Review

Bivalirudin in Acute Coronary Syndromes and Percutaneous Coronary Intervention: Should We Use It?

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Major bleeding remains a major risk factor for percutaneous coronary intervention of acute coronary syndromes and is associated with higher morbidity, mortality, prolonged hospital stay and costs.

With the recognition that bleeding is an important factor in patient outcomes, the prevention of bleeding has become as important a goal as the prevention of ischaemia. The direct thrombin inhibitor bivalirudin has been shown to reduce ischaemia and importantly, is associated with less bleeding.

In this article we review the evidence base that supports the use of bivalirudin across all spectrums of coronary syndromes and percutaneous coronary intervention. An algorithm for the use of bivalirudin in high risk subgroups and coronary syndromes is suggested.

(Heart, Lung and Circulation 2013;22:793–800)

Keywords. Bivalirudin; Antithrombin agent; Bleeding; Glycoprotein IIbIIIa inhibitor (GP IIbIIIa inhibitor); Percutaneous coronary intervention

Background

Anti-thrombotic therapy remains a cornerstone in percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS) management. The search for newer anti-thrombotic drugs is ongoing with the goal to achieve an agent which leads to less bleeding complications without a reduction or indeed improvement in clinical efficacy, resulting in net clinical benefit.

This is because major bleeding remains a significant risk factor for mortality following PCI with higher 30 days and one year mortality reported in numerous studies [1–5]. Bleeding is associated with a five-fold increase in mortality and higher risk of myocardial infarction, stroke and stent thrombosis in ACS [1–5].

The postulated mechanisms for the increase in mortality with major bleeding include the following: anaemia and hypovolaemia which may contribute to myocardial ischaemia and death; bleeding may lead to discontinuation of aspirin, clopidogrel and heparin which may predispose patients to ischaemia, myocardial infarction, stroke and stent thrombosis [1,2,4]. In addition transfusion may increase relative tissue hypoxia and adversely affect outcomes through stored red blood cells acting as nitric oxide sink, which may promote vasoconstriction, platelet aggregation and ineffective oxygen delivery [6].

With the increasing recognition that bleeding is an important factor in patient outcomes, there has been a shift towards reducing bleeding risks [7,8]. Indeed the prevention of bleeding has become as important a goal as the prevention of ischaemia [7].

Bivalirudin is a direct and specific thrombin inhibitor and synthetic analogue of hirudin, which has been shown to reduce bleeding-related complications [9–19]. It has a class 1b indication for use as an anticoagulant during an invasive strategy [20,21]. Bivalirudin is currently recommended as an alternative anticoagulant in PCI. In the 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand (CSANZ) Guidelines for the Management of Acute Coronary Syndromes 2006, bivalirudin is recommended in preference to enoxaparin in the context of an invasive strategy in patients at high risk of bleeding [8]. In this article, we review the current evidence base, which supports its use.

Pharmacology of Bivalirudin v. Heparin

Unfractionated heparin has been the standard adjunctive antithrombin therapy during PCI for more than 30

Received 15 February 2013; received in revised form 8 May 2013; accepted 11 May 2013; available online 31 July 2013

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1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2013.05.636

years. Heparin works indirectly by binding to antithrombin III and converts antithrombin III from a slow to a rapid inactivator of thrombin, factors Xa, XIIa and IXa. The heparin–antithombin III complex inactivates free thrombin but is unable to inactivate thrombin bound within the clot [22]. A possible mechanism for this includes the inability of the bulky heparin–antithrombin III complex to penetrate the clot. In addition the binding site for the heparin–antithrombin complex on thrombin may be masked following attachment of the thrombin to fibrin [22,23]. Heparin is inactivated by inhibitors released by platelets including heparinase and platelet factor 4 [23]. Heparin binds to tissue and plasma proteins, which makes the bioavailability, clearance and thus dosing variable from patient to patient [24]. In addition it has nonlinear anticoagulant response at therapeutic dose and a dose dependent half-life. The anticoagulant effects thus may vary from patient to patient. Heparin also has platelet activating effects [25].

Bivalirudin specifically binds to both the active catalytic site and anion binding exosite of free and clot bound thrombin [22,24]. The binding of bivalirudin to thrombin is reversible as thrombin slowly cleaves the bivalirudin–thrombin bond resulting in recovery of thrombin active site functions. Bivalirudin is able to inhibit both free and clot bound thrombin and is not inhibited by circulating inhibitors. Bivalirudin does not activate platelets and in contrast inhibits thrombin mediated platelet activation. Because bivalirudin binds only to thrombin and has minimal tissue and plasma protein binding, it has predictable, dose dependent and reliable anticoagulant effects [22,24]. Bivalirudin exhibits linear pharmacokinetics with linear dose and concentration proportional anticoagulant activity. The ACT, aPTT, TT and PT are prolonged by bivalirudin in a dose dependent manner. Bivalirudin has a short half-life of 25 min and is cleared both renally and via proteolytic degradation. Dose adjustment is thus required in the presence of renal impairment. The differences between bilvalirudin and unfractionated heparin are summarised in Table 1.

The Evidence

Acute Coronary Syndromes and Percutaneous Coronary Intervention

In the Hirudin Angioplasty study which was performed during the balloon angioplasty era, prior to the routine use of thienopyridines, GP IIbIIIa inhibitors and stenting, bivalirudin was reported to be as effective as high dose heparin in reducing ischaemic complications (11.8% v. 12.9%; $p = 0.26$) and was associated with reduced bleeding (3.8% v. 9.8%; $p < 0.001$) [9]. Furthermore in a subgroup analysis of patients with post infarction angina, bivalirudin resulted in a lower incidence of ischaemic complications (9.1% v. 14.2%; $p = 0.04$) and bleeding (3.0% v. 11.0%; $p < 0.001$) [9].

A meta-analysis of direct thrombin inhibitors including bivalirudin in acute coronary syndromes by the Direct Thrombin Inhibitors Trialists' Collaborative Group reviewed the use of direct thrombin inhibitors v. unfractionated heparin for up to seven days in 35,970 patients in 11 randomised trials performed in the era prior to the routine use of thienopyridines and GP IIbI-IIa inhibitors [10]. Compared with unfractionated heparin, direct thrombin inhibitors were associated with a lower risk of death or myocardial infarction at 30 days [7.4% v. 8.2%; odds ratio (OR): 0.91; 95% CI: 0.84–0.99; $p = 0.02$] principally due to a lower risk of myocardial infarction [2.8% v. 3.5%; OR: 0.80 (0.71–0.9); $p < 0.001$]. The greatest benefit was seen in the use of direct thrombin inhibitors in PCI with 20 events prevented per 1000 patients treated. Both bivalirudin and hirudin prevented death or myocardial infarction. Compared to heparin, bivalirudin was associated with a reduction in bleeding.

The role of bivalirudin in contemporary PCI was examined in the Randomised Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE 2) trial [11]. In this trial, 6010 patients undergoing elective or urgent PCI were randomised to either bivalirudin with provisional GP IIbIIIa inhibition ($n = 2999$) or heparin (65 U/kg bolus with planned GP IIbIIIa inhibition) ($n = 3011$). Bivalirudin with provisional GP IIbIIIa inhibition was noninferior to heparin and planned GP IIbIIIa inhibition in the primary composite endpoint of death, myocardial infarction, urgent repeat revascularisation or in hospital major bleeding [bivalirudin (9.2%) v. heparin and planned GP IIbIIIa inhibitor (10.0%); OR: 0.92; 95% CI: 0.77–1.09; $p = 0.32$]. There was significantly less major bleeding (41% relative reduction) with bivalirudin [bivalirudin (2.4%) v. heparin plus GP IIbIIIa inhibition (4.1%); $p < 0.001$]. At one year, there was a trend towards improved survival with bivalirudin, a survival advantage that was more marked in the highest risk subgroup [12]. Thus in elective or low risk PCI, bivalirudin with provisional GP IIbIIIa inhibition may be similar to heparin and planned GP IIbIIIa inhibitor in suppressing acute ischaemic endpoints and significantly reduces bleeding.

The issue of whether bivalirudin monotherapy was noninferior to heparin plus planned GP IIbIIIa inhibitor in moderate to high-risk acute coronary syndromes was examined in the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial [13]. In this trial, 13,819 patients with moderate to high risk acute coronary syndromes undergoing an early invasive strategy were randomised in an open label multicentre trial to heparin plus a GP IIbIIIa inhibitor, bivalirudin plus a GP IIbIIIa inhibitor or bivalirudin alone. Bivalirudin alone compared to heparin plus a GP IIbIIIa inhibitor was associated with similar rates of ischaemia (7.8% v. 7.3% respectively; $p = 0.32$; relative risk (RR): 1.03; 95% CI: 0.93–1.24) and significantly reduced major bleeding (3.0% v. 5.7%; $p < 0.001$; RR: 0.53; 95% CI: 0.43–0.65) which translated to reduced net clinical outcome of ischaemic endpoints and major bleeding (10.1% v. 11.7%; $p = 0.02$; RR: 0.86; 95% CI: 0.77–0.97). Bivalirudin plus a GP IIbIIIa inhibitor was similar to heparin plus a GP IIbIIIa inhibitor in reducing ischaemic endpoints (7.7% v. 7.3%; $p = 0.39$; RR: 1.07; 95% CI: 0.92–1.23) with similar bleeding endpoints (5.3% v. 5.7%; $p = 0.38$; RR: 0.93; 95% CI: 0.78–1.10) and net clinical outcomes (11.8% v. 11.7%; $p = 0.93$; RR: 1.01;