

New Antithrombotic Drugs in Acute Coronary Syndromes: The Role of Fondaparinux and Bivalirudin in Reducing Major Hemorrhages and Mortality

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The net clinical benefit of any antithrombotic drug for the treatment of acute coronary syndromes (ACS) is described by its favorable effects on major outcomes (mortality, reinfarction, stroke) and its unfavorable effects on bleeding. Traditionally, with most antithrombotic therapies an increased hemorrhagic risk is accepted in order to achieve better efficacy. Recently, the importance of bleeding as an adverse outcome has received wide attention.

Major bleeding in ACS is not rare. In GRACE, the multinational registry of ACS, 4% of patients with unstable angina, STEMI or non-STEMI had a major hemorrhage. In-hospital mortality was 18.6% in those patients who experienced major bleeding versus only 5.1% in those without such an adverse event. What is more interesting is the fact that the appearance of a non-fatal major bleeding event in hospital increases the long-term risk of death and carries a similar prognostic significance to re-infarction. The odds ratio (OR) for 6-month mortality is 5.6 for a patient with re-infarction in hospital and 4.5 for a patient with major hemorrhage in hospital [1].

The antithrombin drugs that are commonly used in the treatment of ACS are unfractionated heparin (UFH) and low molecular weight heparins (LMWH). Both are indirect thrombin inhibitors (requiring antithrombin-III) with anti-Xa and anti-II properties. Both have proved to be effective in reducing death or myocardial infarction in randomized clinical trials with a small and acceptable increase in major bleedings. Consequently they both have a class I indication in current practice guidelines [2]. Enoxaparin has gained popularity because of its practicality. A meta-analysis of trials comparing enoxaparin with UFH showed similar mortality (3 vs 3%), marginally less re-infarction (10.1 vs 11%), with no increase in major bleeding; RR 1.04 [3].

Two newer antithrombins have recently been tested for efficacy and safety in the treatment of ACS. *Fondaparinux* is a synthetic pentasaccharide with exclusive anti-Xa properties. It is an indirect antithrombin (like the LMWH) with excellent bioavailability, longer half life (once daily subcutaneous administration), resistance to platelet factor 4 and no thrombocytopenia risk. OASIS-5 randomized 20,000 patients with ACS to enoxaparin 1 mg/Kg twice daily or fondaparinux 2.5 mg once daily [4]. The composite end point of death, infarction, refractory ischemia at day 9 was identical in the two treatment groups (HR 1.01). However, major bleeding events were halved with fondaparinux (2.1% vs 4%; $p < 0.00001$). At 6 months, mortality was significantly lower with fondaparinux (5.6% vs 6.3%; $p = 0.037$). This reduction is mainly driven by the early avoidance of major bleeding events.

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Direct thrombin inhibitors have an anticoagulant effect against both free and clot bound thrombin, are resistant to plasma protein inactivation and achieve stable aPTT levels. *Bivalirudin* has been tested in patients with ACS treated with an early invasive strategy [5]. The three treatment arms were UFH (or Enoxaparin) + IIB/IIIa inhibitor, Bivalirudin + IIB/IIIa Inhibitor and Bivalirudin alone. The composite end point of death, myocardial infarction and urgent revascularization was 7.3%, 7.7% and 7.8% respectively (ns). Major bleeding rates were 5.7%, 5.3% and 3% ($p < 0.001$ for bivalirudin alone vs heparin + IIB/IIIa inhibitor). Similarly, less bleeding rates were noted in patients undergoing percutaneous coronary intervention (PCI) treated with bivalirudin in comparison with UFH+ IIB/IIIa inhibitors [6].

Both fondaparinux and bivalirudin are recommended in current guidelines as antithrombin therapies in ACS patients with their main advantage being increased safety due to reduced bleeding events [2].

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