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Antithrombotic therapy in PCI: why not heparin?

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In this issue of the journal, Schulz and colleagues present new data describing one-year outcomes from the ISAR-REACT 4 trial.

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This study recruited patients undergoing PCI in the setting of a non-ST-elevation, acute coronary syndrome presentation. Subjects were randomised to two different periprocedural antithrombotic regimes: bivalirudin or combination therapy with unfractionated heparin (UFH) and abciximab. The reported rates of death, non-fatal myocardial infarction and target vessel revascularisation are near identical.

It is interesting to note that an increased risk of bleeding, observed at 30 days[1], in patients receiving abciximab therapy, did not result in differences in key outcome measures at one year. There is now general agreement that bleeding can be associated with less favourable outcomes, including increased rates of ischaemic events and, in the HORIZONS-AMI trial (examining the same therapies in the ST-elevation setting), an impact on all-cause mortality[2].

More puzzling to many observers has been the emergence of bivalirudin as an increasingly popular mainstream therapy in PCI. The drug is not new, and has been evaluated against UFH in a variety of clinical settings and indications for nearly 20 years. It is interesting to consider why bivalirudin has emerged as a popular, and apparently efficacious, clinical agent so late in the natural history of its market availability.

In trying to decide the optimum adjunctive regime for antithrombotic therapy in PCI, we face a complex range of choices. We must not only select individual agents, but consider the safety and efficacy implications of combination therapy. The number of options is substantial and potentially confusing. In an attempt to make sense of the situation, we need to propose a more systematic approach to our reading of the current evidence base.

In the procedural phase and beyond, some form of dual, oral antiplatelet therapy is currently the accepted standard[3,4]. The next choice is in respect of our antithrombin agent. Here we face a mutually exclusive choice among three main agents: UFH, low molecular weight heparin (LMWH), and bivalirudin. LMWH has a number of potential advantages over UFH and, in some studies in PCI, its routine application has secured clinical advantage over the more traditional agent[5,6]. There are, however, no substantial comparative studies between LMWH and bivalirudin. Beyond acknowledging the potential importance of LMWH, and that more studies are justified, we will not consider it further.

Finally, we have the option of using parenteral antiplatelet therapy with a glycoprotein (GP) IIb/IIIa receptor antagonist. It is important to note that, in contrast to our initial treatment described above, the use of this drug class has never been considered "mandatory" for universal application and, just as importantly, is potentially applicable with any other combination of agents.

A growing role for bivalirudin has been supported by trials which, like ISAR-REACT 4[1], randomised patients to treatment with bivalirudin or fixed combination therapy with heparin and a GP IIb/IIIa inhibitor[2,7,8]. This design compromises one of the core principles of scientific experimentation. We generally seek to compare mutually exclusive options for a single factor – in our case one specific aspect of the treatment plan. We use intelligent study design and randomisation with the aim of creating study groups that are balanced in all respects, except for the subject under investigation. Let us consider some specific issues.

Can GP IIb/IIIa inhibitors be used in combination with bivalirudin?

This combination is an accepted option. Bail-out GP IIb/IIIa inhibitor therapy in combination with bivalirudin has been an option in all studies and in HORIZONS-AMI was used in about 7% of patients randomised to bivalirudin[2]. In ACUITY, the combination was used as one of the three study groups created at randomisation[7]. Results in this group were very similar to those in patients receiving UFH plus a GP IIb/IIIa inhibitor, both in terms of ischaemic outcomes and bleeding complications.

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Is "UFH plus mandated, unselected GP IIb/IIIa inhibitor therapy" an accepted, universal treatment strategy?

The short answer is no. Unselected routine use never became established, even at the zenith of GP IIb/IIIa inhibitor popularity. There has been a more than 50% decrease in the use of these agents in the UK since 2005[9] and the rest of Europe is witnessing similar trends. The clinical utility of GP IIb/IIIa inhibitors depends on the risk profile and specific features of the presentation or case[10-18]. Even in the setting of primary PCI (PPCI), their use is recommended in specific indications such as slow or no-reflow after PCI, the presence of large thrombus burden or inadequate antiplatelet loading during PPCI[19,20]. The potent anti-ischaemic efficacy of this drug class must be balanced against the risk of bleeding complications and a selective approach to administration is now the clinical norm.

The advent of more effective oral antiplatelet therapy with a more rapid onset of action, as well as early and high-dose loading regimes may have reduced the potential for incremental anti-ischaemic protection with GP IIb/IIIa inhibitors, whilst retaining the potential for bleeding complications.

Other practice changes over the years since their initial (and, at the time very welcome) introduction may also have had an impact. Thrombus aspiration is in widespread use and will, to some extent, impact on the thrombotic burden. Improved practice patterns and public health measures mean that patients are receiving interventional management earlier in the clinical course when "fresh thrombus" may be easier to treat than after propagation and organisation.

Do we have reason to believe bivalirudin is a more effective antithrombotic agent than heparin?

There are a number of aspects of the pharmacology of bivalirudin that hold out the promise of improved efficacy over the rather "messy" chemistry of the heparins. However, bivalirudin has failed to establish any clear advantage in terms of anti-ischaemic efficacy[1,2,7,8,21-24].

Three major RCTs have performed a direct comparison between heparin and bivalirudin in an elective PCI setting. The first, HAS (Hirulog Angioplasty Study, 1995), concluded that there was no significant difference between the two trial medications for any of the efficacy endpoints[22]. This trial was re-analysed six years later and was presented as BAT (Bivalirudin Angioplasty Trial)[25]. Key features like the number of patients analysed, analysis time points and primary outcome measures were changed, making the results questionable.

REPLACE-1 in 2001 showed that a head-to-head comparison of bivalirudin and "moderate dose" heparin (70 U/kg) in an elective PCI setting resulted in no differences in bleeding or ischaemic complications[24]. The investigators in REPLACE-2 added mandatory GP IIb/IIIa inhibitor administration to the UFH arm and the results, not surprisingly, showed more bleeding complications in this arm as compared to bivalirudin monotherapy[8].

ISAR-REACT 3 (2008)[23] used a significantly higher dose of UFH (150 U/kg) than that in routine use or suggested by current international guidelines[4]. The results again showed no differences in ischaemic outcomes but more bleeding complications in the UFH arm. There is an established relationship between UFH dose and the incidence of bleeding complications. The investigators later conducted a further study, ISAR-REACT 3A, recruiting consecutive patients in a third arm receiving a lower dose of UFH (100 U/kg)[26]. They compared outcomes to the historical controls in the ISAR-REACT 3 trial. They concluded that there was no longer a significant difference in the bleeding outcomes between the patients who received bivalirudin in ISAR-REACT 3 when compared to the patients who received the lower dose of UFH (100 U/kg).

There is no real evidence base to suggest that bivalirudin confers superior anti-ischaemic protection over and above UFH alone. In studies designed to test the efficacy of antithrombin monotherapy against protocol-specified, combined use with GP IIb/IIIa inhibitors, there would have been a strong case to include a "heparin only limb" or to consider a factorial design. Most of the recent bivalirudin studies do not give us any insight into how UFH may have fared as a comparator agent.

Are there any problems with bivalirudin therapy?

There is the issue of cost. Bivalirudin costs about 400 times as much as UFH and a potential cost saving of 500 to 1,000 euros in each case must be attractive. Bivalirudin must be reconstituted at the time of administration and, together with the need to maintain an intravenous infusion, this makes its use a little more labour-intensive and inconvenient. In the event of important acute bleeding there is no agent for immediate reversal, but the shorter half-life means that the antithrombotic effect will be lost over the next few hours.

Both ACUITY[7] and HORIZONS-AMI[2] reported a significantly higher incidence of acute stent thrombosis in the patients who received bivalirudin in comparison to UFH. Following the data from the HORIZONS-SWITCH analysis[27] and a large analysis from the SCAAR registry[28], a growing school of thought is suggesting that administration of UFH along with bivalirudin may be required to reduce acute thrombotic events[29]. It is important to know if heparin alone could be sufficient to do the job.

So what about monotherapy with unfractionated heparin?

A report from the SCAAR registry, presented at the recent EuroPCR conference, analysed 41,537 patients who received UFH or bivalirudin during PCI. The study reported an adjusted odds ratio for 30-day mortality in favour of UFH (1.53 for complete case analysis)[30]. At the conference the designs of two important trials that may throw more light on this question were also presented: EUROMAX[31] and HEAT-PPCI[32]. We await the results with interest.

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