Bivalirudin, abciximab and clopidogrel in modern PCI: interpretation and experience from King's College Hospital

Background

Platelet inhibition is a prerequisite for successful percutaneous coronary interventions (PCI). Aspirin was the first antiplatelet agent with proven benefit in ST-elevation infarction (STEMI) in the era of thrombolysis, significantly lowering death rate and the recurrence of ischaemic events.[1] It has since been widely accepted as an adjunct treatment in ischaemic heart disease. The advent of thienopyridines such as ticlopidine or clopidogrel has further enriched our armamentarium of antiplatelet drugs.

All platelet agonists eventually lead to activation and enhanced expression of the GP IIb/IIIa receptor on the platelet surface, leading to the formation of platelet-rich clots. Therefore, drugs have been developed to directly block the GP IIb/IIIa receptor, aiming to achieve an even stronger inhibition of platelet activity. Eptifibatide, tirofiban and abciximab are the currently available drugs. The strongest evidence for efficacy in stable and unstable angina and ST-segment elevation is for abciximab,[2] which is now most frequently used in the UK. After intravenous injection of a bolus of 0.25 mg/kg, it exerts its full antiplatelet action within 10 minutes, blocking about 80% of all GP IIb/IIIa receptors and prolonging bleeding time up to 30 minutes.

There are some controversies about the usefulness of GP IIb/IIIa antagonists in times of routine administration of aspirin and clopidogrel and the widespread use of coronary stents. Indeed, most studies on GP IIb/IIIa antagonists have been conducted without clopidogrel or ticlopidine pretreatment. This has led to the suggestion that GP IIb/IIIa antagonists are no longer required and it does appear that their use is falling in the UK. In addition, the availability of new direct thrombin inhibitors has challenged the marketplace for the GP IIb/IIIa antagonists. We therefore discuss some recent trials on the evidence of GP IIb/IIIa use in patients with stable coronary heart disease and patients with ST-segment elevation pretreated with aspirin and clopidogrel. In addition, we describe our early experience with the direct thrombin inhibitor bivalirudin.

Stable angina

ISAR-REACT has shown that low and intermediate-risk patients with stable angina undergoing PCI do not profit from abciximab when pretreated with aspirin and clopidogrel.[3] As a consequence of this study, the same research group examined diabetic patients, who are known to be at higher risk for recurrent events. ISAR-SWEET showed that the use of abciximab in diabetic patients undergoing elective PCI had no impact on death or myocardial infarction when pretreated with aspirin and clopidogrel,[4] although the suggestion that abciximab may act as an anti-restenotic agent in diabetics was once again raised. This trial was performed using bare metal stents and most commentators believe the restenosis argument would have been eliminated by the use of drug-eluting stents (and therefore abciximab would confer no additional benefit in relatively stable diabetics undergoing angioplasty).

These recent results have led to a reduction in the use of GP IIb/IIIa antagonists in patients with stable angina, even in patients previously thought to be at higher risk for peri-procedural complications.

Unstable angina and STEMI

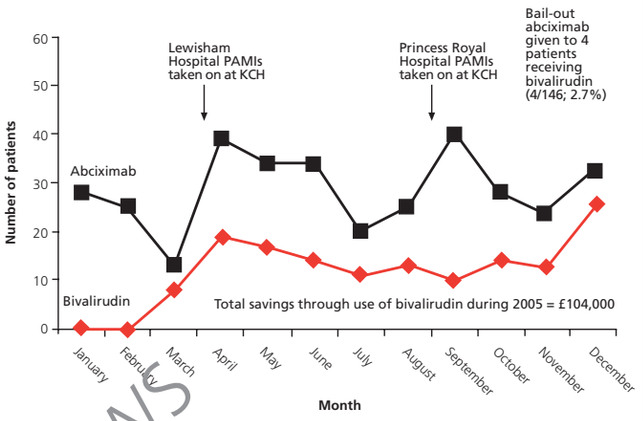
The available data on the use of abciximab in patients with STEMI pretreated with dual oral platelet inhibitors are somewhat controversial. The CADILLAC trial compared stenting and PTCA covered by abciximab or placebo in patients with acute myocardial infarction. Practically all patients were pretreated with aspirin and clopidogrel and were randomised to abciximab or placebo after the diagnostic angiogram. The trial did not show any reduction in the composite end point of death, myocardial infarction and ischaemia-driven target vessel revascularisation at six months and one year in patients given abciximab, compared to placebo.[5] There was no difference in restenosis rates.

The ADMIRAL trial randomised 300 patients with STEMI to stenting plus abciximab or stenting alone.[6] Patients were not routinely pretreated with thienopyridines but received abciximab or placebo before sheath insertion. Ticlopidine 250 mg twice daily was only given after stent placement and continued for one month. The composite end point of death, urgent target vessel revascularisation and myocardial infarction was reached in 6% of patients in the abciximab plus stent group versus 14.6% of patients in the stent only group at 30 days (p=0.01). The difference was maintained at six months (7.4% *vs.*15.9%). Of course, it is not possible to directly compare these two studies due to possible differences in baseline risk.

A substudy of the ADMIRAL trial showed that abciximab was only associated with an improved outcome when given early, i.e. in the mobile coronary unit or emergency room. When administered later, in the coronary care unit or the catheter laboratory, there was no significant benefit. This may explain why there was no difference seen in the CADILLAC trial where patients received their abciximab after the diagnostic angiogram, prior to proceeding to stent placement. A further explanation could be the preprocedural dual antiplatelet therapy used in CADILLAC, minimising the possible additional benefit of abciximab.

Until further studies are available, there is still a place for abciximab in STEMI, even in times of routine aspirin and clopidogrel pretreatment, mainly because of concerns about sufficient loading with oral antiplatelet drugs in an emergency situation such as a STEMI. GP IIb/IIIa antagonists are often used in a non-evidence-based way, after the angiogram. When the use of abciximab is considered, it should be administered early, preferably in the emergency room.

Figure 1. Catheter laboratory use of abciximab and bivalirudin at King's College Hospital during 2005



Key: PAMI = primary angioplasty for myocardial infarction; KCH = King's College Hospital

The position of direct thrombin inhibitors

The current debate about the value of GP IIb/IIIa antagonists in patients pretreated with clopidogrel and aspirin has raised the question of whether additional antiplatelet therapy is necessary. Study results cannot always be extrapolated into clinical practice. In some situations, e.g. rotablation, multivessel PCI, main stem interventions, and treatment of bifurcations, an additional more potent anticoagulant or antiplatelet agent is desirable. This has led to a search for alternative (and cheaper) drugs for patients who are deemed at high risk for periprocedural complications. The direct thrombin antagonist bivalirudin is a drug with such potential.

Bivalirudin directly inhibits the key protein of the coagulation cascade and has more predictable effects than heparin, which acts via antithrombin III. Further disadvantages of heparin are that the heparin-antithrombin-III-complex is unable to inactivate fibrin-bound thrombin, whereas bivalirudin inactivates even fibrin-bound thrombin. Heparin can also activate platelets and may also lead to heparin-induced thrombocytopenia (HIT). Since thrombin is a potent platelet activator, bivalirudin also has an antiplatelet action via inhibition of thrombin. There is no antidote for bivalirudin but due to its short half-life (about 30 minutes), haemorrhagic complications are rare.

Bivalirudin has been shown to be equivalent to abciximab in a low- and moderate-risk group of patients undergoing elective and urgent PCI with regard to ischaemic events in the REPLACE-2 trial, and was associated with significantly less bleeding complications.[7] Thus, bivalirudin could be considered a potential substitute for heparin and additional intravenous antiplatelet agents in high-risk patients undergoing PCI, in patients in whom heparin cannot be given due to HIT or in those at increased bleeding risk.

There are also important financial considerations as the cost of bivalirudin in the UK is generally about a third of that of abciximab. Arguments with regard to cheaper GP IIb/IIIa receptor inhibitors (the small molecules) are less strong.

The bivalirudin experience at King's College Hospital

Based on the results of REPLACE-2, we started to substitute abciximab with bivalirudin in high-risk patients undergoing PCI for stable and unstable angina. This led to reduced use of abciximab during the first three months of 2005. From April 2005, however, the King's primary angioplasty service expanded rapidly to include patients from two of its local district general hospital referral centres who are diverted directly to the King's catheter lab. This led to a corresponding rise in the use of abciximab (figure 1). By giving bivalirudin instead of abciximab (outside the setting of acute myocardial infarction), it was possible to save £104,000 during 2005. During this period, 146 patients (mean age 70 years) were treated with bivalirudin, with a wide spectrum of clinical presentations (table 1). All patients received a loading dose of clopidogrel prior to the intervention or had established clopidogrel therapy. In addition, abciximab bail-out (in line with the REPLACE-2 study protocol) was given in only four patients receiving bivalirudin. The outcome was generally good with a high procedural success rate and no abrupt vessel closures. In one patient, there was a main stem perforation during rotablation, which required pericardial drainage and implantation of a covered stent to seal the leak. Bivalirudin was stopped at

Table 1. Clinical presentations of patients treated with bivalirudin in King's College Hospital during 2005

Patient characteristics (n=146)	
Age (years)	41–91 (mean 70)
Men/women	105/41
Diabetes	35 (24%)
Indication for bivalirudin use	
ACS	78
- PAMI	15
- NSTEMI	63
Stable angina	68
Intervention details	
Rotablation	33
Multivessel interventions	72
Main stem interventions	15
Chronic occlusions	22
PCI on vein grafts	7

Key: ACS = acute coronary syndromes; PAMI = primary angioplasty for myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PCI = percutaneous coronary intervention

the moment of perforation and there were no further complications. Another patient suffered from duodenal bleeding with haemorrhagic shock after a rotablation procedure and died two weeks later of multiorgan failure. Long-term follow-up of these patients is not yet available but the low periprocedural complication rate is promising.

STEMI: abciximab saviour?

Whereas the use of abciximab is decreasing steadily in current interventional practice, its saviour could be the continuing rise in primary angioplasty procedures performed in the UK. Due to the emergency situation, patients may not be sufficiently loaded with oral clopidogrel before primary angioplasty is undertaken. Thus a GP IIb/IIIa antagonist is required for maximal platelet inhibition. We still have no prospective data on the use of bivalirudin in this setting but there is an interesting retrospective study on 91 patients, all pretreated with aspirin and clopidogrel.[8] They received bivalirudin during primary angioplasty for myocardial infarction (PAMI) and the cardiac outcomes were comparable to the CADILLAC and ADMIRAL trials, but with considerably less bleeding complications.

Preliminary results of the Bivalirudin In Acute Myocardial Infarction (BIAMI) study have also been presented recently at the Transcatheter Cardiovascular Therapeutics (TCT) meeting.[9] This was a single arm, open label study in patients who presented with an acute STEMI and underwent primary angioplasty. Patients received bivalirudin instead of abciximab. Baseline characteristics were similar to the patients in the CADILLAC trial. The combined end point at 30 days (death, reinfarction, disabling stroke and ischaemic target vessel revascularisation) was reached in 3.6% of patients in BIAMI compared to 4.4% in CADILLAC. Clinically significant bleeds occurred in 2.5% of patients, and blood product transfusions were necessary in 2% of patients compared to 5% in CADILLAC. In conclusion, bivalirudin had an acceptable safety profile and a similar outcome at 30 days compared to the stent/abciximab arm of the CADILLAC trial. The HORIZONS trial will randomise patients with STEMI undergoing PAMI to either bivalirudin or unfractioned heparin and abciximab and will hopefully give a definite answer on the position of bivalirudin in acute myocardial infarction.[10]

Conclusions

The additional benefit of GP IIb/IIIa antagonists in stable patients undergoing PCI, pretreated with aspirin and clopidogrel is small. In high-risk patients, bivalirudin may be equivalent to abciximab but with less bleeding complications. The question remains if either of them is necessary at all in patients treated with aspirin and thienopyridines. Forthcoming trials such as ACUITY and ISAR-REACT 2, which are due to report in early 2006, may well answer these questions.

We have found our early experience with bivalirudin encouraging and this strategy has helped us to contain costs. Whether this is a cost-effective approach, only time will tell. Abciximab is still indicated as an adjunctive therapy in primary angioplasty but recent (non-randomised) data suggest that bivalirudin may be as effective. Until prospective studies are available, there is clearly a place for abciximab (administered early) in primary angioplasty and this indication may 'save' this compound at least in the short term.

Conflict of interest

None declared.

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