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New Platelet Inhibitors for Acute Coronary Syndromes without ST Elevation

J. R. Collinson[1], M. D. Flather[2]

Acute coronary syndromes including myocardial infarction and unstable angina are common medical emergencies that carry a high burden of morbidity and mortality. There are about one million admissions for acute coronary syndromes each year in Western Europe and the associated cost amounts to 1–2 % of total health care expenditure. Acute coronary syndromes without ST elevation of the presenting ECG are increasingly recognised as carrying a high risk with about 30 % of patients suffering death, new myocardial infarction, refractory angina or readmission for unstable angina over a 6 month period from the initial hospital admission. Recent therapeutic developments to treat acute coronary syndromes include the glycoprotein 2b/3a receptor antagonists that inhibit platelet aggregation. Tirofiban and eptifibatide are two glycoprotein 2b/3a receptor antagonists that have been investigated in well-conducted randomised trials and approved for treating acute coronary syndromes without ST elevation. On average they produce proportional reductions in the rate of death or new myocardial infarction of 30–40 % over the first few days and 15–20 % at 6 months, with absolute reductions of about 2–3 %. Preliminary health economic evaluations suggest that using these new agents to treat higher risk patients adds only a modest cost while helping to avoid substantial numbers of adverse outcomes. The meaningful therapeutic effects observed in clinical trials should help to reduce the burden of disability in acute coronary syndromes if glycoprotein 2b/3a receptor antagonists are used in routine practice. *J Clin Basic Cardiol 2000; 3: 107–10.*

Key words: unstable angina, myocardial infarction, platelets, risk stratification, clinical trials

Acute coronary syndromes (ACS) are a major public health problem [1]. It is estimated that costs of ACS are about 2 % of health care budgets [2]. The term ACS includes a spectrum of disease from myocardial infarction (MI) to unstable angina (UA) and results in about 250,000 hospital admissions per year in the UK, and more than one million in western Europe [3–7]. A clinically useful separation can be made between patients with ST elevation and those without ST elevation on the electrocardiogram (ECG) at presentation. Patients with acute coronary syndromes and significant ST segment elevation have a high likelihood of acute myocardial infarction (MI) and most go on to receive treatment with thrombolytic therapy [8]. Patients without ST elevation are more likely to have unstable angina or less severe MI. The measurement of sensitive enzyme markers such as CKMB, or muscle proteins such as troponin, may help to differentiate between unstable angina and MI during the early stages [9], but even so there may be a 'grey zone' where the diagnosis is still uncertain. The term ACS without ST elevation may be a useful clinical description of non Q-wave MI and unstable angina.

Pathophysiology of acute coronary syndromes

Acute coronary syndromes are usually triggered by rupture of an existing atheromatous plaque causing local exposure of thrombogenic material.This process activates the coagulation system and platelets resulting in thrombus formation [10, 11]. The presence of thrombus and coronary spasm results in a dynamic obstruction to coronary flow [12]. The speed of onset of ACS, degree of occlusion, presence of collateral circulation and ability of local mechanisms to control the problem all influence the severity of the process and the clinical presentation [13]. Thus rapid onset, total coronary occlusion in a large epicardial artery may typically present as acute myocardial infarction with ST segment elevation on the ECG, whereas lesser degrees of occlusion may present as suspected MI without ST elevation or unstable angina [14].

Prognosis of ACS without ST elevation

The short-term prognosis of patients with acute myocardial ischaemia without ST elevation can be determined from the GUSTO-IIb (Global Use of Strategies to Open Occluded Arteries) study, a randomised trial of hirudin compared to heparin [15]. In this trial 8011 patients were enrolled with acute coronary syndromes without ST elevation (mean age 66 years, 67 % men and 32 % prior MI).The 30 day event rate of death or MI was 8.7 %. Data for a similar population of 7800 patients in the OASIS (Organisation to Assess Strategies for Acute Ischaemic Syndromes) registry show a rate of death or MI of 4.8 % in the first 7 days, and 10 % in the first six months [16].The rate of death, MI, refractory angina (angina leading to need for urgent cardiac catheterisation or revascularization) or readmission for unstable angina in the OASIS registry over 6 months was about 20 %. In the PRAIS-UK (Prospective Registry of Acute Ischaemic Syndromes in the United Kingdom) study [17], 1046 patients with ACS without ST elevation were enrolled from 56 hospitals.The overall rate of death or new myocardial infarction was 12.2 % at 6 months and the rate of death, MI, refractory angina or readmission for unstable angina was 30 %.

General management of ACS without ST elevation

The early treatment of ACS without ST elevation usually consists of hospital admission, pain relief, use of antithrombotic therapy with aspirin and heparin and anti-anginal treatment (nitrates, beta blockers and calcium antagonists as required) [18, 19]. In the UK, it is generally accepted that there

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are low rates of early angiography and revascularisation [20] and the PRAIS-UK showed a rate at 6 months of angiography and revascularisation of 27 % and 15 % respectively [21–24]. Rates of angiography and revascularisation vary widely across countries and between institutions. There is uncertainty about the timing and frequency of revascularisation following ACS, but patients with refractory symptoms and those at highest risk of adverse outcomes should have early angiography and revascularization as appropriate.

Platelets and ACS

Platelets have a central role in acute thrombosis and their importance is demonstrated by the efficacy of aspirin [25]. Aspirin acts by irreversibly inhibiting cyclo-oxygenase, the enzyme responsible for converting arachidonic acid to prostaglandin G_2 and H_2 [26].Thromboxane A_2, a potent platelet aggregating substance and vasoconstrictor, is formed by the action of thromboxane synthetase particularly on prostaglandin H_2. Thus aspirin substantially reduces thromboxane A_2 production in the context of acute coronary syndromes, which in turn reduces platelet aggregation [27, 28]. Platelets lack biosynthetic capabilities, therefore this defect lasts for the lifetime of the platelet. Platelet aggregates can still form via other pathways [29]. Similarly, ticlopidine and its analogue, clopidogrel (also a thienopyridine), interfere with the ADP-mediated platelet activation mechanism and the platelet fibrinogen receptor. They therefore cause irreversible non-competitive inhibition of platelet function [30].This appears to prevent ADP inducing the conformational change in the glycoprotein 2b/3a inhibitor that is required for ligand binding [31].

Inhibition of glycoprotein 2b/3a receptors

Direct inhibition of the glycoprotein 2b/3a receptor may be particularly important since platelet aggregation can be reduced whatever the agonist [32]. The glycoprotein 2b/3a receptor is a member of the integrin adhesion receptor family and is found only on platelets and megakaryocytes [33]. Fibrinogen and von Willebrand factor bind to the activated glycoprotein 2b/3a receptor via an arginine-glycine-aspartate amino acid sequence allowing platelet activation [33]. It is this amino acid sequence that has become the target for the recently developed glycoprotein 2b/3a receptor antagonists.

Currently, there are 3 members of this drug class licensed for use in Europe. Abciximab (c7E3 Fab) is a monoclonal antibody that is a non-competitive inhibitor of fibrinogen and has nearly irreversible binding with the glycoprotein 2b/3a receptor [34].Therefore, following treatment with abciximab, recovery of platelet function is slow due to slow dissociation of abciximab from the receptor and production of new platelets [35]. Both eptifibatide and tirofiban are small molecule inhibitors of the Gp2b/3a receptor and have a much shorter half-life than abciximab, giving them a rapid 'on-off' effect. Eptifibatide (Integrilin) is a cyclic heptapeptide competitive inhibitor of the glycoprotein 2b/3a receptor based on the arginine-glycine-aspartate sequence, but with lysine substituted for arginine [36, 37]. Tirofiban (Aggrastat) is a non-peptide inhibitor of the glycoprotein 2b/3a receptor with a rapid onset of action and rapid reversal following drug discontinuation [38].

Benefit has been demonstrated for abciximab, tirofiban and eptifibatide in acute coronary syndromes without ST elevation and those who undergo percutaneous revascularisation. A systematic review of randomised trials of GP 2b/3a platelet receptor antagonists in PTCA and ACS has shown a clear reduction in risk of death or new MI of about 20 % at 30 days [39]. Five randomised trials with a total of about 15,000 patients have evaluated the effects of GP 2b/3a inhibitors in patients presenting with ACS (Table 1, Figure 1) [40–44]. The overall OR for the occurrence of death or new MI at 48–96 hours was 0.81 (95 % CI 0.71–0.92), at 30

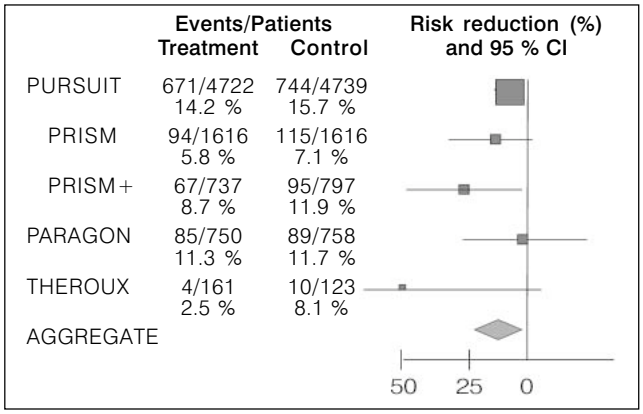

Figure 1. Overview of GP2b/3a trials in ACS: death or MI at 30 days

Table 1. Summary of trials of glycoprotein 2b/3a antagonists in ACS without ST elevation – effects on 30 day outcome of death or new MI

Trial	Treatments		Eligibility	Outcome		RR	P
	Loading dose μg/kg	Infusion mg/kg/min		Treatment	Control		
PURSUIT [40]	Eptifibatide 180	Eptifibatide 1.3 vs. 2.0, 72 hours	UA, non-Q wave MI	14.2 % (671/4722)	15.7 % (744/4739)	0.90	0.04
PRISM [41]	Tirofiban 18	Tirofiban 0.15, 48 hours	UA, non-Q wave MI	5.8 % (94/1616) (tirofiban alone)	7.1 % (115/1616) (heparin alone)	0.80	0.11
PRISM PLUS [42]	Tirofiban 0.6 vs. 0.4	Tirofiban 0.15 vs. 0.10, 48–60 hours	UA, non-Q wave MI	8.7 % (67/773) (tirofiban + heparin)	11.9 % (95/797) (heparin alone)	0.70	0.03
PARAGON [43]	Lamifiban None vs. 300 vs. 750	Lamifiban none vs. 1.0 μg/min vs. 5.0 μg/min, 72–120 hours	UA, non-Q wave MI	11.3 % (85/750) (all lamifiban + heparin)	11.7 % (89/758) (heparin alone)	0.96	0.76
Theroux [44]	Lamifiban 150, 300, 600, 750	Placebo, lamifiban 1 μg, 2 μg, 4 μg, 5 μg, 72–120 hours	UA, non-ST elevation MI	2.5 % (4/161) (2 higher doses of lamifiban)	8.1 % (10/123) (no lamifiban)	0.44	0.03

Results for randomised trials of glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes without ST elevation.UA = unstable angina, MI = myocardial infarction

days OR was 0.88 (95 % CI 0.81–0.97; p<0.01) and 0.88 at 6 months (95 % CI 0.79–0.97). For the composite outcome of death, non-fatal MI and the need for revascularisation there were about 20 fewer events at 6 months per 1000 patients treated.

The cost (about 600 euro for a 3 day treatment) GP2b/3a receptor antagonists for ACS is a potential barrier to widespread use. Szucs et al. [45] have undertaken an incremental cost-consequence analysis of tirofiban from the perspective of the admitting hospital, based on the PRISM-PLUS trial. Ongoing health economic analyses from PRAIS-UK and PRISM-PLUS suggest that treating groups at highest risk of adverse outcome, including those with ST depression, bundle branch block or with evidence of cardiac damage (elevated troponins or CKMB), adds about 5–6 % to the cost of treating ACS but avoids a large proportion of adverse events.

Apart from cost there may be other barriers to the widespread use of GP 2b/3a antagonists.The PRAIS-UK data demonstrated that the low molecular weight heparins are being used in many patients in place of unfractionated heparin. As yet, data demonstrating the safety of combined LMWH and GP IIb/IIIa inhibitor is limited. Cohen et al. have recently evaluated combination therapy with tirofiban and the low molecular weight heparin (LMWH), enoxaparin [46]. Patients with ACS were randomised to double-blind treatment with tirofiban for 48–108 hours together with either enoxaparin (n = 26) or UFH (n = 27) to evaluate pharmacodynamics and safety. The combination of tirofiban and enoxaparin resulted in more predictable and greater inhibition of platelet aggregation without prolonging the bleeding time.There was an increase in the amount of cutaneous bleeding in the enoxaparin group (associated with puncture sites), but no difference in major bleeding. These findings suggest that the combination of tirofiban and LMWH may be justified.

Further studies of these agents are ongoing. The A to Z trial (Aggrastat™ to Zocor™) will enrol 4500 patients in 39 countries. In phase 1 (at hospital admission), qualifying patients will be randomised to receive open label tirofiban in combination with LMWH and aspirin, or UFH and aspirin. In phase 2, clinically stable patients will receive either lipid-lowering therapy with simvastatin 40 mg/day 1–4 days after hospital admission for 30 days; followed by simvastatin 80 mg/day thereafter, or dietary counselling plus placebo for 4 months, followed by simvastatin 20 mg/day thereafter. The primary end-point will be a composite measure of cardiovascular death, MI and readmission for ACS.

The TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservatory Strategy) Trial is a multicentre, randomised trial that will evaluate treatment strategies in patients with UA or non Q-wave MI treated with tirofiban, heparin and aspirin. Patients will be randomised to either invasive therapy (angiography within 4–48 hours and revascularisation if feasible) or a conservative strategy (angiography only if there is provocable ischaemia or recurrent pain at rest). The primary endpoint is the 6 month rate of death, MI or rehospitalisation for ACS. The use of troponins in identifying patients that may benefit from an aggressive approach will also be examined.

Conclusions

Serious adverse outcomes including death, new MI, refractory ischaemia and readmission for unstable angina occurs in about 1 in 3 people within 6 months after a hospital admission for ACS. Glycoprotein receptor 2b/3a antagonists represent an exciting development in the management of ACS. The benefits of these agents are mainly observed during the treatment period, and these early benefits are maintained in the long term. Meta-analyses of the randomised trials show important clinical benefits in ACS and PTCA. Current efforts are being directed towards applying these treatments in practice.Trials evaluating the interaction of GP2b/3a antagonists and low molecular weight heparin, early vs. delayed angiography and troponin directed platelet inhibitor therapy are underway [47]. Economic evaluations of the impact of these agents on health care budgets have shown a generally favourable profile especially in higher risk patients. More work in this area needs to be undertaken. It remains to be seen whether patients will benefit from the clinical application of these important agents since their use in ACS has so far been modest.

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