.

Another example showing the difficulty of comparisons is that some trials define major bleeding as a drop of 3 g/dL of hemoglobin concentration while other studies define it as a drop of 5 g/dL.

Therefore, it is important to consider incidence and predictors of major bleedings in large registries.

INCIDENCE OF MAJOR BLEEDINGS IN NSTE-ACS

Unfractionated heparin and enoxaparin

All patients with NSTE-ACS receive antithrombin treatment consisting of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), in particular, enoxaparin. A meta-analysis of six randomized trials was recently completed (Efficacy Safety Subcutaneous Enoxaparin in Non-Q-wave Coronary Events [ESSENCE], TIMI 11B, Antithrombotic Combination Using Tirofiban and Enoxaparin-II [ACUTE II], INTegrelin and Enoxaparin Randomized assessment of Acute Coronary

syndromes Treatment [INTERACT], Aggrastat to Zocor [A-to-Z], Superior Yield of the New strategy of Enoxaparin, Revascularization and GLYcoprotein IIb/IIIa inhibitors [SYNERGY]).³ This meta-analysis allowed comparison of UHF and enoxaparin in a total cohort of 21 946 patients. The rate of transfusions within a period of 7 days was 7.2% in the enoxaparin group and 7.5% in the UHF group. As prior antithrombotic treatment before admission was liable to influence the results, when patients with prior antithrombotic treatment were excluded, the transfusion rate was 5.0% and 5.5%, respectively. For major bleedings (keeping the definition given in each individual trial), the rate was 4.7% in the enoxaparin group and 4.5% in the UFH group with all patients included, and 3.8% and 3.4% excluding patients having received prior antithrombotic therapy. Thus, on the basis of the findings from this meta-analysis, it was impossible to establish the predictive factors of bleeding.

GpIIb/IIIa receptor inhibitors

Another meta-analysis, carried out by Eric Boersma et al,⁴ included nine randomized clinical trials comparing

• TIMI (Thrombolysis In Myocardial Infarction) definitions:

Major bleeding: Overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of greater than 5 g/dL (0.5 g/L) or in hematocrit of greater than 15% (absolute)

Minor bleeding: Overt clinical bleeding associated with a fall in hemoglobin of 3 to less than or equal to 5 g/dL (0.5 g/L) or in hematocrit of 9% to less than or equal to 15% (absolute)

• GUSTO (Global Use of Strategies to Open occluded coronary arteries) definitions:

Severe bleeding: intracranial hemorrhage or bleeding inducing hemodynamic compromise

Moderate bleeding: requiring transfusion without hemodynamic compromise

Mild bleeding: without transfusion or hemodynamic compromise

Table I. Definitions of bleeding.



different glycoprotein (Gp) IIb/IIIa receptor inhibitors (tirofiban, eptifibatid, lamifiban, abciximab) vs placebo in patients with acute coronary syndromes. Each group received aspirin and heparin. In other words, the comparison was done between single vs dual antiplatelet treatment (GpIIb/IIIa + aspirin vs aspirin alone). The rate of major bleeding was 2.4% with dual antiplatelet treatment vs 1.4% with aspirin alone (odds ratio [OR]: 1.62 [95% CI: 1.36-1.94]; $P < 0.0001$). Intracranial hemorrhage was very rare: 0.09% vs 0.06%.

Thienopyridines

The CURE trial² was conducted in a large group ($n = 12\,562$) of patients with NSTE-ACS. This trial compared clopidogrel (loading dose of 300 mg followed by 75 mg/d) combined with aspirin, with aspirin alone. It was found that the rate of major bleeding was 3.7% with dual antiplatelet treatment vs 2.7% with aspirin alone. It was also shown that the rate of bleeding complications was markedly increased when high doses of aspirin (>200 mg) were used.⁵

Overall, therefore, the rate of major bleedings in several randomized trials of patients with NSTE-ACS is within the range of 2.4% to 4.7%. The most common sites of bleeding are gastrointestinal (31% to 36%), at the arterial puncture site (15% to 25%), and retroperitoneal (3.5% to 6%).

PREDICTORS OF BLEEDING COMPLICATIONS

Most of these trials failed to address the predictors of serious bleedings. The Global Registry of Acute Coronary Events (GRACE) registry⁶ is unique in that it took that issue into account. This registry enrolled 24 045 patients between April 1999

and September 2002 with bleeding status identified. The data came from 94 centers in 14 countries worldwide. Major bleedings were defined as life-threatening bleeding requiring transfusions of ≥ 2 units of packed red cells, or resulting in an absolute decrease in hematocrit of $\geq 10\%$, or causing hemorrhagic/subdural hematoma. Here again, the lack of standardized definitions should be pointed out.

ed with significantly more major bleedings. In contrast, administration of LMWH was associated with a lower risk of major bleeding.

After correcting for the influence of other variables, the best predictors of major bleeding were: advanced age; female sex; prior history of bleeding; and renal insufficiency. Among treatments, the pharmacological interventions that were asso-

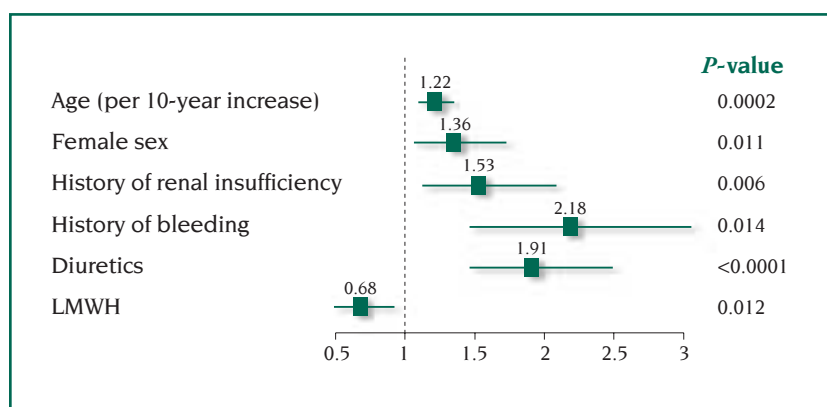


Figure 1. Multivariate model for major bleeding in NSTE-MI.

Abbreviations: LMWH, low-molecular-weight heparin; NSTE-MI, non-ST-segment elevation myocardial infarction.

Adapted from reference 6: Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1815-1823. Copyright © 2003, Oxford Journals.

A total of 933 (3.9%) patients experienced major bleeding during hospitalization. This complication was more frequent in non-ST-segment elevation myocardial infarction (NSTE-MI) (4.7%) than in unstable angina patients (2.3%). Patients who had these complications were significantly older (71.1 years vs 66.2 years), females 5% vs 3.3% in males, with lower body mass index (26.2 kg/m² vs 26.9 kg/m²), more peripheral vessel disease (5.5% vs 3.7%), more renal insufficiency (6.5% vs 3.6%), and more frequent history of prior bleeding (11.5% vs 3.8%) when compared with patients without major bleedings. When considering therapeutic interventions, diuretics, vasopressors, GpIIb/IIIa receptor inhibitors, and UHF were associat-

ciated with major bleedings after control of variables were: diuretics; inotropic drugs; and GpIIb/IIIa receptor inhibitors. Catheterization and percutaneous coronary intervention were also associated with increased risk of bleeding.

The multivariate regression models of factors associated with high risk of major bleeding are shown in *Figure 1*, and *Figure 2* (page 166) for patients with NSTE-MI and unstable angina.

The impact of major bleeding on in-hospital mortality rate is striking: patients experiencing major bleedings have a higher in-hospital mortality rate. This was observed in NSTE-MI and unstable angina

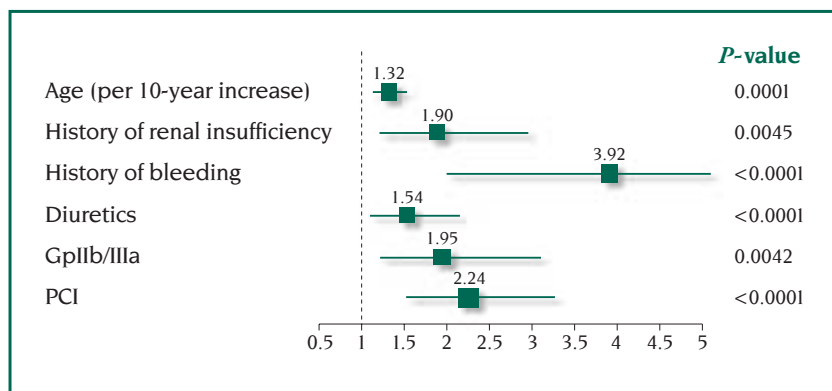


Figure 2. Multivariate model for major bleeding in unstable angina.

Abbreviations: GpIIb/IIIa, glycoprotein IIb/IIIa receptor; PCI, percutaneous coronary intervention. Adapted from reference 6: Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815-1823. Copyright © 2003, Oxford Journals.

patients. Even after adjustment for comorbidities, major bleeding is strongly associated with a higher in-hospital mortality (OR= 1.64 [95% CI: 1.18-2.28]).

RISK STRATIFICATION

The European Society of Cardiology (ESC) recommendations concerning the management of NSTE-ACS have emphasized the need for risk stratification. Thus, we have to consider the acute risk, which is the thrombotic risk (risk of death and large MI in the acute phase) and the long-term risk. The acute risk includes patients who have recurrent chest pain or ischemia, ST-segment depression or elevated troponins, intracoronary thrombus, and all diabetics. These patients are treated with three antiplatelet drugs (aspirin + clopidogrel + infusion of GpIIb/IIIa receptor inhibitor) associated with enoxaparin and an invasive strategy (coronary angiography within the next 48 h) is indicated. This highly aggressive antithrombotic treatment is necessary, owing to the risk of in-hospital death and infarction, but it induces a risk of serious bleedings. Thus, in patients with NSTE-ACS, advanced age, female sex, history of prior bleeding,

are predictive of bleeding and hence should be included in the list of factors denoting high-risk in these patients. Furthermore, the highly aggressive antithrombotic management should perhaps be tempered in these particular groups of patients. In this context, it remains clearly difficult to balance the thrombotic risk against the bleeding risk.

In addition, some of the major bleeding predictors overlap with the markers of long-term risk in NSTE-ACS. This is the case for advanced age, female gender, and renal insufficiency, which are important components of the long-term risk markers such as history of MI, history of coronary artery bypass grafting (CABG), all biological markers (C-reactive protein, interleukin 6, brain natriuretic peptide, soluble CD-40 ligand, etc), and coronary artery disease extension, LV dysfunction, and peripheral vessel disease.

CONCLUSIONS

Major bleedings are relatively frequent in patients presenting with non-ST-segment elevation acute coronary syndromes (≈4%). These events are associated with a higher

rate of in-hospital mortality. Risk stratification to identify patients at higher risk of major bleedings is relatively simple. Elderly patients, female sex, particularly women with a low body mass index, prior history of bleeding, and renal insufficiency are predictive of a high risk of major bleeding. Thus, simple baseline characteristics coupled with simple biological assays (creatinine level, calculated creatinine clearance) are able to predict bleeding complications. Patients undergoing percutaneous coronary interventions need special precautions with regard to vascular access. Use of the radial approach⁷ even in octogenarians,⁸ or of vascular sealing or suturing devices when a femoral approach is performed, should markedly reduce the incidence of these complications.

In addition, when combining GpIIb/IIIa receptor inhibitors with heparin—particularly unfractionated heparin—it is recommended to significantly reduce the doses of heparin. Similarly, when clopidogrel is associated with aspirin as demonstrated in the CURE trial, it is necessary to reduce the dose of aspirin, which should be between 75 and 150 mg/day.

Even though major cardiac adverse events remain a matter of concern in patients presenting with NSTE-ACS, clinicians should now pay special attention to major bleedings, which contribute to the immediate outcome of these patients.



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