Acute coronary syndromes: optimizing the therapeutic options

See page 239, doi:10.1053/euhj.2001.2736 for the article to which this Editorial refers

What do we know?

The 1980s were the era for important therapeutic developments in the management of patients with acute myocardial infarction. Multiple large benchmark trials were published that had simple messages directing the use of thrombolytics in clearly identifiable patients with undeniable presenting features. Clinical uptake was rapid and although issues such as the best agent and adjunctive therapy to improve outcome continue to be unresolved, the perceived overall impact of therapy was relatively uncontested. During the late 1990s, however, the focus of attention was directed more toward non-ST elevation acute coronary syndromes; the grey, potentially preinfarct clinical area comprising heterogeneous groups of patients with varying degrees of acute coronary closure. There are a number of important differences between the two syndromes that make the therapeutic messages from trials in non-ST elevation acute coronary syndromes less easy to apply. In AMI, prospective large randomized trials needed to address one therapy for a single specific time related and easily diagnosed event. The evidence base for treatments in acute coronary syndromes is less straightforward. Importantly patients may at different times be at different risk of further adverse outcome. Treatments need to be directed towards patients as they primarily present, and secondarily towards improving subsequent prognosis, perhaps by dealing with the underlying plaque with percutaneous coronary intervention.

The early prospective randomized trials with the glycoprotein IIb/IIIa receptor blockers were undertaken in patients with acute coronary syndromes undergoing intervention[1], and these clearly showed that such patients benefited from the use of the monoclonal antibody, ReoPro. However, in patients presenting with acute coronary syndromes, who have not as yet, or who do not undergo intervention, identifying those who are most likely to benefit from administration of the glycoprotein IIb/IIIa receptor blockers (non-resolving or recurrent chest pain; recurrent or dynamic ECG changes and most importantly a positive test for troponin) has been based in part on retrospective post hoc subgroup analysis of the various studies. Despite this, European guidelines based on the published data have been issued[2] and make a reasonable case for the use of the various agents in ‘high risk’ patients presenting with acute coronary syndromes. Patients identified at highest risk benefit most; in the PRISM (aggrastat vs placebo) troponin I and troponin T reliably identified
high-risk patients who would benefit from Tirofiban, be they managed medically or by revascularization[3]. Thus for patients randomly assigned to active treatment the pre-percutaneous coronary intervention absolute benefit (death or enzyme defined acute myocardial infarction) has been shown to be 1·4% (4·3% vs 2·9%: placebo vs treatment P=0·001), during percutaneous coronary intervention 3·1% (8·0% vs 4·9%) P=0·001 and post procedure 0·3% (1·6%–1·3%) (ns) [3]. Therefore even though the overall adverse event rate is less pre-percutaneous coronary intervention than as a result of the procedure, provided that the high risk patient can be identified (albeit with a need at times for two troponin tests) benefit seems to be gained from administration of either of the two synthetic ‘small molecule’ agents. For reasons that are still not clear benefit in medically treated appears not to hold for abciximab [6], although in the CAPTURE[3] trial a pre-intervention benefit was shown in those patients selected to go onto percutaneous coronary intervention. Thus there are inconsistencies and uncertainties. Some would even argue that there is no real benefit shown in those treated medically as opposed to those treated in their ‘medical-phase’ prior to intervention.

In those patients undergoing percutaneous coronary intervention the situation at first appears clearer. Percutaneous coronary intervention disrupts plaques and the incidence of subsequent events are reduced with glycoprotein IIb/IIIa receptor blockers. Whether the enzyme release, which was what drove the end points in the trials, has true longer-term clinical significance (‘enzyme bumps’ or ‘prognostically important micro-infarcts’) has been much debated. Consensus generally supports the belief that such enzyme release is bad and thus the use of glycoprotein IIb/IIIa receptor blockers is recommended. Again the situation is confused, however, by the fact that while all three agents have shown benefit compared to placebo, the TARGET trial[6] appeared to demonstrate early superiority of abciximab over aggrastat (event rate: 5·7% vs 7·2%, respectively) and no comparison is available between Integrisilin and the other agents. Additionally for good reasons a significant number of clinicians continue to be unconvinced of the value of the use of such agents in routine ‘cold’, planned percutaneous coronary intervention, despite the recommendations of Health and Technology Assessment Groups such as the National Institute for Clinical Excellence: the incidence of enzyme rise being in some clinician’s opinion, less significant and less frequent. Careful subgroup review of all the trials indicates that only one (EPISTENT[7]) demonstrated benefit in routine cases and even then there may have been case selection with those who would normally receive glycoprotein IIb/IIIa receptor blockers not being randomized. The ESPRIT trial[8] designed as a planned percutaneous coronary intervention study in fact showed benefit in the ‘unstable angina’ group only (stable angina, 25% reduction 7·2% vs 5·4% P=0·029; ‘acute coronary syndromes’ >2 days 48% reduction 11·1% to 5·7% P=0·013).

### Why do percutaneous coronary intervention?

If percutaneous coronary intervention causes further enzyme release in those patients with already jeopardized myocardium (i.e. acute coronary syndromes patients) why do it? The overall value of intervention in acute coronary syndromes has been studied in a number of trials, and the widespread introduction of stenting has reduced the downside of intervention in such patients, as shown in the subgroup analysis of the BENESTENT II trial, where stent implantation appeared safer than balloon alone. Intervention even without the use of glycoprotein IIb/IIIa receptor blockers has, in observational studies, been shown to be associated with a good outcome. Marzocchi et al.[9] reviewed the outcome of stenting in 266 patients with ‘unstable angina’ and reported one death and a stent closure rate of 1·5%. This was supported by the results from the CAPTURE trial and the FRISC II study where at 1 year the invasive approach saved 1·7 lives for every 100 patients treated.

The messages appear to be that acute coronary syndromes patients managed with standard treatment i.e. aspirin and heparin have a poor outcome (PRAIS-UK)[10] and that pre-intervention treatment with the glycoprotein IIb/IIIa receptor blockers synthetic small molecule agents reduces enzyme defined myocardial infarction. Intervention appears to be an important part of the treatment strategy but also that intervention can be made safer by being performed under glycoprotein IIb/IIIa receptor blocker cover, which reduces the higher enzyme-defined myocardial infarction rate seen with percutaneous coronary intervention. Unlike acute myocardial infarction, there are with acute coronary syndromes two, and following CURE now three, interacting therapies to thus be considered. The issues that need consideration are: should those patients admitted with a diagnosis of acute coronary syndromes and deemed high risk undergo intervention during that admission and if so whether it should be done during glycoprotein IIb/IIIa receptor blocker infusion. If an infusion is...
running while either of the small molecules could be continued, (PRISM PLUS and PURSUIT trials) some would contend that in the light of the TARGET study the best agent for percutaneous coronary intervention is abciximab only (changing at the point of percutaneous coronary intervention from small molecule infusion). Should clopidogrel be given in high-risk patients only after angiography to reduce bleeding risk in those requiring coronary surgery?

**Treatment options**

In the current issue, Simoons and colleagues[11] have attempted to throw some light on one of these issues. They ask whether patients benefit from the intervention being undertaken during the period of the infusion. The importance of the subject is not inconsiderable since most patients present to centres without interventional facilities and urgent transfer of patients is already difficult, even without the excess burden the need for peri-infusion transfer would generate. What if the patient cannot be transferred within the 96 h maximally allowed for the infusion and then settles clinically? Should they still be transferred and if so when and what agent should be used to reduce the risk of intervention; the same, small molecule or only ReoPro? Should the infusion be fractionated (48 h early and recommencement on transfer)?

In their report the authors attempt to assess the optimal timing of intervention in patients on glycoprotein IIb/IIIa receptor blockers by undertaking a retrospective analysis of the PURSUIT trial data. They divide patients into four groups of approximately equal size according to the timing of intervention; thus the outcome was assessed in those patients who had intervention within 24 h (day 1), between day 2–3, between day 4–7 and between days 8–30. These appear to be generally rather arbitrary time divisions. There are further patient subdivisions; treated vs placebo and timing of complications (pre-, peri- or post-procedure). All this makes the data a little difficult to follow and leads to some quirks. The situation is made more difficult by the intervention in the original trial being operator driven, and so patients taken to the catheter lab early may have been less well. Unfortunately the data does not tell us about ongoing pain between the groups and troponin levels were not routinely measured in 1996. Those taken to the cath lab early appear in the demographic data only to have a significant excess of previous percutaneous coronary intervention.

One message from their pre-procedural acute myocardial infarction data appears to be that the longer you wait for intervention the higher the risk of infarct. Drug infusion confers benefit during intervention predominantly during the first 24 h. If you have late intervention then having had the drug early appears not to be protective i.e there appears to be no plaque stabilization or longer-term passivation. Patients who underwent intervention on day 1 suffered significantly less peri-procedural events (death or acute myocardial infarction 12.1 vs 7.2 P=0.039) but only because the placebo event rate was high at this time. Why there appeared to be no benefit on day 2–3 (8.5% vs 8.4%) when the treatment was presumably still being given is less clear. Peri-procedural events also appeared to occur less often the later the intervention was undertaken. Presumably the longer you wait for intervention the more the likelihood that the patient will have selected themselves out to have had their peri-procedural event irrespective of treatment group. It is interesting that if intervention was undertaken beyond day 1 late risk of intervention was high irrespective of earlier treatment. Although there is no comparable data for non-intervened patients, whose risk rate may be higher still, and even if the events are driven by enzyme rise, a rate of 17%–18% at 30 days with intervention does question whether such patients benefit from intervention on that admission. The most worrying suggestion from these data is that benefit only accrues when intervention is undertaken after day 1 of the infusion. Since the infusion was for 72 h, does this mean that the pharmacological effects wear off? Is it worth transferring a patient for intervention if it cannot be done within 24 (or at most 48) h of starting the infusion? Of course the reason that there are inconsistencies relates to the fact that this is a retrospective analysis, with arbitrary time divisions. It may have been much better to have considered outcome both on and off the infusion and then at set times time periods following completion of therapy.

**Early to the cath lab: how early is early?**

So what does this paper tell us and can it help direct management? Should we now aggressively strive to get our patients to the cath lab within 24 h of starting the small molecule infusion and if we believe it to be correct for Integrilin as per this Simoons paper, would it hold for Aggrastat as well? Although this was not a randomized prospective study, the data
presented suggests that intervention probably carries less risk if undertaken shortly after the commencement of glycoprotein IIb/IIIa receptor blockers. It should encourage us to focus on identifying high risk patients and to consider their treatment as a strategy that involves administration of glycoprotein IIb/IIIa receptor blockers and intervention undertaken as early as is possible. Whether the information contained in this paper is sufficient to aggressively prioritize patients within an already over-stretched system that needs to accommodate routine cases, potential primary angioplasty, rescue angioplasty and the myriad of other cases is less clear. Unfortunately it also doesn’t tell us whether late intervention should be covered by a second infusion and if so what this should be. The data positively muddies the waters with regard to what to do if either a patient cannot be intervened during the infusion period and/or they settle medically. The British Cardiac Society Guidelines suggest a further exercise test to stratify the patient once they have settled, although many would believe that once a patient has been categorized as high risk they should not be further de-categorized. If a patient is transferred on a small molecule should they have their intervention on this or should it be changed to a monoclonal antibody. How long post-procedure should the small molecule be continued is currently arbitrary and based on trial criteria, which differ between agents. What heparin and how much is required in these circumstances is also under current review? Are the two small molecules equally efficacious when used to settle patients with acute coronary syndromes and when continued during the intervention? Where does clopidogrel fit in? Many of these questions will only be answerable with prospective randomized trials. However further head to head studies are unlikely and careful audit and registry data is essential.

In the meantime Simoons and colleagues have at least started to raise awareness of some of the problems associated with the uptake of therapeutic strategies for acute coronary syndromes. Despite widespread use of thrombolytic treatment for acute myocardial infarction further appropriate trials continue to be undertaken to try to improve and refine therapy. The cardiological community should strive to ensure the same goes for the management of acute coronary syndromes.

A. H. GERSHLICK
Department Cardiology,
University Hospitals of Leicester, U.K.

References