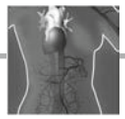
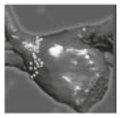


Is heparin sufficient in non-ST-elevation acute coronary syndrome percutaneous coronary intervention?

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> "*A major criticism of the … current guidelines is the fact that bivalirudin has been tested against … heparin and glycoprotein IIb/IIIa inhibitors, but not against heparin alone.*"

KEYWORDS: bivalirudin ■ heparin ■ myocardial infarction ■ percutaneous coronary intervention

Bivalirudin & the present guidelines

Bivalirudin (Angiomax®, The Medicines Company, NJ, USA) is a direct-acting synthetic antithrombotic agent that has been approved as an alternative treatment to unfractionated heparin for patients with acute coronary syndromes who are undergoing percutaneous coronary intervention (PCI). Both European Society of Cardiology and American College of Cardiology/American Heart Association guidelines recommend this antithrombotic agent for the treatment of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) in the setting of PCI [1,2]. This recommendation is primarily based on the ACUITY study [3], which included 13,819 moderate- to high-risk NSTE-ACS patients planned for revascularization with PCI. The patients were randomized to three different treatment groups: bivalirudin alone; bivalirudin and a glycoprotein IIb/IIIa receptor (GPIIb/IIIa) inhibitor; or a GPIIb/IIIa inhibitor and unfractionated heparin/low-molecular-weight heparin. The study demonstrated that none of the strategies were inferior in terms of the composite ischemia end point, consisting of death from any cause, myocardial infarction or unplanned revascularization for ischemia at 30 days. These findings were subsequently confirmed after 1 year of follow-up [4]. However, major bleeding complications were lower in the patients receiving bivalirudin alone compared with the combination of heparin and a GPIIb/IIIa inhibitor (3.0 vs 5.7%; relative risk: 0.53; 95% CI: 0.43–0.65; $p < 0.001$). The number of major bleeding complications did not differ between patients receiving bivalirudin and a GPIIb/IIIa inhibitor, and those receiving heparin and a GPIIb/IIIa inhibitor.

As major bleeding is associated with worse clinical outcomes [5,6], the practical consequence of the ACUITY trial for clinical medicine was the endorsement of bivalirudin over GPIIb/IIIa inhibitors in NSTE-ACS patients scheduled for PCI. However, the present guidelines do not state whether bivalirudin is preferential to heparin alone.

Appraisal of the present guidelines

A major criticism of the preference for bivalirudin in the current guidelines is the fact that bivalirudin has been tested against the combination of heparin and GPIIb/IIIa inhibitors, but not against heparin alone. When the ACUITY trial was performed, the guidelines at the time recommended heparin in combination with GPIIb/IIIa inhibitors in NSTE-ACS for both patients who were to undergo revascularization with PCI, as well as for those who were to receive medical treatment only [7]. The rationale for this recommendation was based on results from studies performed at the beginning of the 1990s, in which patients were treated with bare-metal stents based on stent technology available at that time and before the widespread use of clopidogrel preloading and the arrival of newer P2Y12 antagonists, such as ticagrelor [8], cangrelor [9] and prasugrel [10].

An important study from this era was the EPISTENT trial [11], in which treatment with the GPIIb/IIIa inhibitor abciximab was compared with heparin alone in patients with NSTE-ACS undergoing PCI. Abciximab was associated with an absolute reduction of 5.5% in the combined end point of death, myocardial infarction or urgent target vessel revascularization at 30 days (5.3 vs 10.8%; hazard ratio [HR]: 0.48; 95% CI: 0.33–0.69; $p < 0.001$). All patients in the study received oral aspirin, but treatment with the P2Y12 antagonist available at that time, ticlopidine, was left to the discretion

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of the investigator. Although all patients receiving a stent (only 67%) were treated with ticlopidine, the timing and length of treatment were not reported.

In the more recent ISAR-REACT 2 study, heparin alone was compared with abciximab in patients with NSTE-ACS pretreated with 600-mg clopidogrel [12]. In this study of 2022 patients, treatment with abciximab was associated with an absolute reduction in the combined end point of death, myocardial infarction or urgent target vessel revascularization of 3% (8.9 vs 11.9%; relative risk: 0.75; 95% CI: 0.58–0.97; p = 0.03), with no difference in bleeding events. However, patients who were treated with heparin alone received a bolus of 140 U/kg followed by a 12-h infusion. This dose regimen of heparin is now regarded to be outdated and would typically be replaced with a bolus dose of 100 U/kg without infusion.

> *"...the present guidelines do not state whether bivalirudin is preferential to heparin alone."*

For these reasons, we conclude that it is difficult to assess the validity of the studies discussed above in contemporary practice. We argue that it is not clear whether the addition of a GPIIb/IIIa inhibitor to heparin is superior to heparin alone and, therefore, argue against the present guidelines favoring bivalirudin.

Heparin may not be inferior to bivalirudin

Only two randomized clinical trials have directly compared bivalirudin with heparin in NSTE-ACS patients. In the BAT trial in 1995, 4098 patients with unstable angina or postinfarction angina undergoing PCI without stent were randomized to either heparin alone or bivalirudin [13]. The main finding was an absolute reduction in major bleeding with bivalirudin of 6% (3.8 vs 9.8%; HR: 0.40; 95% CI: 0.30–0.50; p < 0.001). The dose of heparin (170 U/kg) was, however, much higher than the current recommendations. Conversely, at 6-months follow-up, there was a trend towards higher mortality in the bivalirudin group (estimated mortality risk of 1.8 vs 1.1% in the heparin group; HR: 1.6; 95% CI: 0.9–2.7; p = 0.09). The second randomized clinical trial, the ISAR-REACT 3 study, included 4570 patients [14]. The results were similar to the BAT study with a reduction in major bleeding associated with bivalirudin (3.1 vs 4.6%; HR: 0.66; 95% CI: 0.49–0.90; p = 0.008). Although this study is more recent, all patients were biomarker negative and the heparin dose used was rather high (140 U/kg).

Why is it important to determine whether inexpensive unfractionated or low-molecular-weight heparin is noninferior to expensive bivalirudin in the treatment of NSTE-ACS, and why should this be done in the timely manner? Most physicians practice their profession in societies where economic assets are limited. We all have a moral obligation to thoroughly scrutinize the cost–effectiveness before 'enthusiastically' accepting new and costly treatments. We also have an obligation to continuously re-examine the already-endorsed treatment strategies promoted by guidelines, especially as new therapeutic opportunities appear, such as replacement of clopidogrel with the new P2Y12 antagonists and the use of radial access for PCI. The evaluation of new therapeutic combinations could result in a more effective reduction of clinical end points and improved cost–effectiveness, even if it means returning to previously outdated products, such as unfractionated heparin.

> *"We argue that it is not clear whether the addition of a glycoprotein IIb/IIIa inhibitor to heparin is superior to heparin alone and, therefore, argue against the present guidelines favoring bivalirudin."*

In summary, we argue that: unfractionated or low-molecular-weight heparin could be equal alternatives for the treatment of NSTE-ACS patients undergoing PCI; bivalirudin should primarily be considered for patients at higher risk of bleeding; and a randomized clinical trial with proper statistical power is needed for direct comparison of heparin and bivalirudin. Design of such a study should reflect the modern standards of care with a high degree of radial artery access and with all patients treated with one of the newer P2Y12 antagonists (ticagrelor, prasugrel or cangrelor).

Financial & competing interests disclosure

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References

1 Hamm CW, Bassand JP, Agewall S *et al.* ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 32(23), 2999–3054 (2011).

2 Anderson JL, Adams CD, Antman EM *et al.* 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarctiona report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J. Am. Coll. Cardiol.* 61(23), e179–e347 (2013).

3 Stone GW, McLaurin BT, Cox DA *et al.* Bivalirudin for patients with acute coronary syndromes. *N. Engl. J. Med.* 355(21), 2203–2216 (2006).

4 Stone GW, Ware JH, Bertrand ME *et al.* Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the acuity trial. *JAMA* 298(21), 2497–2506 (2007).

5 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.* 24(20), 1815–1823 (2003).

6 Mehran R, Pocock S, Nikolsky E *et al.* Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc. Interv.* 4(6), 654–664 (2011).

7 Silber S, Albertsson P, Aviles FF *et al.* Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur. Heart J.* 26(8), 804–847 (2005).

8 Wallentin L, Becker RC, Budaj A *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 361(11), 1045–1057 (2009).

9 Steg PG, Bhatt DL, Hamm CW *et al.* Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet* doi:10.1016/S0140-6736(13)61615-3 (2013) (Epub ahead of print).

10 Wiviott SD, Braunwald E, McCabe CH *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 357(20), 2001–2015 (2007).

11 EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 352(9122), 87–92 (1998).

12 Kastrati A, Mehilli J, Neumann FJ *et al.* Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 295(13), 1531–1538 (2006).

13 Bittl JA, Strony J, Brinker JA *et al.* Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N. Engl. J. Med.* 333(12), 764–769 (1995).

14 Kastrati A, Neumann FJ, Mehilli J *et al.* Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N. Engl. J. Med.* 359(7), 688–696 (2008).