European Heart Journal (2002) **23,** 95–97
doi:10.1053/euhj.2001.2826, available online at http://www.idealibrary.com on IDEAL®

Editorials

r-Hirudin for percutaneous coronary interventions — time to reconsider?

See page 117, doi:10.1053/euhj.2001.2731 for the article to which this Editorial refers

Since the introduction of percutaneous coronary interventions, intravenous unfractionated heparin in combination with aspirin has remained the primary antithrombotic treatment for the prevention of periprocedural ischaemic complications for more than two decades. However, complications associated with percutaneous coronary interventions remain a clinical challenge despite improvements in interventional procedural techniques such as coronary stent implantation. Further, heparin dosing in clinical practice varies widely and the optimal level of anticoagulation is still debated[1]. In addition, patients with acute coronary syndromes associated with elevated biochemical markers are at increased risk of ischaemic complications when undergoing early percutaneous coronary interventions despite treatment with heparin and aspirin. Although low molecular weight heparins are valuable options in these patients, their role during percutaneous coronary interventions is poorly understood. Conversely, randomized trials evaluating platelet glycoprotein IIb/IIIa receptor antagonists in conjunction with aspirin and unfractionated heparin clearly show the superiority of intensified platelet inhibition on periprocedural outcomes but evidence for durable advantages over heparin is limited. However, despite their efficacy, these agents are infrequently used as demonstrated by registry data from several European countries which suggest that only 10% to 20% of patients who undergo percutaneous coronary interventions are actually given platelet GP IIb/IIIa receptor antagonists (unpublished data from the European registry of cardiac interventions 1999). Therefore, emphasis should be put either on the wider use of these agents in high risk patients or on the general improvement of baseline anticoagulation with more potent, consistent, and safer antithrombotic agents.

In the past decade, a number of agents directly inhibiting thrombin were evaluated; their clinical applications were recently reviewed[2]. Direct thrombin inhibitors such as hirudin overcome many of the limitations of heparin: (1) they inhibit fibrin-bound thrombin as well as circulating thrombin; (2) they produce more predictable anticoagulant response than heparin because they do not bind to plasma proteins and are not neutralized by platelet factor 4; (3) they have a greater ability to inhibit the activity of thrombin and platelet thrombus formation even when compared to very high doses of heparin[3]. In addition, they are potential alternatives to heparin in patients with a history of heparin-induced thrombocytopenia who require percutaneous coronary interventions[2]. Although clinical trials using direct thrombin inhibitors as an adjunct to thrombolytic therapy have revealed their narrow therapeutic window, direct thrombin inhibitors given during percutaneous coronary interventions were at least as effective as unfractionated heparin in three major trials[4–6]. Moreover, the overall results of the OASIS-2 study — a recently reported multicentre trial that randomized 10 141 patients with unstable angina or non-Q-wave myocardial infarction to receive either intravenous lepirudin or unfractionated heparin for 72 h — indicated beneficial effects of hirudin over heparin[7].

Mehta *et al.*[8] have re-addressed the issue of whether direct thrombin inhibitors are superior to unfractionated heparin in patients with acute coronary syndromes undergoing early percutaneous coronary interventions, i.e. within the first 72 h of hospital admission. Among the 1565 patients who underwent percutaneous coronary interventions during the 6-months trial period of OASIS-2, 117 (7·5%) procedures were performed within the first 72 h, i.e. during study drug infusion. The results of this retrospective analysis revealed significantly lower rates of clinical outcomes at 96 h and at 35 days in patients treated with hirudin compared to unfractionated heparin. Most interestingly, the three-fold higher risk of death or myocardial infarction in the unfractionated heparin group related to early intervention compared to conservative management was abolished in the hirudin group. These findings are very

Published online 6 September 2001.

0195-668X/02/020095+11 $35.00/0

remarkable, since the use of hirudin alone seems to neutralize periprocedural ischaemic complications in this clinical setting to a similar degree as reported with the combined use of platelet GP IIb/IIIa receptor antagonists and unfractionated heparin[9]. In addition, the results of this study are supported by findings from two previous percutaneous coronary intervention trials which evaluated direct thrombin inhibitors and demonstrated a highly significant reduction in early cardiac events. In a subgroup of 236 patients who had angina pectoris at rest during the 48 h prior to randomization, the early event rate was 21·6% in the unfractionated heparin group, 5·3% among patients receiving intravenous hirudin for 24 h, and 12·3% among patients receiving intravenous and subcutaneous hirudin for 72 h[4]. Likewise, in 704 patients with unstable postinfarction angina, bivalirudin compared to unfractionated heparin treatment resulted in a significantly lower rate of early death and myocardial infarction (9·1% vs 14·2%), suggesting that ischaemic complications of percutaneous coronary interventions, particularly in this clinical setting, are thrombin-mediated[5]. However, as the authors of the present study admit, an important limitation of their research is the small study sample and the retrospective nature of their comparison even though they adjusted for propensity to undergo early percutaneous coronary interventions. Other important drawbacks of this comparative study are that the protocol allowed the use of open label unfractionated heparin during percutaneous coronary interventions in both treatment groups (which occurred in 27%) and that data on monitoring of the level of anticoagulation in the control group were not reported.

The importance of the issue of the optimal level of anticoagulation with unfractionated heparin during percutaneous coronary interventions has recently been raised following a comprehensive analysis of pooled data from six randomized, controlled trials of novel antithrombotic regimens for percutaneous coronary interventions in which unfractionated heparin constituted the control arm. Importantly, patients with acute coronary syndrome represented 60% of the population studied. The results of this analysis, which included 5216 patients, indicate that in order to achieve the maximum clinical efficacy with unfractionated heparin, the effective activated clotting time (95% assayed by Hemochron®) needs to be 350 s or greater[1]. However, at this level of anticoagulation, major bleeding complications increase towards unacceptably high rates. Although lower doses of unfractionated heparin are safe and effective when combined with abciximab[10], the current trend of downward titration of heparin dosage may compromise antithrombotic efficacy. By contrast, the direct antithrombin bivalirudin has demonstrated a more favourable safety profile than heparin at high levels of anticoagulation[5]. In the OASIS-2 and GUSTO-IIb trials, lepirudin was associated with an increase in bleeding events; but there was no excess in life-threatening episodes or strokes[6,7]. Moreover, although the HELVETICA trial demonstrated higher rates of major and minor bleeding complications associated with hirudin treatment, major haemorrhage was significantly reduced with hirudin compared to heparin when the duration of treatment did not exceed 24 h[4].

A concern in the clinical administration of any protein-based agent such as hirudin is the possibility of antibody formation which has been reported in about 40% of patients treated with lepirudin. However, antihirudin antibodies paradoxically enhance the pharmacological effect of lepirudin in a subset of patients, but otherwise seem to be of low clinical importance[2]. In the OASIS-2 trial, the incidence of thrombocytopenia ($>100\,000\ .\ \mu l^{-1}$) with lepirudin was similar to that with unfractionated heparin (1%).

Thus, has the time come to replace unfractionated heparin with direct thrombin inhibitors in patients with acute coronary syndrome? The answer is not yet. Nevertheless, in the search for an unfractionated heparin replacement with newer antithrombotic agents for improved anticoagulation with percutaneous coronary interventions, the encouraging findings of this study, combined with the results of previous clinical trials, should prompt large-scale trials to assess the role of hirudin in the current era of percutaneous coronary interventions. Given the promising effects of combined antiplatelet therapy with clopidogrel[11] and aspirin and the significant reduction in ischaemic events as demonstrated by the CURE trial[13], dual antiplatelet coverage should be considered the baseline treatment during the periprocedural period and up to 9–12 months thereafter. In patients with acute coronary syndrome undergoing early coronary interventions, hirudin should be compared with high-dose unfractionated heparin at an optimal level of anticoagulation (activated clotting time >350 s) or with low-dose unfractionated heparin (activated clotting time 250–300 s) in combination with platelet GP IIb/IIIa receptor antagonists. Although comparative trials are planned[12], results of the relative safety and efficacy of hirudins and platelet GP IIb/IIIa receptor antagonists are not yet available.

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European Heart Journal (2002) **23,** 97–98
doi:10.1053/euhj.2001.2810, available online at http://www.idealibrary.com on IDEAL®

Stent thrombosis: '(ultra)sound the warning'

See page 124, doi:10.1053/euhj.2001.2707 for the article to which this Editorial refers

Since stenting has become the dominant therapy in interventional cardiology, the most feared complication has been stent thrombosis. Even though glycoprotein IIb/IIIa agents have built their reputation on preventing thrombotic events following coronary stenting, these events are rarely stent thrombosis. Since the combination of aspirin and thianopyridines replaced anticoagulation as the stent adjunct of choice, acute or subacute stent thrombosis has been infrequent in most clinical practices. Nonetheless, this event does occur and was reported in 2·3% of patients treated in a large registry[1]. Review of the NHLBI Dynamic Registry of patients treated in 1997–1999 shows that abrupt closure occurred in 1·8%[2]. The study by Uren *et al*. set out to collect cases of in-stent thrombosis, in which intravascular ultrasound had been performed in order to identify features associated with this complication[3]. The conclusion that ultrasound identified many more abnormal features associated with stent thrombosis than were identified by angiography was probably evident before this survey was done. Angiographically evident abnormalities may have led to further interventions and therefore the relative absence of those features in this study is not surprising. In addition, some features identified by ultrasound are not identifiable by angiography, such as the subtle degrees of stent expansion, cross-sectional area measurements, malapposition, thrombus formation, and minor tears or dissections. The important question raised by the study is whether and how often intravascular ultrasound should be used to detect and conceivably alter these features. Our knowledge of these defects and the assumed mechanism whereby they produce stent thrombosis is clearly expanded by this communication. It is unclear, however, whether altering all or some of these features would reduce the dreaded complication. Although stent under-expansion was common in this group, it was not more common than

Published online 2 October 2001.