

Antiplatelet therapy in cardiovascular disease

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Platelet activation and aggregation are considered to be central to arterial thrombus formation. Antiplatelet therapy is therefore important for both the treatment and prevention of cardiovascular disease. Aspirin, the most widely used antiplatelet agent, inhibits platelet cyclo-oxygenase and the conversion of arachidonic acid to the potent platelet agonist thromboxane A_2 but does not prevent platelet activation occurring via various signalling pathways that are independent of thromboxane A_2 release. Therefore a number of other compounds have been developed to complement aspirin's beneficial effect. These include the thienopyridines (clopidogrel and ticlopidine), dipyridamole, and the $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) receptor inhibitors.

and collagen covered by a layer of connective tissue. Also present in the core are cholesterol-containing macrophages (foam cells), derived from monocytes that have crossed the endothelium from the arterial lumen. These cells produce large amounts of prothrombotic tissue factor together with several inflammatory cell mediators such as tumour necrosis factor- α and various interleukins.^{3 9 10}

The process of thrombosis starts when the atherosclerotic plaque tears and exposes the lipid-rich core to blood in the arterial lumen. Platelet adherence to the exposed subendothelium and collagen results in platelet activation and the release and local accumulation of soluble platelet agonists (thrombin, adenosine diphosphate (ADP), serotonin, and thromboxane A_2). This in turn causes further platelet aggregation, coronary artery vasoconstriction, and subsequent reduction in coronary artery blood flow.¹¹ On the surface of the activated platelet the integrin $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) receptor undergoes a conformational change, allowing the platelets to bind fibrinogen tightly. Fibrinogen acts as a bivalent ligand and allows the formation of stable platelet aggregates through cross linking of $\alpha_{IIb}\beta_3$ receptors.¹² In this way $\alpha_{IIb}\beta_3$ mediates the so-called "final common pathway" of platelet aggregation. It has to be remembered that platelets not only promote thrombosis but also impede fibrinolysis by the secretion of factors such as plasminogen activation inhibitor 1.^{13 14}

Platelets are the "major player" in arterial thrombosis and therefore are attractive targets in the prevention and treatment of cardiovascular disease. Coronary thrombosis often precedes or complicates percutaneous coronary interventions (PCI), including percutaneous transluminal coronary angioplasty (PTCA) and intracoronary stent implantation, and refining antiplatelet therapy to cover these procedures, as well as to treat acute coronary syndromes, has been the objective of many clinical trials.

ASPIRIN

Bayer Co patented acetyl-salicylic acid in 1899 under the trade name of aspirin ("a" stood for acetyl and "spir" stood for spirasaur, the German word for salicylic acid).¹⁵ Aspirin was used initially as an analgesic and an antipyretic; however its effects on haemostasis were recognised as early as 1945.¹⁶ The antithrombotic

The leading cause of morbidity and mortality in the Western world is cardiovascular disease.¹ Thrombotic and thromboembolic occlusions of atherosclerotic blood vessels are the main cause of ischaemic events.^{2 3} Since the observation that thrombi occluding coronary arteries were platelet-rich in content, antiplatelet agents have been extensively researched and developed as potential therapies in the prevention and management of arterial thrombosis.⁴

Platelet activation and aggregation is considered to be central to arterial thrombus production.^{5 6} This review discusses currently available antiplatelet agents and their mechanisms of action (fig 1). There are four main groups: aspirin, the thienopyridines (ticlopidine and clopidogrel), dipyridamole, and the platelet $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) receptors antagonists.

Aspirin has been regarded as the prototype antiplatelet drug and is still the most widely used agent. It inhibits irreversibly the enzyme cyclo-oxygenase, thereby blocking conversion of arachidonic acid to endoperoxides such as thromboxane A_2 in platelets and prostaglandin I_2 in vascular endothelium. However, platelet activation occurs via several pathways that do not rely on amplification by released thromboxane A_2 . A number of other compounds have been developed to complement the therapeutic effect of aspirin.

PATHOGENESIS OF THROMBOSIS

The acute coronary syndromes form a spectrum of coronary disease from unstable angina to non-Q-wave and Q-wave myocardial infarction.⁷ They are caused by the development of thrombus on a ruptured coronary atherosclerotic plaque (fig 2).^{2 8} This plaque consists of a core of lipid

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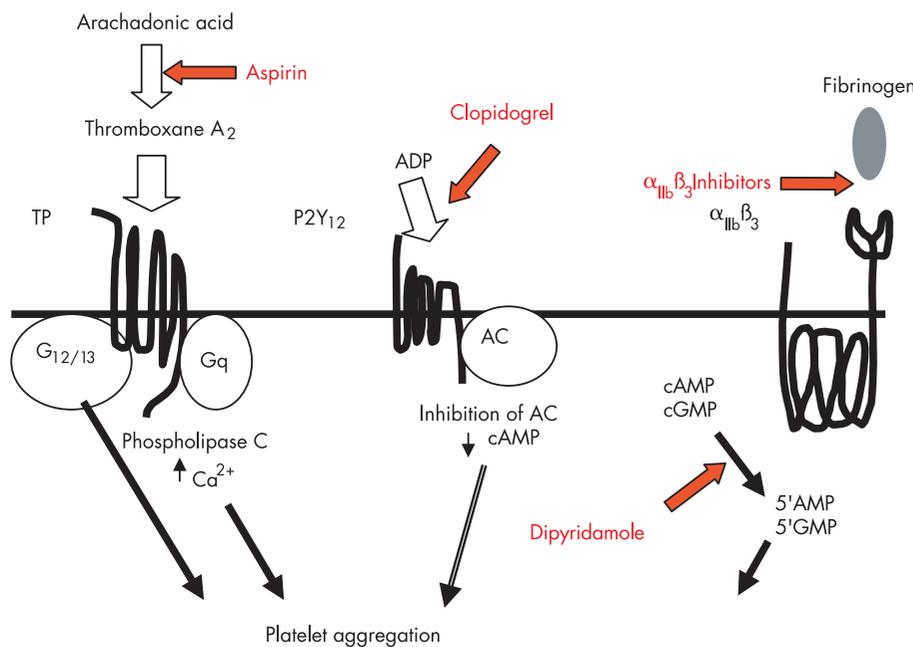


Figure 1 Platelet receptors and their antagonists. The ADP P2Y₁₂ receptor (a G-protein coupled receptor) is linked to adenylate cyclase (AC) via Gi. Upon stimulation the adenylate is inhibited, leading to a fall in cAMP and promotion of platelet aggregation. Clopidogrel irreversibly binds to the ADP P2Y₁₂ receptor preventing the inhibition of adenylate cyclase, therefore maintaining cAMP levels and inhibiting platelet aggregation. Dipyridamole is a phosphodiesterase inhibitor and prevents the breakdown of cAMP and cGMP. Therefore cAMP and cGMP levels are maintained inhibiting platelet aggregation. Thromboxane A₂ is produced from arachidonic acid via cyclo-oxygenase and is released from the platelet to work with the TP receptor. The TP receptor (a G-protein coupled receptor) causes platelet aggregation via both Gq and G12/13. Aspirin irreversibly inhibits cyclo-oxygenase, for the lifetime of the platelet (120 days), preventing thromboxane production. The α_{IIb}β₃ receptor antagonists prevent fibrinogen binding to the α_{IIb}β₃ receptors and therefore inhibit the “final common pathway of platelet aggregation”.

action of aspirin depends on the irreversible inhibition of arachidonate cyclo-oxygenase activity in platelets, thereby reducing the extent of thromboxane A₂ formation that occurs after activation of phospholipase A₂ and release of arachidonic acid.¹⁷ Thromboxane A₂ is a strong platelet agonist that is an effective inducer of platelet granule secretion as well as platelet aggregation. However, phospholipase A₂ activation and arachidonic acid release seem to play a relatively minor part in the action of many platelet agonists, with the notable exception of collagen, such that the antiplatelet effects of aspirin are limited and overall aspirin may be considered a relatively weak antiplatelet agent.

The Antithrombotic Trialists Collaboration meta-analysis of 135 000 patients compared antiplatelet therapy versus control and showed that among “high risk” patients (those with acute or previous vascular disease or other predisposing condition) allocation to antiplatelet therapy reduced the combined outcome of non-fatal myocardial infarction, non-fatal stroke, or vascular death by about one quarter; non-fatal myocardial infarction was reduced by one third, non-fatal stroke by one quarter, and vascular mortality by one sixth.¹⁸ Available evidence suggests a daily aspirin dose of 75–150 mg for long term prevention of serious vascular events is recommended for high risk patients. In clinical situations where an immediate antithrombotic effect is required (such as acute myocardial infarction, stroke, or unstable angina) a loading dose of 300 mg is recommended.^{18 19}

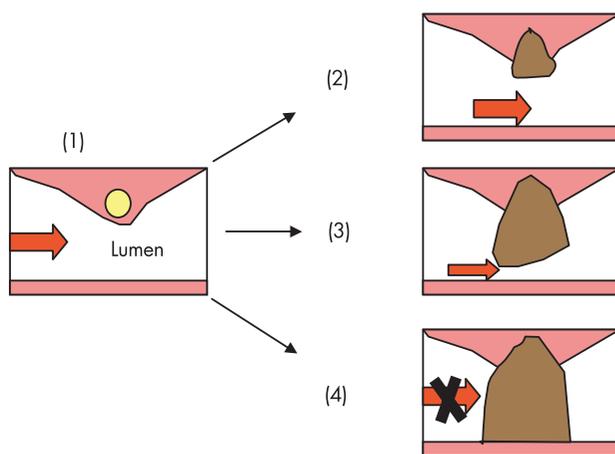


Figure 2 Pathogenesis of thrombosis. In (1) there is a lipid core sealed off by an intact fibrous plaque. The vessel lumen is patent. In (2) there has been a rupture in the plaque covering the lipid core. The exposed prothrombotic lipid-rich core promotes thrombus formation in the plaque. Local platelet activation causes release of platelet agonists, resulting in further platelet activation and vasoconstriction. By (3) the thrombus has extended into the lumen causing partial obstruction. Eventually there is complete luminal obstruction (4).

The effect of aspirin on the outcome of patients with unstable angina has been assessed in four double blind placebo controlled trials.²⁰⁻²³ The Veterans Administration Cooperative Study randomised 1266 men with unstable angina to aspirin 324 mg daily or placebo.²⁰ Death and recurrent non-fatal myocardial infarction at three months were significantly reduced in the aspirin group (12.1% v 5% in the placebo group, p<0.001). The other trials showed similar effects of aspirin and the RISC Study showed that aspirin at a dose of 75 mg daily significantly reduced death and myocardial infarction. Other studies have shown that aspirin reduces the incidence of myocardial infarction and sudden cardiac death in patients with stable angina, without influencing the severity or frequency of angina symptoms or the progression of coronary stenosis.²⁴⁻²⁶ On the basis of these results, aspirin is standard treatment for eligible patients with unstable angina.

With the advent of thrombolytic therapy of myocardial infarction, it became clear that treatment with streptokinase was associated with marked platelet activation, as determined by increased thromboxane A₂ production.²⁷ This issue was addressed by the Second International Study Of Infarct Survival (ISIS-2) which involved 17 187 patients with acute myocardial infarction, randomised to one of four arms of

therapy consisting of placebo, aspirin, streptokinase, or streptokinase plus aspirin.²⁸ Aspirin reduced mortality from 13.2% in the placebo group to 10.7% (23% relative risk reduction, $p < 0.00001$) and streptokinase reduced mortality to 10.4% (25% relative risk reduction). However, the combination of aspirin and streptokinase produced the greatest benefit, reducing mortality to 8.0%, an overall relative risk reduction of 42%, thus establishing aspirin and thrombolysis as standard therapy for eligible patients with acute myocardial infarction.

Long term therapy with aspirin is associated with a significant increase in the incidence of gastrointestinal haemorrhage.²⁹ No evidence exists that reducing the dose or using modified release formulations reduces the incidence of gastrointestinal haemorrhage.³⁰

THIENOPYRIDINES

This group comprises ticlopidine and clopidogrel, which act by causing irreversible blockade of ADP binding to one of its receptors on the platelet surface, the P2Y₁₂ receptor. Both drugs are effective orally, with about 80%–90% absorption. They require metabolism by the hepatic cytochrome P450 enzyme system to acquire their antiplatelet activity.³¹

Ticlopidine has been established as an alternative to aspirin in the prevention of recurrent cerebral ischaemia and stroke but its use has been limited in view of its side effects, including thrombotic thrombocytopenic purpura and potentially fatal severe neutropenia.³² Due to these side effects and its slow onset of action it has been replaced by clopidogrel, which is felt to be safer and, when a loading dose is employed, faster acting. The CAPRIE trial showed that clopidogrel was slightly more effective than aspirin in reducing ischaemic complications (ischaemic stroke, myocardial infarction, or vascular death) in patients with atherosclerotic disease³³ but overall, the safety and tolerability of aspirin and clopidogrel were similar. The CAPRIE Study therefore established clopidogrel as an alternative antiplatelet to aspirin for secondary prevention across a wide spectrum of patients with vascular disease.

Ticlopidine in addition to aspirin has been shown to reduce thrombotic complications after intracoronary stent deployment.³⁴ In the CLASSICS trial, three regimens were compared in 1020 patients after coronary stent implantation, consisting of aspirin 325 mg once a day plus ticlopidine 250 mg twice a day, aspirin plus clopidogrel 75 mg once a day and aspirin plus clopidogrel 300 mg loading dose followed by 75 mg once a day.³⁵ This study confirmed that clopidogrel, with or without the loading dose, is much better tolerated than ticlopidine and showed no significant difference in major adverse cardiac events between the three groups (0.9% ticlopidine, 1.5% clopidogrel 75 mg group, 1.2% clopidogrel 300/75 mg group).

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study investigated the effect of clopidogrel combined with aspirin in the treatment of patients with non-ST elevation acute coronary syndromes.³⁶ A total of 12 562 patients presenting within 24 hours of onset of symptoms were randomly assigned to receive clopidogrel (300 mg immediately followed by 75 mg once daily) or placebo in addition to aspirin for three to 12 months. The primary outcome—a composite of death from cardiovascular causes, non-fatal myocardial infarction or stroke—occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group (relative risk 0.8; $p < 0.001$). The secondary endpoint, a composite of the primary endpoint and refractory ischaemia, was also reduced (relative risk 0.86, $p < 0.001$). The benefits of clopidogrel, observed across various subgroups, were apparent as early as the first 24 hours after randomisation, indicating that the oral loading dose was

rapidly effective. The addition of clopidogrel to aspirin was, however, associated with an increased risk of major bleeding, particularly gastrointestinal haemorrhage. This, in part, reflects one of the limitations of combining other oral antithrombotic agents with aspirin in view of the propensity of aspirin to cause gastric erosions and ulceration with associated compromise to haemostasis.

The PCI CURE Study was designed to test whether treatment with clopidogrel, in addition to aspirin, before PCI and continued beyond the standard course of four weeks after PCI is superior to placebo in preventing major ischaemic events.³⁷ Altogether 2658 patients who were recruited into the CURE Study and underwent PCI in response to refractory ischaemia or adverse events were examined; 1313 were assigned to clopidogrel and 1345 to placebo. A total of 1730 PCI procedures were performed during the initial hospital stay and 928 after discharge. Patients were pre-treated with clopidogrel for a median of 10 days before PCI. After PCI most (>80%) patients in both groups received open label thienopyridine for about four weeks, after which the study drug was restarted for a mean of about seven months. Fewer patients in the clopidogrel group had myocardial infarction or refractory ischaemia before PCI.

The number of patients with the primary endpoint of cardiovascular death, myocardial infarction, or urgent revascularisation was significantly lower in the clopidogrel than in the placebo group. Since the vast majority of patients received open label thienopyridine treatment for the four weeks after the procedure, the improvement in the primary endpoint was presumably caused by pre-treatment with clopidogrel prior to PCI. The results implied that in patients with non-ST elevation acute coronary syndrome in which an invasive strategy was planned, clopidogrel started on admission before the procedure and continued long afterwards was beneficial in reducing both early and late complications.

The efficacy of clopidogrel treatment both pre-PCI and subsequently was also recently addressed by the CREDO (Clopidogrel for the Reduction of Events During Observation) Study.³⁸ Long term clopidogrel therapy was associated with a relative reduction in the combined risk of death, myocardial infarction, or stroke. Overall no risk reduction in death, myocardial infarction, or target vessel revascularisation from pre-treatment with clopidogrel was observed. From a subgroup analysis, however, it appeared that there was a reduction in the combined endpoint (death, myocardial infarction, or urgent revascularisation) if clopidogrel was administered more than six hours before the procedure.

Numerous trials have been initiated to study the benefits of combining aspirin and clopidogrel for other indications, such as stroke prevention (the MATCH study) or stable ischaemic heart disease (CHARISMA). Clopidogrel therapy only yields partial blockade of the P2Y₁₂ receptor,^{39 40} and there is much interest in the development of more effective strategies of P2Y₁₂ receptor antagonism in order potentially to enhance the clinical benefits seen with clopidogrel.

DIPYRIDAMOLE

Dipyridamole inhibits adenosine uptake in erythrocytes and endothelial cells. This increases plasma adenosine levels, which means that there is more available for binding to the adenosine receptor on the platelet. Adenosine activates the release of adenylate cyclase, which converts cyclic adenosine triphosphate (cATP) to cyclic adenosine monophosphate (cAMP). Dipyridamole also blocks the enzyme cyclic guanine monophosphate (cGMP) phosphodiesterase, thereby inhibiting the breakdown of cGMP. Raised levels of cAMP and cGMP within platelets have antiaggregatory effects.

In patients with ischaemic heart disease, dipyridamole in combination with aspirin has not been found to be better

than aspirin alone.⁴¹ In patients with cerebrovascular disease however, the European Stroke Prevention Study 2 (ESPS-2) demonstrated that the co-prescription of modified release dipyridamole (400 mg daily) and aspirin (50 mg daily) was more effective in preventing stroke than either drug alone.⁴² A meta-analysis, of 25 trials comparing dipyridamole plus aspirin with aspirin alone, showed that the addition of aspirin was associated with only a non-significant further reduction in serious vascular events.¹⁸ The current feeling is that there is not yet sufficient evidence to justify adoption of aspirin and dipyridamole as first line treatment for the secondary prevention of stroke.

$\alpha_{IIb}\beta_3$ ANTAGONISTS

The integrin $\alpha_{IIb}\beta_3$ (glycoprotein IIb/IIIa) is a receptor located on the platelet membrane that mediates platelet aggregation.⁴³ These receptors recognise an arginine-glycine-aspartic acid (RGD) sequence contained in adhesive molecules such as fibrinogen and von Willebrand factor. When platelets become activated, $\alpha_{IIb}\beta_3$ is converted into a functional receptor, binding these adhesive proteins⁴⁴ and allowing platelets to aggregate and form a haemostatic plug. Therefore, antagonists of $\alpha_{IIb}\beta_3$ block the final common pathway of platelet aggregation. Three classes of $\alpha_{IIb}\beta_3$ inhibitor have been developed: murine-human chimeric antibodies, such as abciximab; synthetic peptide forms, such as eptifibatide; and synthetic non-peptide (peptidomimetic) forms, such as tirofiban.⁴⁵

The antibody abciximab (ReoPro) has a particularly high avidity for $\alpha_{IIb}\beta_3$ and binds to, and exchanges between, platelets for as long as two weeks, although most of the antithrombotic effect disappears within 12–24 hours after termination of intravenous abciximab infusion. On the other hand, synthetic $\alpha_{IIb}\beta_3$ inhibitors inhibit *ex vivo* platelet aggregation for only a few hours after the end of an intravenous infusion. Eptifibatide (Integrilin) is a synthetic, conformationally constrained, cyclic heptapeptide, fashioned after the integrin antagonist barbourin. Barbourin is a small protein inhibitor of $\alpha_{IIb}\beta_3$ isolated from the venom of the Southeastern pygmy rattlesnake *Sistrurus m barbouri*. It is a highly competitive inhibitor of $\alpha_{IIb}\beta_3$ with a half life of 90–120 minutes and is excreted by the kidneys. The degree of platelet inhibition is related to the drug dose and plasma concentration.^{45–47} Tirofiban (Aggrastat) is the most developed peptidomimetic compound; it is an analogue of tyrosine that is a highly potent antagonist of fibrinogen binding to $\alpha_{IIb}\beta_3$. This also has a short half life of 90–120 minutes and relies on renal clearance.⁴⁵

Drugs from these three groups have been evaluated in the following clinical situations: PCI with and without stenting, medical management of acute coronary syndromes, and acute myocardial infarction both as an adjunct to lytic therapy and for primary PCI. A large and varied group of trials have been carried out (see tables 1–5).

Intravenous $\alpha_{IIb}\beta_3$ receptor antagonists in PCI (see table 1)

The intravenous use of $\alpha_{IIb}\beta_3$ antagonists has been shown to be effective in patients undergoing PCI (EPIC, EPILOG, and CAPTURE) and stenting (EPISTENT).^{48–51} The benefits are additional to those achieved with other antiplatelet agents and are most prominent with abciximab. In the IMPACT II trial negative results were found with eptifibatide in high and low risk patients undergoing PCI.⁵² The results were felt to be due to inadequate platelet inhibition with the dose used, and in ESPRIT (where a higher dose was used) eptifibatide was demonstrated to be highly effective in PCI with stenting.⁵³ TARGET was a head to head comparison of tirofiban versus abciximab in patients with acute coronary

syndromes undergoing PCI. The findings demonstrated that tirofiban offered less protection from major ischaemic events than did abciximab with no significant differences in the rates of major bleeding complications or transfusion.⁵⁴ However, there is evidence that the levels of platelet inhibition during the first four hours after receiving a bolus of tirofiban were suboptimal in this study in contrast to the predictable and generally optimal effects of abciximab in the first few hours after bolus administration.⁵⁵

There is now compelling evidence for the routine use of $\alpha_{IIb}\beta_3$ antagonists as an adjunct to aspirin and heparin in patients undergoing PCI.

Intravenous $\alpha_{IIb}\beta_3$ antagonists in acute coronary syndromes (see table 2)

The role of $\alpha_{IIb}\beta_3$ antagonists in the treatment of acute coronary syndromes, independent of the use of coronary revascularisation, was tested in PRISM, PRISM-PLUS, PURSUIT, PARAGON, and GUSTO IV-ACS.^{56–60} There was overall benefit in the groups treated with $\alpha_{IIb}\beta_3$ antagonists; however, the results of GUSTO IV-ACS were disappointing and revealed no benefit of abciximab when added to aspirin and heparin. In TACTICS an early invasive strategy was compared to an early conservative strategy, and the primary endpoint was significantly reduced in the early invasive group.⁶¹

While there is clear benefit for adjunctive treatment with $\alpha_{IIb}\beta_3$ antagonists in patients with acute coronary syndromes before revascularisation, their role in the purely medical management of these patients is less certain, particularly since many physicians are currently using the combination of aspirin, clopidogrel, and low molecular weight heparin for the management of these patients, which is an advance in practice since trials such as PURSUIT and PRISM.

Intravenous $\alpha_{IIb}\beta_3$ antagonists for primary PTCA in acute myocardial infarction (see table 3)

The use of $\alpha_{IIb}\beta_3$ antagonists has been assessed in primary PTCA for acute myocardial infarction in ADMIRAL, RAPPORT, and CADILLAC.^{62–64} Abciximab was shown to improve the results of primary angioplasty for the treatment of acute myocardial infarction in the ADMIRAL trial. In RAPPORT, abciximab was associated with a significant reduction in early major adverse cardiac events. In the CADILLAC trial, PTCA alone was compared to PTCA plus abciximab therapy, stenting alone, and stenting plus abciximab therapy. There was no long term benefit from abciximab after primary stenting, although abciximab did reduce the rates of subacute thrombosis and recurrent ischaemia leading to repeated revascularisation of the target vessel during the first few weeks after PTCA or stenting.

On the basis of these trials, there is no definite indication for $\alpha_{IIb}\beta_3$ antagonists as an adjunct to primary PTCA as it has been demonstrated to have variable effects.

Intravenous $\alpha_{IIb}\beta_3$ antagonists as adjuncts to lytic therapy in acute myocardial infarction (see table 4)

Combining a $\alpha_{IIb}\beta_3$ antagonist with a thrombolytic has been evaluated in the management of acute myocardial infarction. The combination of half dose recombinant tissue-type plasminogen activator (rt-PA) and abciximab used in the TIMI 14 angiographic patency study resulted in some of the highest rates of optimal (TIMI-3) flow seen among trials of pharmacological reperfusion.⁶⁵

The large GUSTO V outcome study compared reteplase with half dose reteplase plus abciximab in 16 588 patients. The results were disappointing, with no significant difference in 30 day mortality rates. The reduction in the number of the secondary endpoints in the combination group, including reinfarction and the need for urgent revascularisation was

Table 1 $\alpha_{IIb}\beta_3$ Antagonists in percutaneous coronary intervention (PCI)

Trial (year)	Full name	Agent used (n)	Entry criteria	Primary endpoints	Primary endpoint outcome	Complications/comments
EPIC (1994)	Evaluation of $\epsilon 7E3$ for Prevention of Ischaemic Complications	Abciximab (2099)	High risk patients undergoing PCI	30 day composite end point: death, MI, CABG or repeat PCI	12.8% in placebo v 8.3% in abciximab group ($p=0.008$)	More frequent bleeding and transfusions in abciximab treated patients, although risk of ischaemic complications less
EPILOG (1997)	Evaluation in PTCA to Improve Long-term Outcome with Abciximab GPIIb/IIIa Blockade	Abciximab (2792)	High and low risk patients undergoing PCI	30 day composite end point: death, MI or urgent revascularisation	5.7% in abciximab group v 11.7% placebo ($p<0.001$)	No significant differences in bleeding. Abciximab reduces ischaemic complications in patients undergoing PTCA
IMPACT II (1997)	Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II	Eptifibatide (4010)	Patients undergoing elective, urgent, or emergency PCI	30 day composite end point: death, MI, unplanned CABG or repeat PCI or stent for abrupt closure	11.4% placebo, 9.9% in high ($p=0.22$) and 9.1% low dose eptifibatide ($p=0.063$)	No increased bleeding, however dose of eptifibatide used felt to be too low
CAPTURE (1997)	$\epsilon 7E3$ Antiplatelet Therapy in Unstable Refractory Angina	Abciximab (1265)	Refractory unstable angina	Death, MI, or urgent intervention within 30 days	11.3% in abciximab group v 15.9% placebo ($p=0.012$)	Major bleeding more common in abciximab group. By 6 months no difference between groups
RESTORE (1997)	Randomised Efficacy Study of Tirofiban for Outcomes and Restenosis Trial	Tirofiban (2139)	ACS patients undergoing balloon angioplasty or directional atherectomy within 72 hours	30 day composite end point: death, MI, CABG, or repeat angioplasty and stent	Non-significant reduction in primary endpoint but significant reduction at 48 hours and 7 days	No difference in major bleeding between groups. Tirofiban protects against early cardiac events related to thrombotic closure
EPISTENT (1998)	Evaluation of Platelet IIb/IIIa Inhibitor In Stenting	Abciximab (2399)	Patients undergoing elective or urgent coronary intervention suitable for balloon angioplasty or stenting	30 day composite end point: death, MI, CABG or repeat PCI	10.8% in stent + placebo, 5.3% in stent + abciximab, 6.9% PTCA + abciximab	No difference in bleeding. Death and MI still reduced at 1 year. For revascularisation abciximab and stenting offer long term clinical benefits
ERASER (1999)	The Evaluation of ReoPro and Stenting to Eliminate Restenosis	Abciximab (225)	Elective patients requiring one intracoronary stent implantation	% In-stent volume obstruction	No difference in endpoints between all groups	Abciximab does not reduce neointimal proliferation or restenosis
ESPRIT (2000)	Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Receptor Using Integrilin Therapy Trial	Eptifibatide (2064)	Undergoing non-urgent PCI with a variety of stents	Combined endpoint: death, MI, urgent repeat revascularisation, and need for bail out GPIIb/IIIa receptor blockade at 48 hours	Significant reduction from 10.5% to 6.6% ($p=0.0017$)	Higher dose of eptifibatide felt to be responsible for better outcome compared to IMPACT II
TARGET (2001)	Do Tirofiban And ReoPro Give Similar Outcomes Trial	Abciximab v tirofiban	Patients (either elective or urgent) undergoing PCI with "intent to stent". Not acute MI	Death, MI, or urgent revascularisation, at 30 days	7.6% in tirofiban group and 6% in abciximab group ($p=0.037$)	Abciximab found to be superior particularly in ACS patients. No difference in major bleeding

ACS, acute coronary syndromes; CABG, coronary artery bypass graft; MI, myocardial infarction; n, number of patients; PTCA, percutaneous transluminal coronary angioplasty.

counterbalanced by an increase in bleeding complications and no improvement in the survival rates at one year.⁶⁶

More investigation of the use of $\alpha_{IIb}\beta_3$ antagonists with lytic therapy in acute myocardial infarction is required before a definite decision on their role can be made.

Oral $\alpha_{IIb}\beta_3$ antagonists (see table 5)

To date, large trials of oral $\alpha_{IIb}\beta_3$ antagonists (sibrafiban, orbofiban, and xemilofiban), have reported no obvious benefit and there are excess bleeding complications in those assigned these drugs. Both the Orbofiban in Patients with Acute Coronary Syndromes Thrombolysis in Myocardial Infarction 16 trial (OPUS-TIMI 16) and Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischaemic Heart Events Post-Acute Coronary Syndromes 2 (SYMPHONY 2) trial demonstrated statistically significant increased mortality in the treatment groups.^{67, 68} Why there should be a detrimental effect compared to intravenous $\alpha_{IIb}\beta_3$ antagonists remains unclear. The increase in mortality may relate to a prothrombotic effect, unfavourable pharmacokinetics, or indeed there may be paradoxical platelet activation with oral

agents. Understanding why there is apparently an adverse effect from the oral agents may lead to the design of better agents and dosing regimens.

Overall the development and use of $\alpha_{IIb}\beta_3$ antagonists have been crucial in the management of cardiovascular disease. Their benefit when used in conjunction with PCI is undoubted and now is accepted practice. Their use in the management of acute coronary syndromes without mandatory PCI has a lesser effect but has been proven in the majority of trials. Their use must be combined with risk stratification and other antiplatelet agents.

Further development of these agents for the treatment of acute coronary syndromes including acute myocardial infarction is required.

CONCLUSION

Ischaemic heart disease is the biggest killer in the Western world and therefore any treatment that improves its outcome may save large numbers of lives. In recent years much attention has focused on inhibiting platelet aggregation in

Table 2 $\alpha_{IIb}\beta_3$ Antagonists in acute coronary syndromes (ACS)

Trial (year)	Full name	Agent used (n)	Primary endpoints	Primary endpoint outcome	Complications/comments
PRISM (1998)	Platelet Receptor Inhibition in Ischaemic Syndrome Management	Tirofiban (3232)	Death, MI or refractory ischaemia at 48 hours	Heparin group 5.6% v tirofiban group 3.8% ($p=0.01$)	Initial benefit lost after infusion ceased. No difference in major bleeding
PRISM-PLUS (1998)	Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms	Tirofiban (1915)	Death, MI or refractory ischaemia at 7 days	17.9% heparin v 12.9% tirofiban + heparin ($p=0.004$). Benefit present at 30 days and 6 months	Unexpected excess 7 day mortality in tirofiban alone (4.6%) v heparin alone (1.1%). No differences in bleeding
PURSUIT (1998)	Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy	Eptifibatide (10 948)	Death and non-fatal MI at 30 days	Eptifibatide 14.2% v placebo 15.7% ($p=0.04$)	Eptifibatide effective in reducing primary endpoint in patients with ACS. Increased bleeding in eptifibatide group
PARAGON (1998)	Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in the Global Organization Network	Lamifiban (2282)	Death and non-fatal MI at 30 days	Non-significant difference	However low dose Lamifiban and heparin yielded similar bleeding rates as the control group but fewer ischaemic events at 6 months
TACTICS (TIMI 18) (2001)	(Thrombolysis in Myocardial Infarction) Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy	Tirofiban (2200)	Death, non-fatal myocardial infarction, and rehospitalisation for an ACS at six months	In early invasive group 15.9% v 19.4% with conservative strategy ($p=0.025$)	In intermediate to high risk ACS patients an early invasive strategy is preferable. In low risk patients the outcome of both strategies similar. Increased bleeding in early invasive group
GUSTO IV-ACS (2001)	Global Utilisation of Strategies to Open Occluded Arteries-IV	Abciximab (7800)	All cause mortality, composite endpoint of death, or MI, at 30 days	No risk reduction	Abciximab is not beneficial as first line management of ACS

MI, myocardial infarction; n, number of patients.

order to prevent thrombotic occlusion. Currently many agents are available but there is room and evidence for the development of others. Aspirin remains the cornerstone of therapy, although its adverse effects on gastric mucosa contribute to haemostatic compromise. Clopidogrel is beneficial in prevention as well as medical and interventional therapy of acute coronary syndromes. Dipyridamole has not been proven as an effective agent in cardiovascular disease, although it is of benefit in cerebrovascular disease. The $\alpha_{IIb}\beta_3$

antagonists are effective intravenous agents in PCI but their role in the conservative (non-interventional) management of acute coronary syndromes is more controversial.

Platelets not only interact with each other but also leucocytes and it appears increasingly likely that therapy targeted on this interaction could be effective. Antiplatelet therapy is now an accepted weapon in the arsenal of treatment for vascular disease but further research and developments will increase its efficacy.

Table 3 $\alpha_{IIb}\beta_3$ Antagonists for primary percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction (MI)

Trial (year)	Full name	Agent used (n)	Entry criteria	Primary endpoints	Primary endpoint outcome	Complications/comments
RAPPORT (1998)	ReoPro for Acute Myocardial Infarction and Primary PTCA Organization and Randomised Trial	Abciximab (483)	Within 12 hours of the onset of acute MI, referred for angioplasty	All-cause mortality, non-fatal MI, fatal MI, urgent TVR at 6 months	No difference in primary endpoint however abciximab significantly reduced death, reinfarction or TVR at all time points measured (7 and 30 days and 6 months)	Major bleeding occurred significantly more in abciximab group
CADILLAC (2000)	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications	Abciximab (2082)	Symptoms of MI for >30 min within 12 hours and lytic eligible ECG	Composite of death, reinfarction, disabling stroke and ischaemia driven revascularisation of target vessel	At 6 months PTCA alone 20%, after PTCA plus abciximab 16.5%, after stenting 11.5% and after stenting plus abciximab 10.2%	No long term benefit of abciximab after primary stenting, although abciximab did reduce rates of repeated revascularisation during first few weeks post-initial procedure
ADMIRAL (2001)	Abciximab Before Direct Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow Up	Abciximab (300)	Patients undergoing stenting for symptoms of acute MI within 12 hours of enrolment and had ST elevation in 2 contiguous leads	Composite of death, reinfarction or urgent revascularisation at 30 days	Abciximab group 6% v 14.6% in placebo group ($p=0.01$) and remained significant through 6 months of follow up (7.4% v 15.9%, $p=0.02$)	One major bleeding event occurred in the abciximab group compared to none in placebo group

ECG, electrocardiography; n, number of patients; TVR, target vessel revascularisation.

Table 4 $\alpha_{IIb}\beta_3$ Antagonists as adjuncts to lytic therapy in acute myocardial infarction (MI)

Trial (year)	Full name	Agent used (n)	Entry criteria	Primary endpoints	Outcome	Complications/ comments
TIMI 14 (1999)	Thrombolysis In Myocardial Infarction (TIMI) 14 Trial	Abciximab (888)	Chest pain (within 12 hours) and lytic eligible ST elevation on ECG	Angiographic achievement of TIMI grade 3 flow at 90 min	Abciximab and half dose alteplase resulted in high rates of TIMI 3 flow (77% combination v 62% alteplase alone at 90 min, $p=0.02$)	Abciximab increased TIMI 3 flow in conjunction with half dose alteplase, without an increase in major bleeding
SPEED (2000)	Strategies for Patency Enhancement in the Emergency Department	Abciximab (224)	Chest pain and lytic eligible ST elevation on ECG	Angiographic achievement of TIMI grade 3 flow at 60–90 min	Adding reteplase to abciximab treatment of acute MI enhanced the incidence of early complete reperfusion	Adding reteplase to abciximab was associated with a trend towards increased bleeding
GUSTO V (2001)	Global Utilization of Streptokinase and Tissue Plasminogen Activator for the Occluded Coronary Arteries Trial-MI	Abciximab (16 588)	Chest pain >30 min and within 6 hours and lytic eligible ECG	30 day mortality	No significant difference between reteplase (5.9%) v reteplase and abciximab (5.6%)	Reduction in complications of MI by combination group was counterbalanced by increase in bleeding complications and no improvement in 1 year survival
ASSENT-3 (2001)	Efficacy and safety of Tenecteplase in Combination with Enoxaparin, Abciximab or Unfractionated Heparin	Abciximab (6095)	Chest pain within 6 hours and lytic eligible ECG	Composite of 30 day mortality, in-hospital reinfarction, refractory ischaemia or one of above plus in-hospital intracranial haemorrhage or major bleed	There were significantly fewer efficacy, and efficacy plus safety endpoints in the enoxaparin and abciximab groups compared to the unfractionated heparin group	Tenecteplase plus enoxaparin or abciximab appeared to reduce the complications of acute myocardial infarction

ECG, electrocardiography; n, number of patients.

MULTIPLE CHOICE QUESTIONS (ANSWERS AT END OF REFERENCES)In each of the following select the **one** correct option.

1. Which of the following is not a platelet agonist?

- (A) ADP
- (B) Collagen
- (C) Serotonin
- (D) Nitric oxide

2. Aspirin exerts its antiplatelet effect by:

- (A) Blocking the final common pathway of platelet activation
- (B) Irreversibly inhibiting platelet cyclo-oxygenase
- (C) Reversible inhibition of platelet ADP receptors
- (D) Inhibiting the conversion of cAMP to 5'AMP

3. Regarding aspirin therapy, which one of the following is true:

- (A) Reducing the daily dose from 300 mg to 75 mg has been shown to decrease gastrointestinal complications

Table 5 Oral $\alpha_{IIb}\beta_3$ antagonists

Trial (year)	Full name	Agent used (n)	Entry criteria	Primary endpoints	Primary endpoint outcome	Complications/comments
OPUS-TIMI 16 (2000)	Orbofiban in Patients with Unstable Coronary Syndromes	Orbofiban (10 302)	ACS within 72 hours; history of CVD, positive cardiac markers or ECG changes	Death, MI, recurrent ischaemia, urgent revascularisation, or stroke	Trial terminated prematurely because of an unexpected increase in 30 day mortality in the orbofiban group	Orbofiban associated with increased mortality in broad population of ACS patients
SYMPHONY (2000)	Sibrafiban versus Aspirin to Yield Maximum Protection from Ischaemic Heart Events Post- Acute Coronary Syndromes	Sibrafiban (9233)	ACS after stabilisation	Death, MI, and severe recurrent ischaemia at 90 days	No difference between aspirin group (9.8%), low (10.1%), or high dose sibrafiban (10.1%)	Sibrafiban showed no additional benefit over aspirin and was associated with increased major bleeding
EXCITE (2000)	Evaluation of Oral Xemilofiban in Controlling Thrombotic Events	Xemilofiban (7232)	Patients with angio-graphic evidence of CAD requiring PCI	Death, MI and recurrent revascularisation at 30 and 182 days	No difference between placebo (13.5%), low (13.9%) or high dose xemilofiban (12.7%) at 182 days	Significant increase in major bleeding in xemilofiban group
BRAVO (9200)	Blockade of the IIb/IIIa Receptor to Avoid Vascular Occlusion	Lotrafiban (9200)	Recent ACS, TIA, CVA, or PVD	Death, stroke, recurrent ischaemia, or revascularisation at 6/12- 2 years	Stopped at interim analysis because lotrafiban had a higher mortality than placebo (2.7% v 2.0%)	Lotrafiban associated with higher mortality, more major bleeding, and a greater risk of serious thrombocytopenia

ACS, acute coronary syndromes; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; ECG, electrocardiography; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Key points

Aspirin

- This is the first line treatment for patients with vascular disease without contraindications. A daily dose of 75–150 mg for long term prevention of serious vascular events is recommended for high risk patients.
- Where an immediate antithrombotic effect is required (for example, an acute myocardial infarction or cerebrovascular accident) a loading dose of 300 mg is recommended.

Clopidogrel

- Clopidogrel has similar safety and tolerability compared with aspirin and is at least as effective in secondary prevention for patients with vascular disease. Clopidogrel is used for long term prevention in patients who cannot tolerate aspirin.
- In patients with non-ST elevation myocardial infarction, clopidogrel in combination with aspirin is more beneficial than aspirin alone. This combination is associated with an increased incidence of serious haemorrhage.
- Clopidogrel is given to patients after stent insertion during PCI. Recent evidence suggests that clopidogrel should be given to all patients pre-PCI and continued long term afterwards.

GPIIb/IIIa receptor antagonists

- Intravenous GPIIb/IIIa receptor antagonists are an effective treatment in patients undergoing PCI. Their role in the medical management of acute coronary syndromes and as an adjunct to lytic therapy in acute myocardial infarction is less certain.
- Trials of oral GPIIb/IIIa antagonists have reported no benefit and there are excess bleeding complications in those assigned the drugs.

- (B) Aspirin has a very strong antiplatelet effect
- (C) Aspirin is given with streptokinase in acute myocardial infarction to prevent pyrexia
- (D) The Antithrombotic Trialists Collaboration confirmed the overall benefit of antiplatelet therapy for secondary prevention in high risk patients

- Regarding the thienopyridines which one of the following is true:
 - Ticlopidine is as safe as clopidogrel
 - In the CAPRIE trial clopidogrel was found to be not as effective as aspirin for secondary prevention in patients with atherosclerotic disease
 - Clopidogrel acts at the platelet P2Y₁₂ receptor
 - Clopidogrel does not require hepatic metabolism
- Regarding the CURE Study which one of the following is true:
 - There was an increase in major bleeding in the clopidogrel arm of the trial
 - Patients with acute coronary syndromes were randomly assigned clopidogrel or placebo within four weeks of presentation

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- Patients with ST elevation acute coronary syndromes were recruited
- Which of the following is true?
 - Dipyridamole should be used in all patients with ischaemic heart disease
 - Dipyridamole exerts its antiplatelet effect by blocking cyclo-oxygenase in platelets
 - Dipyridamole has been shown to have a significant benefit in the secondary prevention of stroke
 - Which one of the following statements about abciximab is true?
 - Abciximab is a monoclonal antibody
 - Abciximab is a non-peptide inhibitor
 - Abciximab's antiplatelet effect ceases immediately when the infusion is stopped
 - Abciximab is isolated from snake venom
 - Glycoprotein IIb/IIIa receptor antagonists were studied in PCI in which one of the following trials?
 - GUSTO IV
 - PURSUIT
 - PRISM
 - EPIC
 - Which one of the following was not a trial of oral glycoprotein IIb/IIIa receptor antagonists?
 - OPUS
 - SYMPHONY
 - EXCITE
 - CADILLAC
 - Which one of the following statements is true?
 - All trials of glycoprotein IIb/IIIa receptor antagonists as adjuncts to lytic therapy in acute myocardial infarction have shown benefit
 - Intravenous glycoprotein IIb/IIIa receptor antagonists are effective in patients undergoing PCI
 - Oral glycoprotein IIb/IIIa receptor antagonists are now accepted treatment for acute coronary syndromes

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ANSWERS

1. D; 2. B; 3. D; 4. C; 5. A; 6. C; 7. A; 8. D; 9. D; 10. B.

IMAGES IN MEDICINE.....

Painful Horner’s syndrome caused by carotid dissection



Figure 1 Right Horner’s syndrome (published with patient’s permission).

This 45-year old woman presented with 10 days of right sided neck and head pain. Figure 1 demonstrates a right Horner’s syndrome, fig 2, taken with the curtains open, demonstrates the oculosympathetic miosis that is more easily seen in the dark. Magnetic resonance angiography of her cerebral circulation confirmed a right internal carotid dissection (fig 3); fig 4 demonstrates a false aneurysm and intramural thrombus. A painful Horner’s syndrome should be considered due to carotid dissection until proved otherwise. The investigation of choice is magnetic resonance angiography of the cerebral circulation but cross sectional imaging should always include the neck to look for intramural thrombus.

Dissection is believed to cause up to 25% of strokes in younger patients, the majority of whom will have warning symptoms that potentially allow a window of opportunity to prevent an infarct. The patient was managed with low molecular weight heparin, then warfarin, and has had no ischaemic symptoms after three months of follow up.

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Figure 2 Oculosympathetic miosis (published with patient’s permission).



Figure 3 Magnetic resonance angiography confirming a right internal carotid dissection.



Figure 4 Magnetic resonance angiography showing a false aneurysm (arrow) and intramural thrombus.