The evolving role of direct thrombin inhibitors in acute coronary syndromes

ARTICLE *in* JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY · MARCH 2003

Impact Factor: 16.5 · DOI: 10.1016/S0735-1097(02)02687-6 · Source: PubMed

3 AUTHORS, INCLUDING:

John Eikelboom
McMaster University
531 PUBLICATIONS **23,475** CITATIONS
SEE PROFILE

Harvey White
Auckland City Hospital
1,004 PUBLICATIONS **46,262** CITATIONS
SEE PROFILE

Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 41, No. 4 Suppl S
ISSN 0735-1097/03/$30.00
PII S0735-1097(02)02687-6

The Evolving Role of Direct Thrombin Inhibitors in Acute Coronary Syndromes

John Eikelboom, MBBS, MSc, FRACP, FRCPA,* Harvey White, MB, ChB, DSc, FRACP, FACC,† Salim Yusuf, MBBS, Dphil, FRCP (UK), FRCPC, FACC‡

Perth, Australia; Auckland, New Zealand; and Hamilton, Ontario, Canada

The central role of thrombin in the initiation and propagation of intravascular thrombus provides a strong rationale for direct thrombin inhibitors in acute coronary syndromes (ACS). Direct thrombin inhibitors are theoretically likely to be more effective than indirect thrombin inhibitors, such as unfractionated heparin or low-molecular-weight heparin, because the heparins block only circulating thrombin, whereas direct thrombin inhibitors block both circulating and clot-bound thrombin. Several initial phase 3 trials did not demonstrate a convincing benefit of direct thrombin inhibitors over unfractionated heparin. However, the Direct Thrombin Inhibitor Trialists' Collaboration meta-analysis confirms the superiority of direct thrombin inhibitors, particularly hirudin and bivalirudin, over unfractionated heparin for the prevention of death or myocardial infarction (MI) during treatment in patients with ACS, primarily due to a reduction in MI (odds ratio, 0.80; 95% confidence interval, 0.70 to 0.91) with little impact on death. The absolute risk reduction in the composite of death or MI at the end of treatment (0.8%) was similar at 30 days (0.7%), indicating no loss of benefit after cessation of therapy. Supportive evidence for the superiority of direct thrombin inhibitors over heparin derives from the recently reported Hirulog and Early Reperfusion or Occlusion (HERO)-2 randomized trial with ST-segment elevation ACS, which demonstrated a similar benefit of bivalirudin over heparin for the prevention of death or MI at 30 days (absolute risk reduction 1.0%), again primarily due to a reduction in MI during treatment (odds ratio, 0.70; 95% confidence interval, 0.56 to 0.87), with little impact on death. Further evaluation of hirudin and bivalirudin in the antithrombotic management of patients with ACS is warranted. (J Am Coll Cardiol 2003;41:70S–78S) © 2003 by the American College of Cardiology Foundation

The most common underlying pathophysiologic process in patients with non–ST-segment elevation acute coronary syndromes (ACS) involves the formation of nonocclusive thrombus at the site of vessel wall injury (1,2). Spontaneous or mechanical disruption of atherosclerotic plaque exposes thrombogenic material within the plaque to the blood, which leads to platelet adhesion and aggregation, coagulation activation, and thrombin generation (3). Thrombin plays a central role in the process of thrombus formation, converting fibrinogen to fibrin, activating platelets, and recruiting additional platelets into the platelet-rich thrombus. The resulting intracoronary thrombus reduces myocardial perfusion and leads to unstable angina or acute myocardial infarction (MI).

Recognition of the pivotal role of thrombin in the initiation and propagation of intracoronary thrombus formation has led to intensive efforts to develop new therapies that block thrombin generation or activity (4). Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) indirectly inhibit thrombin through an antithrombin-dependent mechanism and are widely used in the management of arterial and venous thrombosis. In aspirin-treated patients with non–ST-segment elevation ACS, the addition of heparin is associated with a 30% reduction in the risk of recurrent MI or death during the first week (5). An important limitation of heparin, however, is its inability to inhibit clot-bound thrombin (Fig. 1). When thrombin is bound to fibrin, to soluble fibrin degradation products, or to exposed subendothelial matrix proteins, it is protected from inactivation by heparin but remains enzymatically active. In such a scenario, thrombin is able to amplify its own generation through a positive feedback loop via coagulation factors V and VIII, thereby continuing to promote thrombus formation (6,7).

Direct thrombin inhibitors have important biologic and pharmacokinetic advantages over heparins (Table 1) (8). Direct thrombin inhibitors are able to specifically block both fluid-phase and tissue-bound thrombin and, therefore, reduce thrombin activity more effectively than UFH and LMWH (Fig. 1). Because they do not bind to plasma proteins and are not inactivated by heparinases, direct thrombin inhibitors also produce a more predictable anticoagulant response than UFH. Experimental results have shown that direct thrombin inhibitors are highly effective in the prevention of thrombus formation in models of arterial thrombosis (9,10). The accumulating evidence has led to a large number of clinical trials of direct thrombin inhibitors in patients with ACS (11).

Please refer to the Trial Appendix at the back of this supplement for the complete list of Clinical Trials.

From the *Department of Medicine, University of Western Australia and Department of Haematology, Royal Perth Hospital, Perth, Australia; †Cardiology Department, Green Lane Hospital, Auckland, New Zealand; ‡Division of Cardiology, Department of Medicine, McMaster University, and Population Health Institute, Hamilton Health Sciences Corporation, McMaster University, Hamilton, Ontario, Canada. Drs. White and Yusuf have received grant support from Aventis Pharmaceuticals. Dr. White has been a consultant for the Medicines Company.

Manuscript received May 7, 2002; revised manuscript received October 4, 2002, accepted October 10, 2002.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
aPPT = activated partial thromboplastin time
GP = glycoprotein
LMWH = low-molecular-weight heparin
MI = myocardial infarction
PEG = polyethylene glycol
RR = relative risk
UFH = unfractionated heparin

The objectives of this paper are twofold: 1) to review the results of randomized clinical trials of direct thrombin inhibitors compared with UFH in patients with ACS overall, and subdivided, according to the absence or presence of persistent ST-segment elevation on the presentation electrocardiogram; and 2) to discuss the current role of direct thrombin inhibitors for the management of patients with ACS in the context of emerging anticoagulant and antiplatelet therapies, particularly glycoprotein (GP) IIb/IIIa inhibitors.

DIRECT THROMBIN INHIBITORS

The prototype direct thrombin inhibitor is hirudin, a naturally occurring 65-amino acid polypeptide first isolated from the salivary gland of medicinal leeches and now available through recombinant DNA technology (12). Many other direct thrombin inhibitor preparations have been developed, but only those that have been evaluated in patients with ACS are listed in Table 2.

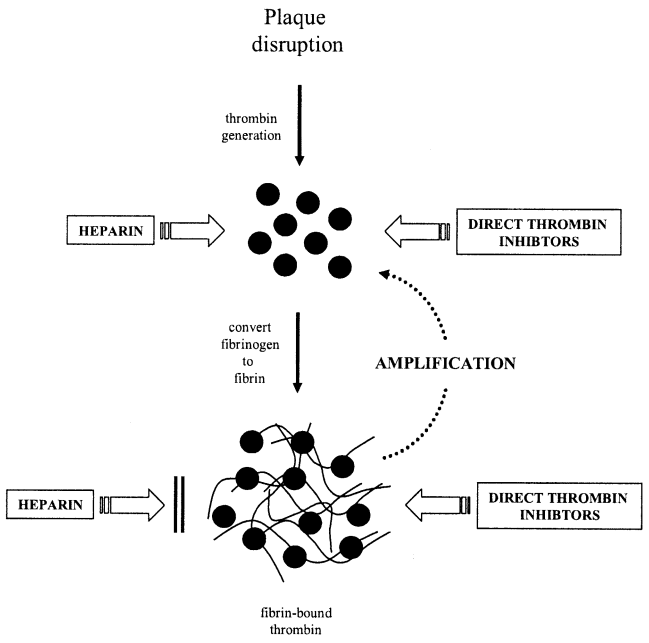

Figure 1. Schematic demonstrating the antithrombin activity of heparin compared with direct thrombin inhibitors. Both heparin and direct thrombin inhibitors block circulating thrombin, but only direct thrombin inhibitors block tissue-bound thrombin. Tissue-bound thrombin remains enzymatically active, promoting further platelet and coagulation activation and thrombin generation.

Hirudin is a potent and almost irreversible inhibitor of thrombin, blocking the active catalytic site as well as the substrate recognition exosite (13). It has a half-life of approximately 60 min after intravenous administration and is primarily excreted through the kidneys, which may lead to its accumulation in patients with renal impairment. A polyethylene glycol-complexed preparation, PEG-hirudin, with an extended half-life, has also been developed.

Bivalirudin is a 20-amino acid polypeptide that was synthesized by linking an active site-directed, short-peptide chain to an analogue of the carboxy-terminal of hirudin (14). Consequently, bivalirudin, like hirudin, is able to form a bivalent complex with thrombin, blocking both the active site and the substrate recognition exosite. However, it has a substantially shorter plasma half-life of 20 to 25 min because of cleavage by thrombin of the active site-binding peptide. This may provide two important advantages to bivalirudin. First, it may grant a safety advantage for bivalirudin over hirudin by allowing earlier re-exposure of the active site of thrombin, permitting hemostasis to occur. Second, it may confer an efficacy advantage by allowing thrombin activation of the natural anticoagulant, protein C (15). Bivalirudin is excreted primarily via nonrenal mechanisms.

Several synthetic univalent direct thrombin inhibitors have been evaluated in phase 1 and 2 ACS trials, including the noncovalent inhibitors argatroban and inogatran and the reversible covalent inhibitor efegatran (16–18). These agents target only the active site of thrombin, have a short half-life, and appear to be more potent inhibitors of fibrin-bound thrombin than the bivalent inhibitors hirudin and bivalirudin (6,19).

RANDOMIZED DIRECT THROMBIN INHIBITOR TRIALS IN ACS

Major phase 3 randomized trials that have been performed in patients with ACS are summarized in Tables 3 and 4.

Hirudin. Initial studies demonstrating the feasibility of hirudin as an anticoagulant in patients with stable or unstable coronary disease (20–23) were followed by phase 2 heparin-controlled trials in patients with ACS based on angiographic or clinical outcomes (24–29). Several angiographic studies demonstrated improvements in coronary artery patency with hirudin compared with heparin (24–26), while the initial clinical trials revealed promising reductions in important clinical outcomes during treatment (27–29). These results prompted several study groups to initiate a series of major phase 3, randomized, heparin-controlled, direct thrombin inhibitor trials in ACS, including the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO), Hirudin for Improvement of Thrombolysis (HIT), Thrombolysis In Myocardial Infarction (TIMI), Organization to Assess Strategies for Ischemic Syndromes

JACC Vol. 41, No. 4 Suppl S
February 19, 2003:70S–78S

Table 1. Advantages of Direct Thrombin Inhibitors Over Heparins

	Unfractionated Heparin	Low-Molecular-Weight Heparin	Direct Thrombin Inhibitor
Pharmacokinetic			
Plasma protein/endothelial binding	Yes	Partial	No
Inactivated by heparinases	Yes	Partial	No
Biologic effects			
Anticoagulant effects	Xa = IIa	Xa ≫ IIa	IIa
Antithrombin-dependent	Yes	Yes	No
Inactivates clot-bound thrombin	No	No	Yes
Inhibits platelet function	Yes (paradoxical activation?)	Limited	Yes, thrombin-induced only
Vascular permeability	Increased	Not increased	Not increased
Thrombocytopenia	Yes	Rare	No
Liver toxicity (enzyme rise)	Common	Uncommon	No

(OASIS), and, most recently, Hirulog and Early Reperfusion or Occlusion (HERO).

Three trials (GUSTO-2A, TIMI-9A, and HIT-3) were stopped due to excessive bleeding. In GUSTO-2A (30), investigators randomized ACS patients to a 72- to 120-h infusion of either hirudin (0.6 mg/kg bolus, 0.2 mg/kg/h infusion) or UFH, with a target activated partial thromboplastin time (aPPT) of 60 to 90 s for UFH and no dose adjustment for hirudin. Excessive intracranial bleeding occurred primarily in patients receiving thrombolytic therapy (incidence 1.8%) with only 0.3% occurring in the non–ST-segment elevation ACS group.

The TIMI-9A trial (31) randomly assigned patients with ST-segment elevation ACS receiving thrombolytic therapy to 96 h of treatment with hirudin (0.6 mg/kg bolus, 0.2 mg/kg/h infusion) or UFH. The Data and Safety Monitoring Board terminated the trial prematurely because of a high rate of hemorrhagic complications in both treatment groups, particularly in the hirudin group.

In the HIT-3 study (32), patients were randomized to 48 to 72 h of either hirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion) or heparin as an adjunct to tissue plasminogen activator. The dose of both hirudin and UFH was adjusted during infusion to a target aPTT ratio of 2.0 to 3.5. The trial was terminated early because of an excess of intracranial bleeds in patients receiving hirudin (3.4% vs. 0%, p = NS).

Table 2. Direct Thrombin Inhibitors Evaluated in Randomized Trials of Patients With ACS

	Acute Coronary Syndromes	
Trial Phase	Non–ST-Segment Elevation	ST-Segment Elevation
Phase 1 or 2	Argatroban	Argatroban
	Bivalirudin	Bivalirudin
	Efegatran	Efegatran
	Hirudin (PEG-hirudin*)	Hirudin
	Inogatran	
Phase 3	Bivalirudin†	Bivalirudin
	Hirudin	Hirudin

*Pilot studies also have been performed with a PEG-complexed form of hirudin; †Study abandoned by sponsoring company before completion.
ACS = acute coronary syndromes; PEG = polyethylene glycol.

The GUSTO-2B (33) and TIMI-9B (34) trials were subsequently recommenced with lower doses of both hirudin (0.1 mg/kg bolus, 0.1 mg/kg/h infusion) and UFH, with a target aPTT of 60 to 85 s and 55 to 85 s, respectively. The projected recruitment was successfully achieved in both studies. In the GUSTO-2B trial at 30 days there was a borderline significant reduction in the primary composite outcome of death or MI with hirudin compared with UFH (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.79 to 1.00), with consistent results when compared as an adjunct to thrombolysis or in non–ST-segment elevation ACS. In the TIMI-9B trial there was no benefit of hirudin over UFH at 30 days, either on the primary composite outcome of death, MI, cardiac failure, or cardiogenic shock or the composite of death or MI. However, there was a trend to reduction in nonfatal MI both during hospitalization and at 30 days. Neither GUSTO-2B nor TIMI-9B demonstrated an excess of major or intracranial bleeding with hirudin compared with heparin.

The OASIS-2 trial (35) randomized 10,141 patients with non–ST-segment elevation ACS to a 72-h infusion of hirudin (0.4 mg/kg bolus, 0.15 mg/kg/h infusion) or UFH, with a target aPTT of 60 to 100 s. This study demonstrated a nonsignificant difference between hirudin and heparin in the primary outcome of cardiovascular death or MI at seven days (3.6% vs. 4.2%). However, at the completion of study drug infusion, there was a significant reduction in cardiovascular death or MI with hirudin relative to heparin (2.0% vs. 2.6%). Compared with UFH, hirudin was associated with a significantly increased risk of major bleeding (1.2% vs. 0.7%), but not life-threatening bleeding (0.4% vs. 0.4%). There were no cases of intracranial bleeding during study drug infusion with hirudin and one case with UFH.

A pooled analysis of the OASIS, GUSTO-2B, and TIMI-9B trials confirms the superiority of hirudin compared with heparin for the prevention of death or MI at the completion of treatment (relative risk [RR], 0.78; p = 0.0004), 7 days (RR, 0.84; p = 0.002), and 30 to 35 days (RR, 0.90; p = 0.016) (35).

Table 3. Phase 3 Trials Comparing Direct Thrombin Inhibition With Heparin in ACS

Trials (DTI)	Patients (n)	Primary End Point	Dose: Bolus (mg/kg); Infusion (mg/kg/h)/Duration of Infusion
GUSTO-2A* (Hirudin)	ACS (2,564)	Death or MI at 30 days	0.6; 0.2/72–120 h
GUSTO-2B (Hirudin)	ACS (12,142)	Death or MI at 30 days	0.1; 0.1/72 h
HERO-2 (Bivalirudin)	ST-segment elevation ACS (17,073)	Death at 30 days	0.25; 0.5/12 h, followed by 0.25/36 h
HIT-3* (Hirudin)	ST-segment elevation ACS (302)	Death or MI	0.4; 0.15/48–72 h
TIMI-9A* (Hirudin)	ST-segment elevation ACS (757)	Death, MI, CHF, cardiogenic shock, or LVEF < 40% at 30 days	0.6; 0.2/96 h
TIMI-9B (Hirudin)	ST-segment elevation ACS (3,002)	Death, MI, CHF, cardiogenic shock, or LVEF < 40% at 30 days	0.1; 0.1/96 h
OASIS-2 (Hirudin)	Non–ST-segment elevation ACS (10,132)	Cardiovascular death or MI at 7 days	0.4; 0.15/72 h
TIMI-8† (Bivalirudin)	Non–ST-segment elevation ACS (133)	Death or MI at 14 days	0.1; 0.25/72 h

*Stopped early by data safety monitoring board due to high rates of bleeding; †Study abandoned by sponsoring company before completion (planned enrolment 5,320).

ACS = acute coronary syndromes; CHF = congestive heart failure; DTI = direct thrombin inhibitor; GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HERO = Hirulog and Early Reperfusion or Occlusion; HIT = Hirudin for Improvement of Thrombolysis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OASIS = Organization to Assess Strategies for Ischemic Syndromes; TIMI = Thrombolysis In Myocardial Infarction.

Bivalirudin. After uncontrolled studies that demonstrated the feasibility of bivalirudin (36,37), several highly promising heparin-controlled pilot studies were performed with bivalirudin in patients with ACS (38–40). A meta-analysis of these trials (41) that included data from patients undergoing percutaneous coronary intervention (42,43) confirmed the superiority of bivalirudin over heparin for the prevention of death or MI at 30 to 50 days (OR, 0.73; 95% CI, 0.57 to 0.95) with a reduction in risk of major bleeding (OR, 0.41; 95% CI, 0.32 to 0.52). This meta-analysis also included data from the prematurely terminated (for "business" reasons by the sponsors) phase 3 TIMI-8 trial that compared a 72-h infusion of bivalirudin with heparin in patients with non–ST-segment elevation ACS (target enrolment 5,320). Although only 133 patients were randomized before study termination, there was already a highly promising reduction in the risk of death or MI with bivalirudin compared with UFH at 14 days (2.9% vs. 9.2%) (44).

Further evidence of the superiority of bivalirudin over heparin in ACS derives from the recently completed HERO-2 study (45). This trial randomized 17,073 patients with acute MI receiving thrombolytic therapy to a 48-h infusion of bivalirudin or heparin. In order to test the hypothesis that exposure of tissue-bound thrombin by thrombolytic therapy is an important trigger for recurrent ischemic events, bivalirudin and heparin were administered before thrombolytic therapy. In the absence of major bleeding, dose reduction of bivalirudin was not allowed after 12 h

Table 4. Results of Completed Phase 3 Trials of Direct Thrombin Inhibitors Compared With Heparin in ACS

Trials	Results	Odds Ratio	95% CI
GUSTO-2B	With hirudin:		
	Reduction in death or MI	0.89	0.79–1.00
	As adjunct to thrombolysis	0.86	0.70–1.05
	Non–ST-segment elevation	0.90	0.78–1.06
HERO-2	With bivalirudin:		
	No difference in death at 30 days	0.99	0.90–1.09
	Reduced death or MI at 30 days	0.92	0.83–1.01
	Reduced MI at 96 h	0.70	0.56–0.87
	Increased bleeding	1.32	1.00–1.74
	Reduced death, MI, nonfatal stroke, 30 days	0.91	0.83–1.00
TIMI-9B	No benefit with hirudin		
	Primary end point	1.09	0.80–1.31
	Composite of death or MI	1.02	0.80–1.31
	Trend to less nonfatal MI		
	In hospital	0.65	0.42–1.01
	At 30 days	0.81	0.56–1.18
OASIS-2	No difference in primary outcome at 7 days:	0.84	0.69–1.02
	With hirudin:		
	Less cardiovascular death or MI at end of treatment	0.76	0.59–0.99
	More major bleeding	1.73	1.13–2.63
	No more life-threatening bleeding	0.99	0.54–1.85

ACS = acute coronary syndromes; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; HERO = Hirulog and Early Reperfusion or Occlusion; MI = myocardial infarction; OASIS = Organization to Assess Strategies for Ischemic Syndromes; TIMI = Thrombolysis In Myocardial Infarction.

JACC Vol. 41, No. 4 Suppl S
February 19, 2003:70S–78S

Table 5. Direct Thrombin Inhibitor Trialists' Collaboration: Direct Thrombin Inhibitors Compared With Heparin in Patients With ACS With or Without ST-Segment Elevation at the End of Treatments

Outcomes	DTI (n = 15,866)	Heparin (n = 14,651)	OR (95% CI)
Death or MI			
ACS	726/15,866 (4.6%)	786/14,651 (5.4%)	0.85 (0.76–0.94)
ACS with ST-segment elevation	325/5,148 (6.3%)	332/4,799 (6.9%)	0.91 (0.77–1.06)
ACS without ST-segment elevation	401/10,718 (3.7%)	454/9,852 (4.6%)	0.80 (0.70–0.92)
Death			
ACS	353/15,866 (2.2%)	343/14,651 (2.3%)	0.95 (0.82–1.10)
ACS with ST-segment elevation	213/5,148 (4.1%)	186/4,799 (3.9%)	1.07 (0.88–1.31)
ACS without ST-segment elevation	140/10,718 (1.3%)	157/9,852 (1.6%)	0.82 (0.65–1.03)
MI			
ACS	434/15,866 (2.7%)	499/14,651 (3.4%)	0.80 (0.70–0.91)
ACS with ST-segment elevation	130/5,148 (2.5%)	161/4,799 (3.4%)	0.75 (0.59–0.94)
ACS without ST-segment elevation	304/10,718 (2.8%)	338/9,852 (3.4%)	0.82 (0.70–0.96)

Data adapted from reference 50. Reprinted with permission from Elsevier Science (Lancet 2002;359:294–302).
ACS = acute coronary syndrome; CI = confidence interval; DTI = direct thrombin inhibitor; MI = myocardial infarction; OR = odds ratio.

unless the aPTT was >150 s, or after 24 h unless the aPTT was >120 s.

The HERO-2 study demonstrated no difference in the primary outcome of death at 30 days in patients treated with bivalirudin compared with heparin. There was, however, an 8% reduction in the composite of death or MI at 30 days and a 30% reduction in the incidence of new MI at 96 h, a benefit that was maintained to 30 days. Modest excess bleeding occurred with bivalirudin compared with heparin (1.4% vs. 1.1%) with a similar trend for severe excess bleeding (0.7% vs. 0.5%, $p = 0.07$). This was somewhat unexpected in view of the reduced risk of bleeding seen in earlier studies performed with this agent, but may be due to the higher aPTT levels at 12 h (median aPPT, 108 vs. 77 s; $p < 0.0001$) and 24 h (median aPPT, 80 vs. 57 s; $p < 0.0001$) in patients receiving bivalirudin compared with heparin. However, the incidence of moderate (major) and intracranial hemorrhage in this trial remained low compared with contemporary thrombolysis trials in patients with ACS, and the composite net clinical benefit outcome of death, MI, and nonfatal disabling stroke at 30 days favored bivalirudin ($p = 0.049$).

Univalent direct thrombin inhibitors. There has been only limited evaluation of univalent direct thrombin inhibitors in ACS, and the results have largely been disappointing. Although these agents were generally well tolerated with no excess major bleeding compared with heparin, most of the phase 2 trials were unable to demonstrate superiority of argatroban, efegatran, or inogatran compared with heparin, based on surrogate (angiographic, electrocardiographic) or clinical outcomes. In some cases the results suggested that they may be inferior (46–49).

DIRECT THROMBIN INHIBITOR TRIALISTS' COLLABORATION META-ANALYSIS

Despite several large, randomized trials, there has been uncertainty regarding the clinical benefit of direct thrombin inhibitors compared with heparin in patients with ACS, whether early treatment benefits are maintained long-term, and whether excess bleeding offsets any benefit of these agents. The reasons for this uncertainty include the possibility that direct thrombin inhibitors are not superior to UFH. Alternatively, the benefits may be modest, and larger trials than those conducted may be needed. Further, several of the trials may have chosen to measure the outcome several days or weeks after cessation of treatments, so that any real benefit may have been "diluted" by events occurring subsequent to treatment cessation.

To address these issues, the Direct Thrombin Inhibitor Trialists' Collaboration recently reported the results of a systematic review of major randomized trials of direct thrombin inhibitors compared with UFH in patients with unstable coronary disease (11,50). Trials included in the meta-analysis had to randomize patients with ACS or patients undergoing percutaneous coronary intervention, compare a direct thrombin inhibitor with heparin, and record data on the key irreversible outcomes of death and MI. The primary outcome was the composite of death or MI at the end of treatment when the maximal benefit of antithrombotic therapy is likely to be evident. Outcomes at day 7 and day 30 also were examined. Small trials (<200 patients or <100 controls) and trials performed with excessive doses of direct thrombin inhibitor or heparin (TIMI-9A, GUSTO-2A, HIT-3) were not included.

Overall, there was a 15% reduction in death or MI at the end of treatment with direct thrombin inhibitors compared with heparin (4.3% vs. 5.1%; OR, 0.85; 95% CI, 0.77 to 0.94; $p = 0.001$), equivalent to preventing eight events for every 1,000 patients treated (50) (Table 5). This absolute reduction in death or MI was maintained to 30 days (Table 6). A similar benefit was evident in all categories of trials, including ACS, and subdivided according to ST-segment elevation or non–ST-segment elevation (Table 5). The benefit was seen with hirudin (OR, 0.83; 95% CI, 0.74 to

Table 6. Direct Thrombin Inhibitor Trialists' Collaboration: DTI Compared With Heparin in Patients With ACS With or Without ST-Segment Elevation at 30 Days

Outcomes	DTI (n = 15,866)	Heparin (n = 14,651)	OR (95% CI)
Death or MI			
ACS	1,288 (8.1%)	1,285 (8.8%)	0.92 (0.85–1.00)
ACS with ST-segment elevation	506 (9.8%)	489 (10.2%)	0.96 (0.84–1.10)
ACS without ST-segment elevation	782 (7.3%)	796 (8.1%)	0.90 (0.81–0.99)
Death			
ACS	672 (4.2%)	629 (4.3%)	0.99 (0.88–1.10)
ACS with ST-segment elevation	317 (6.2%)	271 (5.6%)	1.10 (0.93–1.30)
ACS without ST-segment elevation	355 (3.3%)	358 (3.6%)	0.91 (0.78–1.05)
MI			
ACS	771 (4.9%)	800 (5.5%)	0.88 (0.80–0.98)
ACS with ST-segment elevation	228 (4.4%)	254 (5.3%)	0.83 (0.69–1.00)
ACS without ST-segment elevation	543 (5.1%)	546 (5.5%)	0.91 (0.81–1.03)

Data adapted from reference 50. Reprinted with permission from Elsevier Science (The Lancet, 2002;359:294–302).
ACS = acute coronary syndrome; CI = confidence interval; DTI = direct thrombin inhibitors; MI = myocardial infarction; OR = odds ratio.

0.92) and bivalirudin (OR, 0.53; 95% CI, 0.24 to 1.17) but not univalent thrombin inhibitors (OR, 1.35; 95% CI, 0.89 to 2.05). The greatest benefit of direct thrombin inhibitors compared with heparin appeared to be in patients undergoing percutaneous coronary intervention during study infusion, where there was a 32% reduction in death or MI (4.6% vs. 6.6%; OR, 0.68; 95% CI, 0.57 to 0.83).

Although direct thrombin inhibitors compared with heparin were not associated with an overall excess of major bleeding or intracranial bleeding in the ACS trials, pooled results from all the trials (including percutaneous coronary intervention trials) demonstrated that hirudin was associated with an increased risk of major bleeding (1.7% vs. 1.3%; OR, 1.28; 95% CI, 1.06 to 1.55), while both bivalirudin (4.2% vs. 9.0%; OR, 0.44; 95% CI, 0.34 to 0.56) and univalent inhibitors (0.7% vs. 1.3%; OR, 0.55; 95% CI, 0.25 to 1.20) were associated with a reduced risk of major bleeding. The shorter half-life and a more transient inhibition of the active site of thrombin may account for the reduced risk of major bleeding associated with bivalirudin compared with hirudin (51), although this was not confirmed in the HERO-2 trial (45).

CURRENT ROLES AND FUTURE DIRECTIONS OF DIRECT THROMBIN INHIBITORS IN ACS

The consistent results of the HERO-2 trial (45), hirudin (35) and bivalirudin (41) meta-analyses, and Direct Thrombin Inhibitor Trialists' Collaboration meta-analysis (50) provide clear evidence for the superiority of the direct thrombin inhibitors, particularly hirudin and bivalirudin, over heparin in ACS, with or without ST-segment elevation. Although the bulk of the randomized evidence in non–ST-segment elevation ACS derives from trials comparing hirudin with heparin, the consistency of the treatment effects of bivalirudin in patients with ST-segment elevation and undergoing percutaneous coronary intervention suggests that this agent is likely to be similarly effective in patients without ST-segment elevation. By contrast, there are currently no data supporting the use of univalent direct thrombin inhibitors in patients with ACS.

There are a number of unresolved issues. First, the greater efficacy of direct thrombin inhibitors in reducing death or MI in patients with ACS is balanced, in part, by an excess of major bleeding, particularly with hirudin, which may limit its use to patients at highest risk of future vascular events in whom the benefits are more likely to outweigh the bleeding risks. One such high-risk group may be patients with ACS undergoing percutaneous coronary intervention in whom both the relative and absolute benefits of hirudin in reducing death or MI appear to be greatest (50,52).

Second, available trials comparing hirudin with UFH in patients with ACS were largely performed before the widespread use of intravenous GP IIb/IIIa inhibitors. However, intravenous GP IIb/IIIa inhibitor agents appear to be beneficial only when administered in combination with heparin and compared against placebo (53). Furthermore, indirect comparison of trials comparing the incremental benefit of direct thrombin inhibitors versus UFH, and GP IIb/IIIa inhibitors plus UFH, versus UFH alone, indicate a similar magnitude of benefit on end-of-treatment (RR reduction of 15% and 16%, respectively) and 30-day (RR reduction of 8% and 9%, respectively) outcomes of death and MI (Table 7, Fig. 2). The reason for this may be that direct thrombin inhibitors have both anticoagulant and antiplatelet properties (54), while GP IIb/IIIa inhibitors have only antiplatelet activity and require the addition of an anticoagulant, such as heparin, to block coagulation. This suggests a possible role for direct thrombin inhibitors as a single drug that replaces the combination of GP IIb/IIIa inhibitors and heparin in patients with ACS, particularly high-risk patients undergoing percutaneous coronary intervention. At least one study comparing bivalirudin with or without a GP IIb/IIIa inhibitor versus UFH plus a GP IIb/IIIa inhibitor (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events [REPLACE] trial) is further testing this hypothesis (55).

JACC Vol. 41, No. 4 Suppl S
February 19, 2003:70S–78S

Table 7. Indirect Comparison of the Relative Efficacy and Safety of Direct Thrombin Inhibitors Versus Heparin With GP IIb/IIIa Inhibitors Versus Heparin in Patients With Acute Coronary Syndrome Trials

	Direct Thrombin Inhibitors vs. Heparin				GP IIb/IIIa Inhibitors vs. Heparin			
Outcomes	DTI (n = 15,866)	Heparin (n = 14,651)	OR (95% CI)	RRR	GP IIb/IIIa (n = 18,297)	Heparin (n = 13,105)	OR (95% CI)	RRR
End of Rx*								
Death/MI	726 (4.6%)	786 (5.4%)	0.85 (0.76–0.94)	15%	1,042 (5.7%)	901 (6.9%)	0.84 (0.77–0.93)	16%
MI†	434 (2.7%)	499 (3.4%)	0.80 (0.70–0.91)	20%	821 (4.5%)	733 (5.6%)	0.83 (0.75–0.92)	17%
Death	353 (2.2%)	343 (2.3%)	0.95 (0.82–1.10)	5%	221 (1.2%)	168 (1.3%)	0.93 (0.76–1.14)	7%
30 days								
Death/MI	1,288 (8.1%)	1,285 (8.8%)	0.92 (0.85–1.00)	8%	1,980 (10.8%)	1,550 (11.8%)	0.91 (0.85–0.98)	9%
MI†	771 (4.9%)	800 (5.5%)	0.88 (0.80–0.98)	12%	1,349 (7.4%)	1,065 (8.1%)	0.92 (0.85–1.00)	8%
Death	672 (4.2%)	629 (4.3%)	0.99 (0.88–1.10)	1%	631 (3.4%)	485 (3.7%)	0.91 (0.81–1.03)	9%

Direct thrombin inhibitor and GP IIb/IIIa data adapted with permission from Elsevier Science (Lancet 2002:359:294–302 and Lancet 2002;359:189–98).

*Outcomes from direct thrombin inhibitor trials are at end of protocol-defined treatment + 24 h; outcomes from GP IIb/IIIa inhibitor trials are at five days; †direct thrombin inhibitor data are for fatal plus nonfatal myocardial infarction; GP IIb/IIIa inhibitor data are for nonfatal MI.

DTI = direct thrombin inhibitor; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; OR = odds ratio; RRR = relative risk reduction; RX = treatment.

It is interesting to compare the development of the direct thrombin inhibitor and that of the intravenous GP IIb/IIIa inhibitors. The latter agents were initially tested in patients undergoing percutaneous coronary intervention (Evaluation of IIb/IIIa Platelet receptor antagonist 7E3 in preventing Ischemic Complications [EPIC]) (56), a scenario in which patients were treated before mechanical rupturing of plaques by balloon angioplasty. In EPIC, outcomes were measured relatively early (at 30 days), and the benefits of GP IIb/IIIa inhibitors compared with heparin were relatively large (RR reduction, 35%). Subsequent trials of GP IIb/IIIa inhibitors in ACS have shown much more modest benefits, especially when percutaneous coronary intervention rates were not high (53). By contrast, although there was an early trial of direct thrombin inhibitors in percutaneous coronary intervention (Hirudin in a European restenosis prevention triaL VErsus heparin Treatment In PTCA patients [HELVETICA]) (57), outcomes were measured late (180 days). However, the 30-day outcomes for the prevention of the composite outcome of death or MI were similar in HELVETICA and EPIC (RR reduction of 39% and 35%, respectively). Most subsequent trials of direct thrombin inhibitors were in broad populations with ACS where the overall benefits, compared with heparin, are almost identical to the overall benefits of GP IIb/IIIa inhibitors versus placebo when added to heparin in patients with ACS (53). These considerations raise the possibility that direct thrombin inhibitors (at least hirudin and bivalirudin) are similar in efficacy to GP IIb/IIIa inhibitors, and further suggest that the sequence and types of trials may have affected the

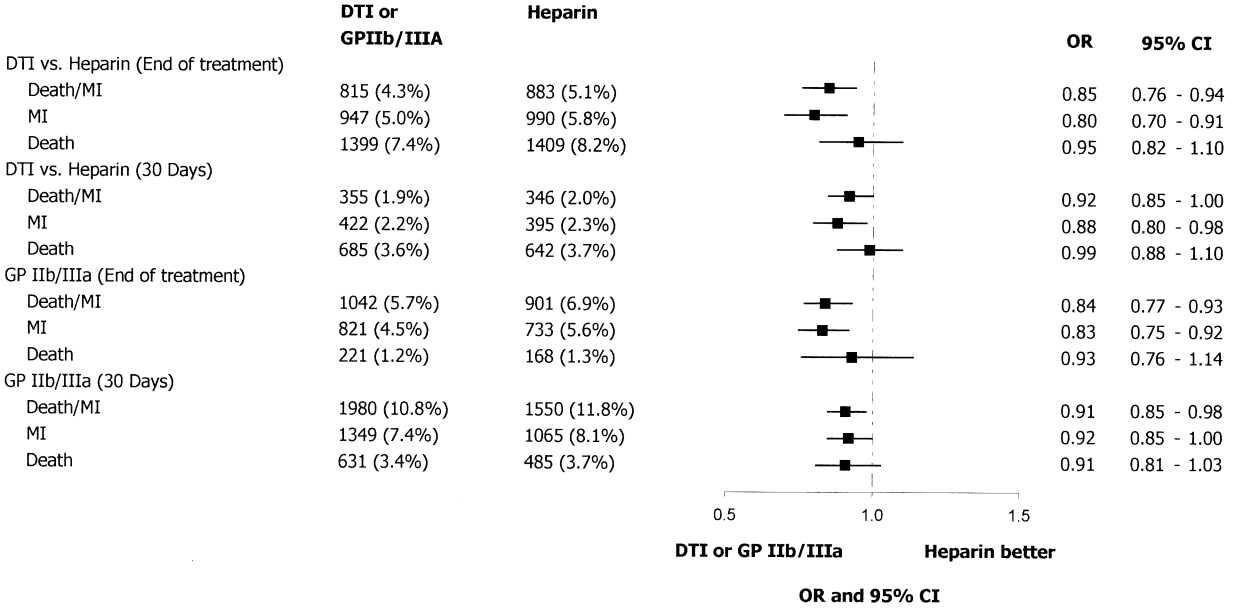

Figure 2. Indirect comparison of the relative efficacy and safety of direct thrombin inhibitors versus heparin with glycoprotein (GP) IIb/IIIa inhibitors versus heparin in trials of patients with acute coronary syndrome. Direct thrombin inhibitor and GP IIb/IIIa data are adapted from references 50 and 53, respectively. CI = confidence interval; DTI = direct thrombin inhibitor; MI = myocardial infarction; OR = odds ratio. Reprinted with permission from Elsevier Science (Lancet 2002:359;294–302 and Lancet 2002:359;189–98).

perception of their efficacy. The REPLACE trial will be of great scientific and medical importance as it is likely to further clarify the relative "merits" of these two classes of agents.

Finally, randomized trials of direct thrombin inhibitors in patients with non–ST-segment elevation ACS were performed before the widespread use of clopidogrel (58), LMWH (5), and third-generation fibrin-specific thrombolytic agents (59). Further data are required to determine the efficacy and safety of direct thrombin inhibitors in the context of current antithrombotic strategies before they can be used in routine clinical practice in patients with ACS.

Reprint requests and correspondence: Dr. John Eikelboom, Department of Medicine, University of Western Australia, Department of Haematology, Royal Perth Hospital, Wellington Street, Perth Box X2213 GPO, Perth WA 6897, Australia. E-mail: john.eikelboom@heath.wa.gov.au.

REFERENCES

1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–50.
2. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:310–8.
3. Furie B, Furie BC. Molecular and cellular biology of blood coagulation. N Engl J Med 1992;326:800–6.
4. Hirsh J, Weitz JI. New antithrombotic agents. Lancet 1999;353: 1431–6.
5. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000;355:1936–42.
6. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. J Clin Invest 1990;86:385–91.
7. Weitz JI, Leslie B, Hudoba M. Thrombin binds to soluble fibrin degradation products where it is protected from inhibition by heparin-antithrombin but susceptible to inactivation by antithrombin-independent inhibitors. Circulation 1998;97:544–52.
8. Verstraete M. Direct thrombin inhibitors: appraisal of the antithrombotic/hemorrhagic balance. Thromb Haemost 1997;78:357–63.
9. Heras M, Chesebro JH, Penny WS, Bailey KR, Badimon L, Fuster V. Effects of thrombin inhibition on development of acute platelet-thrombus deposition during angioplasty in pigs. Circulation 1989;79: 657–65.
10. Badimon L, Badimon JJ, Lassila R, Heras M, Chesebro JH, Fuster V. Thrombin regulation of platelet interaction with damaged vessel wall and isolated collagen type I at arterial flow conditions in a porcine model: effects of hirudins, heparin, and calcium chelation. Blood 1991;78:423–34.
11. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes and during percutaneous coronary intervention: design of a meta-analysis based on individual patient data. Am Heart J 2001;141:E2–6.
12. Markwardt F. Past, present and future of hirudin. Haemostasis 1991;21:11–26.
13. Wallis RB. Hirudins: from leeches to man. Semin Thromb Hemost 1996;22:185–96.
14. Maraganore JM, Bourdon P, Jablonski J, Ramachandran KL, Fenton JW. Design and characterisation of hirulogs: a novel class of bivalent peptide inhibitors of thrombin. Biochemistry 1990;29:7095–101.
15. Bates SM, Weitz JI. Direct thrombin inhibitors for treatment of arterial thrombosis: potential differences between bivalirudin and hirudin. Am J Cardiol 1998;82:12P–8P.
16. McKeage K, Plosker GL. Argatroban. Drugs 2001;61:515–22.
17. Shuman RT, Rothenberger RB, Campbell CS, Smith GF, Gifford-Moore DS, Gesellchen PD. Highly selective tripeptide thrombin inhibitors. J Med Chem 1993;36:314–9.
18. Uriuda Y, Wang QD, Grip L, Ryden L, Sjoquist PO, Mattsson C. Antithrombotic activity of inogatran, a new low-molecular-weight inhibitor of thrombin, in a closed chest porcine model of coronary artery thrombosis. Cardiovasc Res 1996;32:320–7.
19. Berry CN, Girardot C, Lecoffre C, Lunven C. Effects of the synthetic thrombin inhibitor argatroban on fibrin- or clot-incorporated thrombin: comparison with heparin and recombinant hirudin. Thromb Haemost 1994;72:381–6.
20. Zoldhelyi P, Webster MWI, Fuster V, et al. Recombinant hirudin in patients with chronic stable coronary artery disease: safety, half-life and effect on coagulation parameters. Circulation 1993;88:2015–22.
21. Fox KA. r-Hirudin in unstable angina pectoris: rationale and preliminary data from the APT pilot study. Eur Heart J 1995;16:28–32.
22. Zeymer U, von Essen R, Tebbe U, et al. Recombinant hirudin and front-loaded alteplase in acute myocardial infarction: final results of a pilot study: HIT-I (Hirudin for the Improvement of Thrombolysis). Eur Heart J 1995;16:22–7.
23. von Essen R, Zeymer U, Tebbe U, et al. HBW 023 (recombinant hirudin) for the acceleration of thrombolysis and prevention of coronary reocclusion in acute myocardial infarction: results of a dose-finding study (HIT-II) by the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte. Coron Artery Dis 1998;9:265–72.
24. Topol EJ, Fuster V, Harrington RA, et al. Recombinant hirudin for unstable angina pectoris: a multicenter, randomized angiographic trial. Circulation 1994;89:1557–66.
25. Molhoek GP, Laarman GJ, Lok DJ, et al. Angiographic dose-finding study with r-hirudin (HBW 023) for the improvement of thrombolytic therapy with streptokinase (HIT-SK): interim results. Eur Heart J 1995;16:33–7.
26. Cannon CP, McCabe CH, Henry TD, et al. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 5 trial. J Am Coll Cardiol 1994;23:993–1003.
27. Lee LV. Initial experience with hirudin and streptokinase in acute myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 6 trial. Am J Cardiol 1995;75:7–13.
28. Neuhaus KL, Molhoek GP, Zeymer U, et al. Recombinant hirudin (Lepirudin) for the improvement of thrombolysis with streptokinase in patients with acute myocardial infarction: results of the HIT-4 trial. J Am Coll Cardiol 1999;34:966–73.
29. Organisation to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Comparison of the effects of two doses of recombinant hirudin compared with heparin in patients with acute myocardial ischemia without ST elevation: a pilot study. Circulation 1997;96: 769–77.
30. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIa Investigators. Randomized trial of intravenous heparin versus recombinant hirudin for acute coronary syndromes. Circulation 1994;90:1631–7.
31. Antman EM. Hirudin in acute myocardial infarction: safety report from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9A trial. Circulation 1994;90:1624–30.
32. Neuhaus KL, von Essen R, Tebbe U, et al. Safety observations from the pilot phase of the randomized r-Hirudin for Improvement of Thrombolysis (HIT-III) study: a study of the Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausarzte. Circulation 1994;90: 1638–42.
33. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. N Engl J Med 1996;335:775–82.
34. Antman EM. Hirudin in acute myocardial infarction: Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. Circulation 1996;94:911–21.
35. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial isch-

JACC Vol. 41, No. 4 Suppl S
February 19, 2003:70S–78S

aemia without ST elevation: a randomised trial. Lancet 1999;353:429–38.
36. Sharma GV, Lapsley D, Vita JA, et al. Usefulness and tolerability of hirulog, a direct thrombin-inhibitor, in unstable angina pectoris. Am J Cardiol 1993;72:1357–60.
37. Lidon RM, Theroux P, Juneau M, Adelman B, Maraganore J. Initial experience with a direct antithrombin, hirulog, in unstable angina: anticoagulant, antithrombotic, and clinical effects. Circulation 1993; 88:1495–501.
38. Fuchs J, Cannon CPA. Hirulog in the treatment of unstable angina: results of the Thrombin Inhibition in Myocardial Ischemia (TIMI) 7 trial. Circulation 1995;92:727–33.
39. Theroux P, Perez-Villa F, Waters D, Lesperance J, Shabani F, Bonan R. Randomized double-blind comparison of two doses of hirulog with heparin as adjunctive therapy to streptokinase to promote early patency of the infarct-related artery in acute myocardial infarction. Circulation 1995;91:2132–9.
40. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Circulation 1997;96:2155–61.
41. Kong DF, Topol EJ, Bittl JA, et al. Clinical outcomes of bivalirudin for ischemic heart disease. Circulation 1999;100:2049–53.
42. 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 1995;333:764–9.
43. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty study. Am Heart J 2001;142: 952–9.
44. Antmann E, Braunwald E. A second look at bivalirudin. Am Heart J 2001;142:929–31.
45. White HD, on behalf of the Hirulog and Early Reperfusion or Occlusion (HERO) Study Group. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet 2001;358:1855–63.
46. Jang I-K, Brown DF, Giugliano RP, et al. A multicentre, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (TPA) in acute myocardial infarction: myocardial infarction with novastan and TPA (MINT) study. J Am Coll Cardiol 1999;33: 1879–85.
47. Kaplinsky E. Direct antithrombin-argatroban in acute myocardial infarction (ARGAMI-2) in late breaking clinical trials. J Am Coll Cardiol 1998;32:1–7.
48. Klootwijk P, Lenderink T, Meij S, et al. Anticoagulant properties, clinical efficacy and safety of efegatran, a direct thrombin inhibitor, in patients with unstable angina. Eur Heart J 1999;20:1101–11.
49. The TRIM Investigators. A low molecular weight, selective thrombin inhibitor, inogatran, vs heparin in unstable coronary artery disease in 1209 patients: a double-blindrandomized dose-finding study. Thrombin Inhibition in Myocardial Ischaemia (TRIM) study group. Eur Heart J 1997;18:1416–25.
50. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: a meta-analysis based on individual patient data. Lancet 2002;359:294–302.
51. Bates SM, Weitz JI. Direct thrombin inhibitors for treatment of arterial thrombosis: potential differences between bivalirudin and hirudin. Am J Cardiol 1998;82:12P–8P.
52. Mehta S, Eikelboom JW, Natarajan M, et al. Early percutaneous coronary intervention in hirudin and unfractionated heparin-treated patients with acute coronary syndromes. Eur Heart J 2002;23:17–23.
53. Boersma E, Harrington RA, Moliterno D, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189–98.
54. Verstraete M. Modulating platelet function with direct thrombin inhibitors. Haemostasis 1996;26:70–7.
55. REPLACE Study-Angiomax in the modern PCI setting. Information available at: http://www.themedicinescompany.com/. Accessed October 4, 2002.
56. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956–61.
57. Serruys PW, Herrmann JP, Simon R, et al. A comparison of hirudin with heparin in the prevention of restenosis after coronary angioplasty: HELVETICA investigators. N Engl J Med 1995;333: 757–63.
58. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, on behalf of the 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 elevation. N Engl J Med 2001;345:494–502.
59. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet 2001;358:605–13.