

VIEWPOINT

Antiplatelet treatment in unstable angina: aspirin, clopidogrel, glycoprotein IIb/IIIa antagonist, or all three?

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Evidence on the role of antiplatelet agents in patients with non-ST elevation acute coronary syndrome is reviewed, and a strategy for their use in unstable angina is presented

Plaque rupture, platelet activation, and thrombus formation are recognised as key events in the pathogenesis of acute coronary syndromes (ACS). The ability of aspirin to reduce recurrent ischaemic events in ACS has been clearly and consistently demonstrated.^{1,2} There is also convincing evidence that adding a low molecular weight heparin in aspirin treated patients leads to a further reduction in ischaemic events.^{3,4} Despite advances in the treatment of non-ST elevation ACS, this group remains at high risk of subsequent adverse cardiac events; for example, the PRAIS-UK study demonstrated that 12.2% of patients with non-ST elevation ACS died or sustained non-fatal myocardial infarction within six months.⁵ The recognition of the central role of the platelet in ACS has led to intense investigation of various antiplatelet agents in an attempt to improve clinical outcomes further in this group of patients.

INTRAVENOUS GLYCOPROTEIN IIB/IIIA ANTAGONISTS

Activation of the glycoprotein (GP) IIb/IIIa receptor on platelets is the final common pathway leading to platelet aggregation, intracoronary thrombus formation, and myocardial ischaemia. The effectiveness of intravenous GP IIb/IIIa antagonists in preventing ischaemic complications following percutaneous coronary intervention (PCI) has been well documented.⁶ Seven major randomised controlled trials have examined the effect of four different intravenous GP IIb/IIIa antagonists in patients presenting with non-ST elevation ACS (table 1).^{7–12} These trials differed notably in design, particularly with respect to the use of heparin, duration of GP IIb/IIIa antagonist treatment, use of early intervention, and clinical end points. There was also pronounced heterogeneity in the outcomes of these trials. The CAPTURE, PRISM PLUS, and PURSUIT trials all showed a significant reduction in their primary end points at 30 days. However, the PRISM, PARAGON A, PARAGON B, and GUSTO IV trials failed to show a significant difference in their primary end points at 30 days. Boersma and colleagues recently published a meta-analysis of six large randomised trials studying the GP IIb/IIIa antagonists in patients

with ACS who were not routinely scheduled to undergo early coronary revascularisation. This meta-analysis found a 9% reduction in the odds of death or myocardial infarction at 30 days with GP IIb/IIIa inhibitors compared with placebo or control.¹³ It is important to note that this meta-analysis assumed a class effect of the glycoprotein IIb/IIIa inhibitors, an assumption which may not be valid. The differences in the pharmacological properties between these agents have been well documented.¹⁴ It is possible the apparent divergence in efficacy among the various GP IIb/IIIa inhibitors in the cardiac catheterisation laboratory and in ACS may possibly be explained by differences in the level and duration of platelet inhibition achieved by the various regimens in these different settings.

The treatment effect of these agents appears greatest among those patients with evidence of myonecrosis (that is, elevation of troponin) and those undergoing early PCI. Impressive reductions in death or myocardial infarction of 42–74% were observed in the troponin positive patients of PARAGON B, PRISM, PRISM-PLUS, and CAPTURE, many of whom underwent early PCI. In contrast, there was no significant benefit demonstrated among troponin negative patients in any of these studies.¹⁵ In patients undergoing early PCI there is clear evidence of stabilisation during the period before intervention as well as suppression of postprocedural period ischaemic events.¹⁶ However, no trial of GP IIb/IIIa inhibition has demonstrated a significant reduction in its primary end point in patients treated with medical therapy alone. This is an important point as only 6% of patients admitted with ACS in the UK undergo revascularisation during their admission.⁵ It should also be noted that it is not uncommon for these patients to have to wait significantly longer than 72 hours, the maximal duration of infusion before PCI in most of the trials, before undergoing revascularisation.

Adverse events include an increase in major bleeding and thrombocytopenia. The majority of trials of GP IIb/IIIa antagonists in non-ST elevation ACS have shown a significant increase in bleeding (table 1). Meta-analysis of the use of GP IIb/IIIa inhibitors in ACS suggested that their use led to a significant increase in major bleeding (2.4% v 1.4%, $p < 0.0001$).¹³ No increase in intracranial haemorrhage has been observed with the GP IIb/IIIa antagonists.

Abbreviations: ACS, acute coronary syndromes; GP, glycoprotein; PCI, percutaneous coronary intervention; RR, relative risk

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Table 1 Major trials of antiplatelet agents that have been used as adjuncts to aspirin in patients with non-ST elevation acute coronary syndromes

| Study | Treatment arms | Angiography + revascularisation | % PCI | Death or MI at 30 days | Major bleeding |
|---------------------|---|---|-------|---------------------------------|----------------|
| CAPTURE (n=1265) | Abciximab v placebo (for 19–25 hours) | PCI planned in all subjects | 98 | 9.0% v 4.8%, RR 0.53, p=0.003 | Increased |
| PRISM (n=3232) | Tirofiban v heparin (for 48 hours) | Discouraged during the first 48 hours | 21 | 5.8% v 7.1%, RR 0.80, p=0.11 | Similar |
| PRISM PLUS (n=1915) | *Tirofiban v tirofiban + heparin v heparin (for 48–96 hours) | Encouraged between 48 and 96 hours | 31 | *8.7% v 11.9%, RR 0.7, p=0.006 | Similar |
| PURSUIT (n=10948) | Eptifibatide v placebo (up to 96 hours) | At discretion of the attending physician | 24 | 14.2% v 15.7%, RR 0.90, p=0.04 | Increased |
| PARAGON A (n=2282) | Low dose lamifiban ± heparin v high dose lamifiban ± heparin v placebo (for 72–120 hours) | Discouraged during the first 48 hours | 14 | †11.3% v 11.7%, RR 0.96, p=0.80 | Increased |
| PARAGON B (n=5225) | Lamifiban v placebo (for 72–120 hours) | At discretion of the attending physician | 27 | 10.6% v 11.5%, RR 0.92, p=0.32 | Increased |
| GUSTO IV (n=7800) | Abciximab for 24 hours v abciximab for 48 hours v placebo (for 24–48 hours) | Discouraged during the first 60 hours | 19 | 8.2% v 9.1% v 8.0%, p=0.19 | Increased |
| CURE (n=12562) | Clopidogrel v placebo (for 9 months) | Early intervention discouraged | 21 | ‡3.9% v 4.8%, RR 0.79, p=0.007 | Increased |
| PCI-CURE (n=2658) | Clopidogrel v placebo (for 9 months) | Substudy of patients in CURE undergoing PCI | 100 | §4.4% v 2.9%, RR 0.66, p=0.04 | Similar |

*Results for tirofiban + heparin v heparin. The tirofiban group alone was stopped early because of excess mortality.
†Results for all lamifiban + heparin v placebo.
‡This is the combined end point of cardiovascular death or MI at 30 days rather than death from all causes or MI at 30 days.
§This is the combined end point of cardiovascular death or MI within 30 days of PCI rather than 30 days after randomisation to treatment.
CV, cardiovascular; MI, myocardial infarction; % PCI, percentage of study patients undergoing percutaneous coronary intervention; RR, relative risk; TVR, target vessel revascularisation.

A number of economic evaluations of the cost effectiveness of GP IIb/IIIa antagonists in the treatment of non-ST elevation ACS have been published. Unfortunately all of these analyses have been performed in countries other than the UK. The relevance of these analyses to the UK health system is limited. McDonagh and colleagues¹⁷ reported the results of two unpublished economic evaluations of the cost effectiveness of these drugs in non-ST elevation ACS in the UK. The first of these studies looked at the cost effectiveness of eptifibatide in the UK using the results of the western European patients in the PURSUIT trial, and found that treatment with eptifibatide was “dominant” to placebo in costs per life-years gained at 30 days—that is, the costs for eptifibatide were lower and the effects more favourable. The second study looking at tirofiban used the results of the PRISM-PLUS study to calculate cost effectiveness ratios in the UK. This study estimated the cost to prevent the occurrence of one composite end point event (death, myocardial infarction, refractory ischaemia or readmission with a non-ST elevation ACS) at six months to be £9955.

ORAL IIB/IIIA ANTAGONISTS

The phase III trials exploring the role of oral glycoprotein IIb/IIIa inhibition have been consistently disappointing. Despite clinical trial experience with over 40 000 patients and the study of four different oral GP IIb/IIIa antagonists, no reduction in ischaemic events with this group of drugs has been demonstrated. Of greater concern is the emerging evidence suggesting an increase in mortality with these agents.¹⁸

CLOPIDOGREL

Clopidogrel, a thienopyridine, blocks platelet aggregation induced by adenosine diphosphate. The CAPRIE trial¹⁹ showed that clopidogrel was slightly more effective than aspirin in reducing ischaemic complications (ischaemic stroke,

myocardial infarction, or vascular death) in patients with atherosclerotic vascular disease. The recently published CURE trial²⁰ was designed to investigate whether combining clopidogrel with aspirin may lead to a further reduction in ischaemic complications in patients presenting with non-ST elevation ACS. The CURE trial randomised 12 562 patients with non-ST elevation ACS to clopidogrel or placebo for 3–12 months (mean duration of treatment nine months). All patients received aspirin and the use of GP IIb/IIIa antagonists was discouraged except in patients with refractory ischaemia and during PCI. CURE was designed to examine clopidogrel in the setting of a conservative approach to ACS management; despite this, around a third of the patients underwent a revascularisation procedure while on study drug.

Benefit was seen as early as the first day and there was a highly significant reduction in the composite primary end point, of cardiovascular death, non-fatal myocardial infarction, or stroke in the clopidogrel group (relative risk (RR) 0.80; $p < 0.001$) after a mean duration of treatment of nine months. There was no significant reduction in death or stroke. The reduction in the primary end point was mainly driven by a 23% reduction in myocardial infarction from 6.7% to 5.3%. The secondary end point, a composite of the primary end point and refractory ischaemia, was also reduced (RR 0.86, $p < 0.001$). The clinical effect was consistent across conventional subgroups and was irrespective of whether or not patients underwent revascularisation. Significant benefit was demonstrated during the first 30 days of treatment and from 30 days until the end of follow up. This benefit was at the cost of increased bleeding, with significantly more patients experiencing major bleeding in the clopidogrel group (3.7% v 2.7%, RR 1.38, $p = 0.001$). No cost analysis relating to the CURE study has been published as yet. The treatment costs of clopidogrel are compared to those of the GP IIb/IIIa inhibitors in table 2.

Table 2 Cost of treatment with adjunctive antiplatelet agents

| Drug | Treatment regimen | Treatment duration | Treatment cost for a 70 kg patient |
|--------------|---|--------------------|------------------------------------|
| Abciximab | Bolus 0.25 mg/kg Maintenance 0.125 µg/kg/min | 48–72 h | £1400–£1680 |
| Eptifibatide | Loading 180 µg/kg Maintenance 2 µg/kg/min | 48–72 h | £308–£406 |
| Tirofiban | Loading 0.4 µg/kg/min for 30 min Maintenance 0.1 µg/kg/min | 48–72 h | £292–£438 |
| Clopidogrel | Loading 300 mg Maintenance 75 mg/day | 9 months | £351 |

The results of the PCI-CURE study have also recently been published.²¹ PCI-CURE was a prospectively designed observational study looking at the 2658 patients in the CURE study who underwent PCI in response to refractory symptoms or adverse events. Of these 1313 received clopidogrel and 1345 placebo. PCI was performed during the initial hospital stay in 1730, and after discharge in the remaining 928. Patients were pretreated with clopidogrel for a median of 10 days before PCI. After PCI most patients (> 80%) in both groups received open label thienopyridine for about four weeks, after which the study drug was restarted for a mean of seven months. The most common reason for use of open label thienopyridine following PCI was the deployment of a stent.

The benefit of clopidogrel was clearly apparent during pretreatment before PCI with significantly fewer patients in the clopidogrel group experiencing a myocardial infarction or refractory ischaemia (12.1% v 15.3%, RR 0.76, $p = 0.008$). The primary end point—a composite of cardiovascular death, myocardial infarction or urgent target vessel revascularisation 30 days following PCI—was also significantly reduced in patients treated with clopidogrel (4.5% v 6.4%, relative risk 0.70, $p = 0.03$). Given that the vast majority of patients received open label thienopyridine treatment for the weeks after the procedure, the improvement in the primary end point is presumably caused by pretreatment with clopidogrel before PCI.

A key question raised by these two studies is that of the optimal duration of clopidogrel treatment. Therapy should be thought of being in two phases: firstly, pacification following acute plaque rupture or intervention; and secondly, prevention of the thrombotic complications of subsequent episodes of

plaque rupture or erosion. The CURE trial demonstrated treatment with clopidogrel resulted in a similar relative risk reduction in the primary end point in both these phases (21% during the first 30 days and 18% for the period from 30 days until the end of follow up). As most adverse cardiac events occur within a few months following the initial presentation with ACS, one would expect the absolute benefits of clopidogrel treatment to be less during the secondary prevention phase compared to the acute phase. As the excess risk of bleeding with clopidogrel is the same during these two phases, the risk:benefit ratio of clopidogrel treatment would also be lower during the secondary prevention phase.

There is an increasing body of evidence to suggest that an early interventional strategy is associated with decreased risk of subsequent ischaemic events.²² Therefore the benefit of secondary prevention may differ in those treated conservatively compared to those undergoing early revascularisation. In PCI-CURE treatment with clopidogrel compared to placebo resulted in a significant reduction in cardiovascular death or myocardial infarction before PCI and in the 30 days following PCI. However, treatment with clopidogrel between 30 days following PCI and the end of follow up resulted in a smaller risk reduction (RR 0.79, 95% confidence interval 0.53 to 1.20), which was not significant. Clearly, not all individuals will be at the same risk of subsequent ischaemic events. An individual with no risk factors and single vessel disease, who has been treated with PCI, has a much lower risk of subsequent events when compared to a diabetic patient with three vessel disease that is not suitable for revascularisation. These factors need to be taken into account when making decisions about the duration of treatment.

COMBINATION OF CLOPIDOGREL AND GP IIB/IIIA ANTAGONISTS

Another of the major questions raised by the CURE study is whether early treatment with a GP IIB/IIIA antagonist is still necessary in patients already receiving aspirin and clopidogrel. The CURE study did not address this question directly, as it excluded patients given early treatment with GP IIB/IIIA antagonists. However, in those patients who later received an intervention and a GP IIB/IIIA antagonist, the same 20% relative risk reduction with clopidogrel was seen, suggesting that the benefit may be additive in this subgroup. Further evidence for an additive benefit of these agents in patients undergoing PCI comes from a post hoc analysis of the TARGET trial in which patients pretreated with clopidogrel were found to have fared significantly better than those not pretreated, irrespective of the GP IIB/IIIA antagonist used.²³

CONCLUSIONS

Patients presenting with non-ST elevation ACS are a heterogeneous group with substantial variation in their risk of subsequent death or infarction. Early risk stratification in these patients is essential and allows both the intensity of pharmacologic treatment and the use of invasive therapy to be

Trial acronyms

CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events

CAPTURE: Chimeric 7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

GUSTO: Global Use of Strategies To open Occluded coronary arteries

PARAGON: Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network

PRASIS-UK: Prospective Registry of Acute Ischaemic Syndromes in the UK

PRISM: Platelet Receptor Inhibition in ischemic Syndrome Management

PRISM-PLUS: Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms

PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy

TARGET: do Tirofiban and Abciximab Give similar Efficacy Trial

targeted appropriately, depending on the level of risk. After reviewing the available evidence we suggest the following strategy for the use of antiplatelet agents in non-ST elevation ACS.

- Patients without significant ECG changes or troponin elevation are at very low risk and should be treated with aspirin alone
- Clopidogrel should be started in addition to aspirin in patients presenting with ECG changes or positive biochemical markers as soon as possible
- High risk patients should undergo early angiography and intervention where this facility is available
- The available evidence does not support the routine use of GP IIb/IIIa antagonists in non-ST elevation ACS
- GP IIb/IIIa antagonists should be reserved for those undergoing PCI or for patients with refractory ischaemia who do not have ready access to a cardiac catheterisation laboratory
- There is insufficient evidence at present to support the routine continuation of clopidogrel for more than 30 days following PCI.

A reasonable strategy for deciding on the duration of combination therapy would be to reassess patients' ongoing risk of subsequent ischaemic events and bleeding at the time of outpatient review following the index event and, based on this, decide on the appropriateness of continuing the combination antiplatelet treatment as a part of their overall secondary prevention strategy. What is not clear is whether those individuals remaining at high risk should receive clopidogrel in addition to aspirin for life or only nine months.

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