Introduction

In the management of acute coronary artery disease, as in the words of the ancient Chinese proverb, we live in 'interesting times'. The rate of development of diagnostic techniques, of improved pharmacological and interventional therapies and of prognostic tools is unprecedented. No sooner have guidelines for the management of acute coronary artery disease appeared in print, or even in electronic format, than they require updating in the light of the latest evidence. In addition, educational, logistic and financial challenges mean that clinical practice lags well behind the evidence and consensus recommendations. Each major advance in management requires careful consideration to optimise benefit and minimise hazard. Thus, this series of articles sets out to put the recent findings concerning the use of clopidogrel into a wider clinical context, as part of the effort to bridge the gap between evidence and practice.

The advent of more sensitive markers of myocardial damage has led to a change in the diagnostic criteria for myocardial infarction. This may be a scientific advance but it presents conceptual and educational challenges. The reclassification will increase the burden of myocardial infarction for healthcare providers.

Greater diagnostic sensitivity has caused medical language to change. Newer terms like 'acute coronary syndromes' and a number of terms that are used interchangeably but which may not be synonymous—such as non-ST elevation myocardial infarction (NSTEMI) and non-Q-wave myocardial infarction—are now part of everyday parlance, but when we use such terms imprecisely they may cause confusion.

The evidence base to guide doctors when and how best to intervene with diagnostic angiography and revascularisation is growing and demonstrating consistent findings. This challenges the providers of cardiovascular medicine to provide sufficient human, technical and financial resources to achieve the potential gains in health benefit.

Changes in the requirements for caring for patients with coronary artery disease have altered the roles of all those involved in the delivery of care, irrespective of the locus of care. Consequently, primary care physicians and nurses now play an increasing role in the triage and management of these patients. This widens the educational and quality control challenges to ensure that standards are consistently high and to ensure that relevant personnel receive appropriate training.

Advances in pharmacology have increased the number of therapeutic options available but evidence about new drugs is rarely absolute or complete, and the emergence of these agents may present dilemmas for those who care for patients. The list of effective agents grows longer and it is critical to identify those agents that add to clinical benefit and those agents that have been superseded or replaced.

Keith Fox
Guest Editor

The emergence of guidelines can be helpful but too often guidelines from different national and international sources have caused confusion. There is a risk that 'guideline overload' may lead to inertia. Fortunately, the recent American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines on the management of acute coronary syndromes are concordant in most aspects and they give simple, clear, evidence-based guidance. Guidelines resolve some of the apparent or real dilemmas in treatment options but they do not remove the need for clinical judgement nor should they be used as thoughtless directives insensitive to the needs of each individual patient.

Clopidogrel is a relatively new antiplatelet agent that has already had widespread clinical experience in many parts of the world. It has a large evidence base to support its deployment, with more than 30,000 patients randomised in completed studies and a large number of studies already started or planned. This emerging evidence base does not, however, answer all our questions about the role of clopidogrel in cardiovascular disease.

For this supplement we have assembled an expert faculty from a range of professional backgrounds in order to focus on some of the clinically relevant questions about clopidogrel. We have attempted to provide clear evidence about where clopidogrel might fit in these 'exciting times'.

Keith Fox
Professor of Cardiology
The Royal Infirmary of Edinburgh, 1 Lauriston Place,
Edinburgh, EH3 9YW.
(email: k.a.a.fox@ed.ac.uk)

The role of platelets and antiplatelet therapy in atherothrombotic disease

ALISON H GOODALL

Abstract

Platelet-initiated thrombus plays a central role in the pathogenesis of arterial thrombotic disease. Platelets are activated by a range of physiological agonists including thrombin, ADP, thromboxane and collagen, acting in co-operation. ADP, though a weak agonist on its own, is important in enhancing platelet activation induced by other agents. Activation results in platelet adhesion, aggregation and degranulation leading to thrombus growth. Platelets also reinforce thrombus formation through platelet-mediated thrombin generation and the release of PAI-1 that inhibits fibrinolysis. Antiplatelet therapy is therefore of potential benefit both prior to and during a thrombotic episode. The commonly used antiplatelet drugs inhibit specific, single pathways of platelet activation but have overall benefit. Inhibition of intracellular activation pathways can be achieved with aspirin (which inhibits platelet cyclo-oxygenase) and dipyridamole (which inhibits phosphodiesterase). Two related thienopyridine derivatives, ticlopidine and clopidogrel, are specific inhibitors of the $P2Y_{12}$ ADP receptor. They have comparable pharmacological activity but clopidogrel has a better safety profile. A number of potent glycoprotein IIb/IIIa antagonists have been developed for therapeutic use. They are effective in percutaneous coronary intervention, though data from primary stenting trials are less positive. The recent update of the meta-analysis of trials of antiplatelet therapy by the Antithrombotic Trialists' Collaboration has confirmed the benefit of antiplatelet therapy in secondary prevention.

Key words: platelet biology and pathophysiology, plaque rupture, thrombosis, antiplatelet drugs, ATTC study.

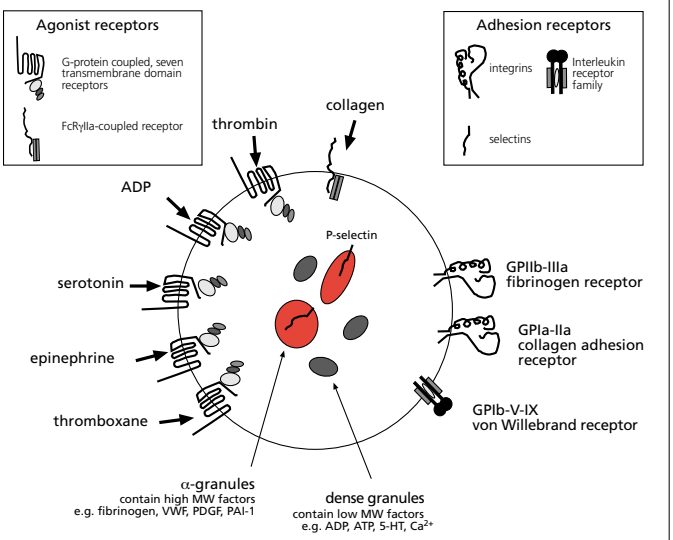
Introduction

It is well accepted that platelet-initiated thrombus plays a central role in the pathogenesis of arterial thrombotic disease.[1,2] With the publication of the latest meta-analysis from the Antithrombotic Trialists' Collaboration (ATTC 2002)[3] the importance of antiplatelet therapy in secondary prevention in patients at high risk has been confirmed. This article reviews our current understanding of the role of platelets in arterial thrombosis, and the mechanism of action of the commonly used antiplatelet drugs.

Department of Clinical Biochemistry, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Groby Road, Leicester, LE3 9QP.
Alison H Goodall, Reader

Correspondence to: Dr A H Goodall
(email: ahg5@le.ac.uk)

Figure 1. The major platelet agonist and adhesion receptors



Key: ADP = adenosine diphosphate; ATP = adenosine triphosphate; 5-HT = serotonin; GP = glycoprotein; MW = molecular weight; PAI-1 = plasminogen activator inhibitor-1; PDGF = platelet-derived growth factor; VWF = von Willebrand factor

Platelets and arterial wall thrombosis

Arterial disease is characterised by the formation of white, or platelet-rich, thrombus at the site of damage to an atherosclerotic plaque. Plaque rupture is estimated to account for 70–80% of acute coronary thrombotic events, with plaque erosion accounting for the majority of the rest.[4] Occlusive thrombotic events are predominantly associated with unstable plaques, defined as type VI lesions.[5] Such lesions are relatively acellular, are full of extracellular lipid and denuded of fibrous collagen.[4,6] They are rich in prothrombotic tissue factor, predominantly in the form of microparticles derived from apoptotic cells within the plaque.[7] The content of such lesions has been shown to be particularly thrombogenic after disruption.[4,6,8]

Thus the resultant 'gruel' within the plaque contains a range of potent prothrombotic factors, which on exposure to the circulating blood cause an explosive thrombotic response. Central to this response are platelets, and their ability to adhere to the vessel wall and promote mural thrombus under conditions of high arterial flow/high wall shear rates. Platelet activation is orchestrated by specific agonist and adhesion receptors on the platelet surface (figure 1).

Platelets adhere to von Willebrand factor (VWF) in the vessel wall under high wall shear rates, via the glycoprotein (GP)Ibα receptor.[9] Locally released platelet agonists (e.g. thrombin, collagen, adenosine diphosphate [ADP]), acting through specific receptors, cause intracellular signalling events that ultimately lead to a conformational change in the GPIIb-IIIa receptor complex.[10] This 'final common pathway' of platelet activation allows the receptor to bind fibrinogen, resulting in platelet-platelet aggregation, and so recruiting further platelets to the growing thrombus. It is this interaction that is targeted by the various classes of GPIIb/IIIa antagonists (table 1). Activated platelets degranulate, releasing factors that potentiate the thrombotic response, in particular ADP and serotonin (5-HT), from the dense granules. Degranulation exposes α-granule P-selectin, which acts as a primary adhesion molecule for leucocytes, serving to recruit granulocytes and monocytes, which contribute inflammatory factors, proteases and fibrinolytic inhibitors to the growing thrombus.

Platelets play other roles, too, in the generation and maintenance of thrombus. Platelet adhesion to collagen can induce plasma membrane phospholipids to 'flip' to the outer surface of the phospholipid bilayer, producing a negatively charged surface for the formation of the tenase and prothrombinase complexes.[11] This leads to a local increase in thrombin generation, activating more platelets and promoting fibrin formation. Platelet-rich thrombus is resistant to fibrinolysis, partly by virtue of forming an impenetrable mass, but more specifically because platelets secrete large amounts of plasminogen activator inhibitor-1 (PAI-1), which stabilises fibrin formed on the activated platelets.[1,12]

Thus platelets provide a reinforced loop in the generation of a thrombus, providing a source of thrombin and other agonists that recruit new platelets. These not only increase and strengthen the thrombus mass, but increase the resistance to fibrinolysis. The logical corollary is that inhibition of platelet activation prior to the onset of a thrombotic event, as well as during a thrombotic episode, should be beneficial.

Mechanisms of platelet activation

Platelets are activated by a number of physiological agonists, each acting through specific receptors and signalling pathways, but all producing the same end results of aggregation and degranulation. With the exception of collagen all agonists act through members of the G-protein-coupled, seven transmembrane domain receptor family, the majority of which give rise to an IP_3-dependent rise in intracellular calcium, predominantly from intracellular stores.

Table 1. Antiplatelet agents

GP IIb/IIIa receptor antagonists	
Humanised murine monoclonal antibodies	abciximab (ReoPro, c7E3)
Synthetic peptides	Integrilin
Non-peptide derivatives	Lamifiban Tirofiban
Orally active agents	Xemilofiban Orbofiban
Thromboxane pathway inhibitors	
COX-1 inhibitors	Aspirin Sulfinpyrazone Indobufene
Thromboxane synthase inhibitors	Dazoxiben
Thromboxane receptor antagonists	GR32191 Sulotroban
Combined thromboxane synthase/ thromboxane receptor inhibitors	Ridogrel Picotamide
Phosphodiesterase inhibitors	Dipyridamole Cilostazol
ADP receptor antagonists	
$P2Y_{12}$ antagonists:	
Thienopyridines	Ticlopidine Clopidogrel
Adenosine analogues	AR-C69931MX
$P2Y_1$ antagonists:	
Adenosine analogues	A2P5P/A3P5P/A3P5PS MRS2279/MRS2179

The platelet response to thrombin

Thrombin activates platelets through PAR-1, which is the prototype member of the Protease Activated Receptor (PAR) family.[13] Human platelets possess a second member of this family, PAR-4, which is cleaved by trypsin and high-dose thrombin. PAR-1 and PAR-4 signal the platelet through both Gq and Gi pathways, raising intracellular calcium (Ca^{2+}) both through IP_3-mediated release of intracellular stores and through reduction of cAMP levels.[13] Thrombin is a 'strong' platelet agonist, capable of producing full aggregation and degranulation. To date no specific inhibitors of the thrombin agonist receptors have been developed for clinical use. Inhibition of this pathway of platelet activation has been through thrombin inhibitors such as heparin, hirudin or newer antithrombins.[14]

The platelet response to ADP

ADP is a 'weak' platelet agonist, capable of inducing platelet adhesion and aggregation but by itself causing relatively little or no degranulation.[15] Two platelet ADP receptors have been recently identified.[16] Both are G-protein coupled receptors belonging to the P2Y family of purinoceptors. $P2Y_1$ is a Gq-coupled receptor that induces platelet shape change via a PLCβ-

mediated elevation in intracellular free Ca^{2+} from intracellular stores. The $P2Y_{12}$ receptor is a Gi-linked receptor responsible for a sustained aggregation response, by inhibiting adenylate cyclase, thus decreasing levels of cAMP inside the platelet. It seems that $P2Y_1$ is the primary receptor that initiates the response to ADP whilst the $P2Y_{12}$ receptor augments the response to ADP and to low levels of other agonists.[16,17] Platelets also carry a P2X1 receptor, which is an ATP-gated ion channel responsible for the rapid influx of calcium into platelets stimulated with ADP.[16] Whilst ADP is a relatively weak agonist on its own it is recognised to be an important co-factor for platelet activation induced by other agonists such as thrombin and collagen,[16-18] which release ADP from platelet-dense granules that feeds back onto the P2Y receptors.

The thienopyridine drugs ticlopidine and clopidogrel are specific inhibitors of the $P2Y_{12}$ ADP receptor. Synthetic ADP receptor antagonists have also been developed: one of these, AR-C69931MX, has a favourable pharmacological profile, with good separation between its antiplatelet effects and its effect on bleeding time, and has been used in preliminary trials (table 1).[19]

The platelet response to thromboxane

Thromboxane is generated within platelets through the stimulation of phospholipase A_2 (PLA_2), which is itself generated in response to stimulation by other agonists. PLA_2 releases arachidonic acid (AA) from membrane phospholipids, which is rapidly transformed in platelets by cyclo-oxygenase-1 (COX-1), first to the unstable endoperoxides PGG_2 and PGH_2, and then converted to thromboxane A_2 (TxA_2) by thromboxane synthase. TxA_2 released from the platelet can then act at close range on thromboxane receptors (TP) on platelets and other vascular cells. The effects of thromboxane are most evident in the response to ADP and other weak agonists, where it induces full activation and degranulation. Strong agonists such as thrombin, although generating TxA_2, do not require thromboxane to exert their full effect.

Aspirin is the main drug used to inhibit this pathway although a number of other inhibitors of COX-1 and thromboxane synthase and antagonists of the thromboxane receptor have been used as antiplatelet agents (table 1).[20]

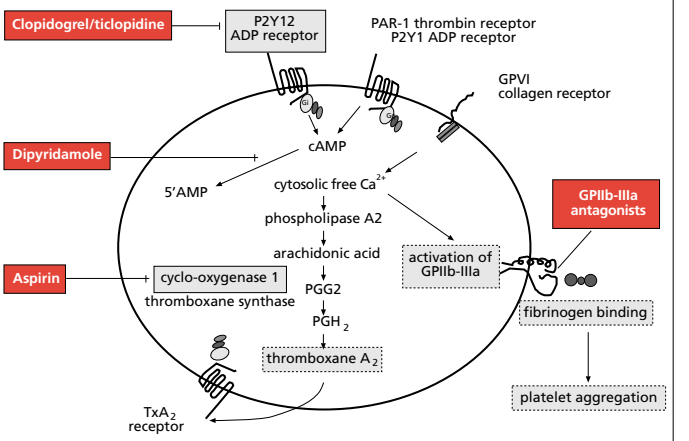
The platelet response to collagen

Several collagen receptors have been described in platelets but from recent evidence it is now clear that the main collagen receptors are the integrin $\alpha_2\beta_1$, which serves as the primary adhesive receptor for collagen, and GPVI, which principally mediates signalling.[21] GPVI is unique amongst the platelet agonist receptors in that it is a member of the immunoglobin superfamily of membrane receptors, associated with the Fc-gamma receptor, FcRγIIa. No antiplatelet agents targeting GPVI have yet been developed.

Combined agonist effects

While each of the platelet agonists has its unique receptor-mediated signalling pathway, there is considerable interdependence between them. ADP and 5-HT are released on degranulation; thromboxane is synthesised, and thrombin can be generated.

Figure 2. The sites of action of the main antiplatelet drugs used in patients at high risk of arterial thrombotic disease



Key: AMP = adenosine monophosphate; ADP = adenosine diphosphate; GP = glycoprotein; PAR = protease activated receptor; PG = prostaglandin; TxA_2 = thromboxane A_2

Against this picture of agonist co-operation, inhibition of platelets by targeting specific pathways of activation is effective in reducing the overall platelet response. However, the downside of effective platelet inhibition is that adequate haemostasis must be maintained to prevent bleeding. This balance is an important consideration for effective antiplatelet strategies.

Antiplatelet agents

The sites of action of the main antiplatelet drugs used in patients at high risk of arterial thrombotic disease are shown in figure 2. Although there are many pathways of platelet activation, relatively few have been exploited for antiplatelet therapy. Of the commonly used antiplatelet agents only the GPIIb/IIIa antagonists have been specifically developed as antiplatelet agents, while the antiplatelet effects of aspirin and the thienopyridine drugs ticlopidine and clopidogrel were serendipitous findings.

Inhibition of intracellular activation pathways

Aspirin

Aspirin is a potent inhibitor of platelet cyclo-oxygenase, capable of complete prevention of the conversion of arachidonic acid to TxA_2.[20] It reacts with the cyclo-oxygenase binding site of COX-1 to cause selective and irreversible acetylation of serine reside 529. Because platelets lack the ability to synthesise COX-1 *de novo*, the effects of aspirin last for the life of the platelet (8–10 days). Aspirin has been available for over a hundred years and is, for most patients, the agent of choice for first-line therapy. It has proven antiplatelet efficacy, is generally well tolerated, and its antiplatelet affects are achieved with doses that avoid many of the problems associated with its use as an anti-inflammatory agent. The effects of aspirin are cumulative so that on repeated

low-dose administration more than 95% of platelet COX-1 activity is suppressed after seven days' treatment.

During the 1980s there was considerable debate concerning the 'correct' dose of aspirin since at high doses it inhibits the COX-2 in vascular endothelial cells, leading to a reduction in the release of the platelet inhibitory factor, prostacyclin (PGI_2) from the vessel wall. Doses of around 100 mg were found to inhibit production of TxA_2 in platelets whilst preserving prostacyclin generation by the endothelium. The minimum effective dose for aspirin, taken from evidence from secondary prevention studies, is in the order of 75 mg per day for patients at risk of arteriothrombotic events and 160 mg/day for treatment of acute myocardial infarction.[20]

Aspirin has proven efficacy in reducing thrombotic events in groups of patients,[3,22] has the distinct advantage of low cost and may provide additional anti-inflammatory effects. It is in many ways surprising that aspirin is so effective as it is relatively ineffective against strong agonists like thrombin. Additionally, in a significant subset of patients aspirin is contraindicated because of bleeding problems in patients with haemostatic defects or on anticoagulant therapy. However, the data from the recent Antithrombotic Trialists' Collaboration indicate that in patients with myocardial infarction the risk of major bleeding (i.e. requiring transfusion) is approximately 100 times less than the benefit in terms of prevention of a thrombotic risk.[3] 'Aspirin resistance' has been reported both in patients on long-term aspirin therapy[21,23,24] and as a short-term effect following coronary artery bypass surgery.[23] The mechanism for this apparent loss of inhibitory effects of aspirin is unclear but possible candidates include COX-2[23] or 12-HETE.[24]

Dipyridamole

Of the phosphodiesterase inhibitors (table 1), dipyridamole is the most widely used. This drug is a weak antiplatelet agent that acts to prevent the conversion of cyclic AMP (cAMP) to inactive 5'AMP. Since cAMP inhibits the release of calcium from intracellular stores in the platelet, this has the effect of inhibiting platelet activation and secretion. The antiplatelet effect of dipyridamole is hard to demonstrate *in vitro* but it has shown a significant benefit in secondary stroke prevention, especially in combination with aspirin.

ADP receptor inhibitors

Thienopyridines

The two related thienopyridine derivatives, ticlopidine and clopidogrel are specific inhibitors of the $P2Y_{12}$ ADP receptor.[16,25,26] They have identical pharmacological profiles but different pharmacokinetics.[26] Both drugs are inactive until metabolised in the liver. Metabolites of ticlopidine appear in the circulation three hours after treatment but three days are required for the antiplatelet effect to be seen.[20,26] Side effects from ticlopidine, such as neutropenia (<0.45 x 10^9/L in 0.9% patients) and thrombocytopenia are seen in a significant number of patients as well as rash (5%–10%) and diarrhoea (15%). Although these are reversible on discontinuation of the drug, these side effects have inhibited the use of ticlopidine in long-term, prophylactic therapy.

A number of clinical studies have demonstrated long-term benefit with ticlopidine, over and above the benefits of aspirin, in patients with cerebrovascular ischaemic disease.[27,28] In patients with unstable angina ticlopidine reduced the combined end point of vascular death and non-fatal myocardial infarct by 46% compared to the placebo group.[29] It also performed well against oral anticoagulant regimes in patients undergoing intracoronary stenting,[30] and this has been borne out in the ISAR, FANTASTIC, STARS and MATTIS trials.[31]

Clopidogrel is a closely related compound that has been developed to replace ticlopidine: it lacks many of the adverse effects of the latter drug on the bone marrow and the gastrointestinal (GI) system. Clopidogrel has comparable pharmacological activity to ticlopidine and a better safety profile.[26,32] The S-enantomer of clopidogrel is rapidly metabolised in the liver to form an active metabolite, which has recently been described.[33] Full antiplatelet effect is achieved after either four days on 75 mg/day or within three hours following a loading dose of 300 mg clopidogrel. In the CLASSICS study clopidogrel, in combination with aspirin, gave significant benefit in patients undergoing intracoronary stenting.[34] Because of its better safety profile clopidogrel is being used in the long-term treatment in patients at risk of thrombotic events. The CAPRIE study of 19,185 patients with atherosclerotic cardiovascular or peripheral vascular disease, randomised to receive either clopidogrel (75 mg) or aspirin, showed a small but significant reduction in the combined end point in the clopidogrel group over the three-year follow-up, and the incidence of significant neutropenia was similar in both groups.[35]

One issue that will emerge is the relative benefits of combined therapy with clopidogrel and aspirin for long-term therapy. The combination of aspirin and a thienopyridine shows a greater effect on platelet function than either drug on its own,[26,36] but can increase the bleeding time.[36] The data from CLASSICS showed that combined short-term therapy gave no increase in bleeding complications over aspirin alone.[34] The CURE study of long-term therapy with clopidogrel plus aspirin in patients with non-ST elevation ACS showed a 1% actual increase in major bleeding.[37]

GPIIb/IIIa antagonists

Regardless of the mechanism of activation, the final common pathway for platelet activation is the aggregation of platelets through fibrinogen bound to GPIIb-IIIa via the RGD (arginine-glycine-alanine) sequence in the fibrinogen α-chain. A number of potent GPIIb/IIIa antagonists have been developed for therapeutic use (table 1).[38] Abciximab (c7E3 or ReoPro) is a 'humanised' Fab fragment of the 7E3 mouse monoclonal antibody; eptifibatide (Integrilin) is a synthetic heptapeptide modelled on the binding site for a snake venom 'disintegrin' that prevents fibrinogen binding to GPIIb/IIIa; while tirofiban (Aggrastat) is a synthetic small molecule RGD peptide mimetic. The appreciation of the potential benefits of long-term antiplatelet therapy has led to the development of orally active, small molecular weight, non-peptide agents with short plasma half-lives (table 1).[38]

Because GPIIb/IIIa antagonists block platelet aggregation they are capable of producing a 'thrombasthenic state' with the associated risk of bleeding. To prevent this, dosing is designed to give <100% receptor occupancy so that some residual platelet function remains. In the case of a severe bleed, the presence of a GPIIb/IIIa antagonist in the circulation presents a potential problem which is proportional to the strength of binding of the drug to its receptor and its plasma half-life. Although they are effective inhibitors of platelet aggregation, the GPIIb/IIIa antagonists have little effect on platelet degranulation. This can result in activated platelets in the circulation that express P-selectin, which can bind to leucocytes. Conversely, GPIIb/IIIa antagonists may have a beneficial antithrombotic effect over and above the prevention of platelet aggregation, since they can reduce platelet-mediated thrombin generation by inhibiting the 'outside-in' signalling that occurs when fibrinogen binds to GPIIb/IIIa.[39] The newer, synthetic GPIIb/IIIa antagonists were designed to be specific for platelet GPIIb/IIIa ($\alpha_{IIb}\beta_3$) but abciximab also binds to the vitronectin receptor ($\alpha_v\beta_3$) present on platelets, smooth muscle cells and leucocytes and it has been suggested that this may produce additional anti-restenotic, anti-atherosclerotic and anti-inflammatory benefits by inhibiting smooth muscle cell proliferation and monocyte recruitment.

The intravenous use of GPIIb/IIIa antagonists has been shown to be effective in patients undergoing percutaneous coronary intervention (PCI).[30,40,41] Abciximab has been evaluated in the EPIC, CAPTURE, IMPACT-II and RESTORE trials, with an overall positive outcome, and is approved for use in percutaneous revascularisation. Data from primary stenting trials have been less promising. Whilst there was a reduction in the primary end point with abciximab in the ADMIRAL trial, RAPPORT and CADILLAC saw no benefit with abciximab, and there was an increased incidence of bleeding in the abciximab-treated groups in RAPPORT and ADMIRAL.[30,40,41] The data from GUSTO-IV[42] have thrown into some doubt the benefit of using abciximab in patients with acute coronary syndromes, without PCI. Longer-term studies of tirofiban and the orally active agents lamifiban and eptifibatide in patients with non-ST elevation acute coronary syndromes (PRISM, PRISM-PLUS, PARAGON A and B and PURSUIT) gave an overall benefit in the groups treated with the GPIIb/IIIa antagonists. However, secondary prevention trials with orally active agents (SYMPHONY, 2nd SYMPHONY, OPUS TIMI-16 and EXCITE trials) have been fairly disappointing, with no overall antithrombotic benefit and increased bleeding.[30,40,41]

The issue of combined therapy with IIb/IIIa antagonists and other antiplatelet or antithrombotic agents is important. Overall the results of recent trials have resulted in a diminished enthusiasm for the IIb/IIIa antagonists. It is to be hoped that research will continue to refine the treatment strategies, in particular in relation to combination therapy.

The Antithrombotic Trialists' Collaboration meta-analysis

The recent update of the meta-analysis of trials of antiplatelet therapy by the Antithrombotic Trialists' Collaboration (ATTC)[3] has confirmed the overall benefit of antiplatelet therapy in secondary prevention. The investigators studied data from 195 randomised, case-controlled trials involving 135,640 patients in which aspirin was compared with a placebo control, and 166 trials (81,731 patients) in which another antiplatelet drug was used. The analysis was limited to randomised trials of 200 patients or more, unconfounded by other variables. The primary end points were 'serious vascular events' – fatal and non-fatal MI and fatal and non-fatal stroke. Deaths from unknown causes were included on the likelihood that they would be due to a vascular event. The analysis investigated all eligible trials that were completed before September 1997, so many of the more recent trials with thienopyridines and GPIIb/IIIa antagonists were not included.

There was a highly significant overall benefit of antiplatelet therapy compared to placebo with an odds reduction (OR) of 22% (p<0.0001). The greatest benefit was seen in patients treated for acute MI (OR 30%; p<0.0001; mean treatment period one month) and for secondary prevention following MI (OR 25%; p<0.0001; mean treatment duration 27 months). Antiplatelet therapy was also effective in secondary stroke prevention (OR 22%; p<0.0001; mean treatment duration 29 months) but was less effective in preventing thrombotic events in acute stroke (OR 11%; p=0.0009). Among high-risk patients highly significant benefits were seen in unstable angina (OR 46%), coronary angioplasty (OR 53%) and stable angina (OR 33%). Aspirin was the major antiplatelet agent used, either in studies of single agents (65 trials), or against another antiplatelet agent (27 trials). There was no significant effect of aspirin dose. A total of 101 trials in which an alternative antiplatelet agent was used were analysed. Overall analysis showed no clear advantage but the CAPRIE trial, which was the only trial included with a head-to-head comparison of clopidogrel versus aspirin (19,185 patients), showed a modest benefit of clopidogrel over aspirin (OR 10%; p=0.03).

Key messages

- Effective antiplatelet strategies must balance platelet inhibition with maintenance of haemostasis
- Aspirin is for most patients the agent of choice for first-line therapy, and is surprisingly effective
- Secondary prevention trials with orally active GP IIb/IIIa antagonists have been fairly disappointing
- Results of the ATTC meta-analysis confirm the positive benefits of antiplatelet therapy for secondary prevention of arterial thrombosis in high-risk patients

Conclusions

The results of the ATTC confirm the positive benefits of antiplatelet therapy for secondary prevention of arterial thrombosis in high-risk patients. Aspirin remains an ideal first-line

agent and a low dose (75–150 mg) is as effective as a high dose (150–1,500 mg). Of the newer antiplatelet agents clopidogrel offers some therapeutic benefit over aspirin, with less risk of bleeding than the GPIIb/IIIa antagonists. It remains to be seen whether combined therapy with two antiplatelet agents targeting different pathways of platelet activation, or with combined antiplatelet and antithrombotic drugs, can achieve the necessary therapeutic balance, improving thrombotic outcome without increasing the risk of bleeding.

References

1. Topol EJ. Towards a new frontier in myocardial perfusion therapy; emerging platelet preeminence. *Circulation* 1998;**97**:211-8.
2. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; **340**:115-26.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002;**321**:71-86.
4. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995;**92**:657-71.
5. Stary HC, Chandler AB, Dinsmore RE *et al*. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: A report from the committee on vascular lesions of the council on Atherosclerosis, American Heart Association. *Circulation* 1995;**92**:1355-74.
6. Badimon L. Atherosclerosis and thrombosis: lessons from animal models. *Thromb Haemost* 2001;**86**:356-65.
7. Toschi V, Gallo G, Lettino M *et al*. Tissue factor modulates thrombogenicity of human atherosclerotic plaques. *Circulation* 1997;**95**:594-9.
8. Davies MJ, Richardson PD, Woolf N *et al*. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993;**69**:377-81.
9. de Groot PG, Sixma JJ. Platelet adhesion In: Gresele P, Page C, Fuster V, Vermylen J. *Platelets in thrombotic and non-thrombotic disorders*. Cambridge: Cambridge University Press 2002, 304-18.
10. Savage B, Cattaneo M, Ruggeri ZM. Mechanisms of platelet aggregation. *Curr Opin Hematol* 2001;**8**:270-6.
11. Zwaal RF, Schroit AJ. Pathophysiologic implications of membrane phospholipid asymmetry in blood cells. *Blood* 1997;**89**:1121-32.
12. Zhu Y, Carmeliet P, Fay WP. Plasminogen activator inhibitor-1 is a major determinant of arterial thrombolysis resistance. *Circulation* 1999;**99**: 3050-5.
13. Coughlin SR. Protease-activated receptors in vascular biology. *Thromb Haemost* 2001;**86**:298-307.
14. Harker LA, Hanson SR, Kelly AB. Antithrombotic strategies targeting thrombin activities; thrombin receptors and thrombin generation. *Thromb Haemost* 1997;**78**:736-41.
15. Janes SL, Wilson DJ, Cox AD *et al.* ADP causes partial degranulation of platelets in the absence of aggregation. *Br J Haematol* 1994;**86**:568-73.
16. Gachet C. ADP receptors of platelets and their inhibition. *Thromb Haemost* 2001;**86**:222-32.
17. Jin J, Kunapuli SP. Coactivation of two different G protein-coupled receptors is essential for ADP-induced platelet aggregation. *Proc Natl Acad Sci USA* 1998;**95**:8070-4.
18. Cattaneo M, Canciani MT, Lecchi A *et al*. Released adenosine diphosphate stabilizes thrombin-induced human platelet aggregates. *Blood* 1990;**75**:1081-6.
19. Humphries RG. Pharmacology of AR-C69931MX and related compounds: from pharmacological tools to clinical trials. *Haematologica* 2000;**85**:66-72.
20. Patrono C, Coller B, Dalen JE *et al.* Platelet-active drugs: the relationships among dose, effectiveness and side effects. *Chest* 2001;**119**:395-635.
21. Watson SP. Collagen receptor signalling in platelets and megakaryocytes. *Thromb Haemost* 1999;**82**:365-76.
22. Collaborative overview of randomised trials of antiplatelet therapy. –I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994;**308:**81-106.
23. Weber AA, Przytulski B, Schanz A *et al.* Towards a definition of aspirin resistance: a typological approach. *Platelets* 2002;**13**:37-40.
24. Buchanan MR, Brister SJ. Individual variation in the effects of ASA on platelet function: implications for the use of ASA clinically. *Can J Cardiol* 1995;**11**:221-7.
25. Storey RF. The $P2Y_{12}$ receptor as a therapeutic target in cardiovascular disease. *Platelets* 2000;**12**:197-209.
26. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999;**100**:1667-72.
27. Gent M, Blakely JA, Easton J *et al*. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;**1**:1215-20.
28. Hass WK, Easton JD, Adams HP *et al*. A randomised trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;**321**:501-7.
29. Balsano F, Rizzon P, Violi F *et al*. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. *Circulation* 1990;**82**:17-26.
30. Lablanche JM, McFadden EP, Bonnet JL *et al.* Combined antiplatelet therapy with ticlopidine and aspirin. A simplified approach to intracoronary stent management. *Eur Heart J* 1996;**17**:1373-80.
31. Aronow HD, Topol EJ. Antiplatelet therapy in cardiology In: Gresele P, Page C, Fuster V, Vermylen J. *Platelets in thrombotic and non-thrombotic disorders.* Cambridge: Cambridge University Press 2002,1013-39.
32. Savi P, Herbert JM. Pharmacology of ticlopidine and clopidogrel. *Haematologica* 2000;**85**:73-7.
33. Savi P, Pereillo JM, Uzabiaga MF *et al*. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost* 2000; **84**:891-6.
34. Bertrand ME, Rupprecht HJ, Urban P *et al*. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: The clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624-9.
35. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lance*t 1996;**348**:1329-39.
36. Payne DA, Hayes PD, Jones CI *et al*. Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic anti-platelet action. *J Vasc Surg* 2002;**35**:1204-9.
37. CURE Investigators. Effect of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494-502.
38. Topol EJ, Byzova TV, Plow EF. Platelet GPIIb-IIIa blockers. *Lancet* 1999;**353**:227-31.
39. Butenas S, Cawthern KM, van't Veer C *et al*. Antiplatelet agents in tissue-factor induced blood coagulation. *Blood* 2001;**97**:2314-22.
40. Bhatt DL, Topol EJ. Current role of platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. *JAMA* 2000;**284**:1549-58.
41. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000;**36**:970-1062.
42. GUSTO-IV ACS Investigators. Effects of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early revascularisation; the GUSTO-IV ACS randomised trial. *Lancet* 2001;**357**:1915-22.

Clopidogrel in coronary artery disease

SCOTT A HARDING, KEITH AA FOX

Abstract

Platelets play a central role in both acute coronary syndromes and the ischaemic complications following percutaneous coronary intervention (PCI). Aspirin is a relatively weak antiplatelet agent and only inhibits one of many pathways leading to platelet activation. The thienopyridines, ticlopidine and clopidogrel inhibit platelet activation via the adenosine diphosphate (ADP) pathway.

Ticlopidine, the first generation thienopyridine, is effective in reducing cardiovascular events but is associated with serious haematological toxicity that has limited its use. Clopidogrel, the second generation thienopyridine has improved tolerability and safety. The CAPRIE trial demonstrated that treatment with clopidogrel in patients with vascular disease is associated with a modest reduction in vascular events when compared to aspirin therapy. The CURE trial found that the addition of clopidogrel to aspirin in patients with non-ST segment elevation acute coronary syndromes resulted in a 20% relative risk reduction in the combined end point of cardiovascular death, myocardial infarction or stroke. This benefit was at the cost of a 1% increase in major bleeding. In addition the combination of clopidogrel and aspirin is effective in preventing periprocedural ischaemic events in patients undergoing PCI.

Key words: clopidogrel, ticlopidine, platelets, acute coronary syndromes, percutaneous coronary intervention.

Introduction

Platelet activation, aggregation and thrombus formation are key events in the pathogenesis of both acute coronary syndromes (ACS) and ischaemic complications following percutaneous coronary intervention (PCI). In addition to their role in thrombus formation, activated platelets are a rich source of cytokines, chemokines and growth factors and have important proinflammatory activity.[1,2] Treatment with aspirin has been shown to be of substantial benefit in a wide range of patients with vascular disease. Aspirin treatment markedly reduces the risk of future adverse vascular events among patients with acute myocardial infarction (27% reduction, p<0.001), unstable angina (46% reduction, p<0.0001), stable angina (33% reduction, p=0.0004) and patients undergoing coronary angioplasty (53% reduction, p<0.0002).[3]

Despite the remarkable success of aspirin, patients with cardiovascular disease remain at a substantial risk of future ischaemic events. Based upon data from the international GRACE registry, patients with non-ST elevation ACS experience an 8–13% risk of death, a 1.5–3% risk of stroke and a 30% risk of rehospitalisation within six months of presentation, despite treatment with aspirin in more than 90%.[4] This is not surprising as aspirin is a relatively weak antiplatelet agent which only inhibits one of the many pathways involved in platelet activation and aggregation. In addition, previous studies have estimated that 8 to 45% of the population are 'resistant' to the effects of aspirin.[5]

There has been intense interest in the combination of aspirin with other antiplatelet agents in an attempt to improve further outcomes in patients with cardiovascular disease. One of the first combinations to be studied was dipyridamole and aspirin. Unfortunately, the results have been disappointing. A meta-analysis of 25 trials comparing the combination of dipyridamole and aspirin to aspirin alone, found that the addition of dipyridamole was only associated with a non-significant 6% reduction in serious vascular events.[3]

The use of intravenous glycoprotein (GP) IIb/IIIa antagonists in PCI is of substantial benefit in reducing periprocedural ischaemic complications. However, the use of these agents in non-ST elevation acute coronary syndromes has been less successful. Trial results have been mixed and meta-analysis suggests that overall their addition to aspirin is of modest benefit.[6] The advent of orally active GP IIb/IIIa antagonists provided the opportunity to test the effect of long-term GP IIb/IIIa inhibition in the secondary prevention of coronary disease. Unfortunately, mortality was increased in all five of the trials with oral GP IIb/IIIa antagonists and a combined analysis revealed a 35% relative increase in the risk of death.

The thienopyridines, ticlopidine and clopidogrel inhibit platelet activation via the adenosine diphosphate (ADP) pathway. Experience with these agents to date suggests that they may provide an effective alternative or supplement to aspirin therapy.

Cardiology Department, Royal Infirmary of Edinburgh, 1 Lauriston Place, Edinburgh, EH3 9YW.
Scott A Harding, Lecturer in Cardiology
Keith AA Fox, Professor of Cardiology
Correspondence to: Dr S Harding
(email: Scott.Harding@ed.ac.uk)

Table 1. Trial acronyms

CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CLASSICS	CLopidogrel ASpirin Stent International Cooperative Study
CREDO	Clopidogrel for Reduction of Events During Observation
CURE	Clopidogrel in Unstable angina to prevent Recurrent Events
FANTASTIC	Full ANTicoagulation versus ASpirin and TIClopidine
FRISC	Fragmin and Fast Revascularisation during InStability in Coronary artery disease
GUSTO	Global Use of Strategies To open Occluded coronary arteries
GRACE	Global Registry of Acute Coronary Events
ISAR	Intracoronary Stenting and Antithrombotic Regimen trial
MATTIS	Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting
PRISM	Platelet Receptor Inhibition in ischemic Syndrome Management
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
STARS	Stent Anti-Thrombotic Regimen Study
TASS	Ticlopidine Aspirin Stroke Study
TOPPS	Ticlid Or Plavix Post Stent

We review the current and future potential role of ADP blockade in coronary artery disease. For details of the trial acronyms used in this article, see table 1.

The thienopyridines – pharmacology

The thienopyridines, ticlopidine and clopidogrel inhibit platelet activation via the ADP pathway. Both of these drugs are metabolised by the hepatic cytochrome P450-1A enzyme system and it is their active metabolites that exert the major antiplatelet effect by binding to the ADP PY_{12} receptor.[7] Both drugs are rapidly and well absorbed after an oral dose. The bioavailability of these drugs is not affected by food but may be decreased by antacids.

Dosing of ticlopidine and clopidogrel is based on *ex vivo* platelet aggregation studies. A maximum anti-aggregatory effect is achieved with 250 mg ticlopidine twice daily and 75 mg clopidogrel once daily. Maximal inhibition of platelet aggregation is only achieved after 3–5 days with ticlopidine 250 mg twice daily and after 4–7 days with clopidogrel 75 mg daily.[8] For this reason, in situations where it is desirable to achieve rapid platelet inhibition a loading dose is recommended. Although a loading dose of 300 mg clopidogrel is suggested, recent studies have demonstrated that loading doses of 450–600 mg result in more rapid platelet inhibition.[9,10] The thienopyridines irreversibly inhibit ADP-mediated platelet responses. Therefore, the inhibitory effects of clopidogrel are terminated by the production of new platelets; platelet function takes approximately seven days to return to pre-treatment levels.[11]

Ticlopidine has uncommon (0.5–3.0%) but very serious haematological toxicity, including neutropenia (1–2.5%), thrombocytopenia, thrombotic thrombocytopenia purpura and (very rarely) aplastic anaemia.[12] Complete blood counts are recommended every two weeks during the first three months of therapy. Gastrointestinal side effects and rash are common, and require discontinuation of ticlopidine in 10% of patients.[13] Clopidogrel has a significantly better safety profile. Rash and diarrhoea occur, but are infrequent. Clopidogrel has been associated with gastrointestinal upset and bleeding, but at lower rates than those observed with aspirin.[14] Recently, there have been a number of reports associating clopidogrel with thrombotic thrombocytopenia purpura, neutropenia and aplastic anaemia.[15-18] These case reports must be put into perspective: to date more than 17,000 patients have been treated with clopidogrel in major randomised controlled trials (table 2) but an increased incidence of thrombocytopenia or neutropenia has not been noted. This suggests that if clopidogrel does cause serious haematological toxicity, it must be very rare.

Ticlopidine

Ticlopidine was the first generation ADP antagonist. A decade ago several randomised trials demonstrated that treatment with ticlopidine, when compared to placebo, markedly reduced the rate of adverse cardiovascular events in patients with recent stroke, intermittent claudication or unstable angina.[19-21] Furthermore, the TASS study demonstrated that ticlopidine when compared to aspirin was associated with a 12% relative risk reduction in the combined end point of all-cause mortality and non-fatal stroke and a 21% reduction in stroke in patients with recent transient ischaemic attack or minor stroke.[22] Several trials in the mid-1990s (STARS, ISAR, FANTASTIC, MATTIS) clearly demonstrated the superiority of the combination of aspirin and ticlopidine over the combination of aspirin and warfarin in reducing ischaemic and haemorrhagic complications after stenting.[23-26] As a result, the combination of aspirin and ticlopidine became the standard antithrombotic therapy following percutaneous coronary intervention with stent placement. The major drawback of ticlopidine therapy is its side-effect profile.

Clopidogrel – clinical trials in coronary artery disease

The CAPRIE trial[14] compared the use of clopidogrel 75 mg daily to aspirin 325 mg daily for the prevention of subsequent cardiovascular events in patients with recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. Treatment with clopidogrel was associated with a modest reduction in the primary end point, a composite of ischaemic stroke, myocardial infarction (MI) or vascular death (relative risk reduction 8.7%; 95% confidence interval 0.3–16.5%; p=0.043). Subgroup analysis suggested that the majority of this additional benefit was seen in the group of patients with peripheral vascular disease.

Despite advances in the treatment of acute coronary syndromes, patients with non-ST elevation ACS remain at considerable risk of further adverse cardiovascular events. The CURE trial[27] was designed to determine whether the addition of clopidogrel to

Table 2. Major randomised controlled trials of clopidogrel in coronary artery disease

Study	Clinical setting	Treatment	Efficacy end point	Safety end point
CAPRIE[14] (n=19,185)	Patients with recent MI, recent stroke or symptomatic PVD	Clopidogrel *vs*. aspirin	Vascular death, MI or ischaemic stroke (5.3% *vs*. 5.8%; p=0.04)	Any bleeding disorder (9.3% *vs*. 9.3%; p=NS)
CURE[27] (n=12,562)	Non-ST elevation ACS	Clopidogrel + aspirin *vs*. aspirin	Cardiovascular death, MI or stroke (9.3% *vs*. 11.4%; p<0.001)	Major bleeding (3.7% *vs*. 2.7%; p=0.001)
Muller *et al.*[34] (n=700)	Post coronary stenting	Clopidogrel + aspirin *vs*. ticlopidine + aspirin	Cardiac death, MI, urgent revascularisation or stent thrombosis (3.1% *vs*. 1.7%; p=NS)	Non-cardiac death, stroke, haemorrhagic event or adverse event resulting in early drug discontinuation (4.5% *vs*. 9.6%; p=0.01)
CLASSICS[35] (n=1,020)	Post coronary stenting	Clopidogrel loading (300 mg) followed by 75 mg/day + aspirin *vs*. clopidogrel (75 mg/day) + aspirin *vs*. ticlopidine + aspirin	Cardiac death, MI or emergency target lesion revascularisation (1.2% *vs*. 1.5% *vs*. 0.9%; p=NS)	Major bleeding or vascular complications, neutropenia, thrombocytopenia or early drug discontinuation (4.6% *vs*. 9.1%; p<0.005)
TOPPS[36] (n = 1,016)	Post coronary stenting	Clopidogrel + aspirin *vs*. ticlopidine + aspirin	Cardiac death, MI or target lesion revascularisation (3.9% *vs*. 4.6%; p=NS)	Failure to complete 14 days of allocated treatment (1.6% *vs*. 3.6%; p=0.04)

aspirin would lead to a further reduction in ischaemic complications in patients with non-ST elevation ACS. The study was performed principally in centres where revascularisation was ischaemia-driven rather than routine. Nevertheless, 36% of patients underwent revascularisation during the course of the study, a frequency similar to that seen in PURSUIT, PRISM, GUSTO IV and the GRACE registry.[4,28-30] The use of GP IIb/IIIa antagonists was discouraged except in patients with refractory ischaemia and during PCI.

The trial randomised 12,562 patients to clopidogrel (300 mg loading dose followed by 75 mg daily) or placebo in addition to aspirin (75–325 mg daily) for a mean duration of nine months. The primary end point, a composite of cardiovascular death, non-fatal MI or stroke, was significantly reduced in the clopidogrel group (relative risk 0.80; 95% confidence interval 0.72–0.90; p<0.001). Benefit was seen as early as the first day of treatment. The reduction in the primary end point was mainly driven by a 23% reduction in MI, from 6.7 to 5.3%. There was a non-significant trend towards a reduction in cardiovascular death and ischaemic stroke. In addition, refractory ischaemia, revascularisation procedures, use of GP IIb/IIIa antagonists and congestive heart failure were all reduced in the clopidogrel group. The clinical effect was consistent across conventional subgroups and occurred irrespective of revascularisation.

The addition of clopidogrel to aspirin in CURE was associated with a 1% excess of major bleeding (3.7% *vs*. 2.7%; relative risk 1.38; 95% confidence interval 1.13–1.67; p=0.001). There was no significant increase in life-threatening bleeding, bleeding requiring surgical intervention or haemorrhagic stroke. Overall, there was no significant increase in major bleeding episodes in the 2,072 patients who underwent coronary artery bypass grafting (CABG) (1.3% *vs*. 1.1%; relative risk 1.26; 95% confidence interval 0.93–1.71). However, in the majority of patients study medication was stopped prior to CABG. Further analysis revealed a strong trend towards increased bleeding in those treated with clopidogrel within five days of CABG (clopidogrel 7.8% *vs*. placebo 5%; relative risk 1.55; 95% confidence interval 0.93–2.57). By contrast, there was no evidence of increased bleeding in patients discontinuing clopidogrel more than five days prior to CABG.[31]

Recently, two observational trials have also found that treatment with clopidogrel within a week of CABG is associated with increased bleeding. In these studies there was a 7–10-fold increase in reoperation for bleeding and higher transfusion requirements.[32,33] Therefore the available evidence suggests that, where possible, clopidogrel should be stopped at least five days prior to surgery. Patients who are unstable and awaiting in-hospital CABG may benefit from short-term replacement of clopidogrel with a small molecule GP IIb/IIIa antagonist as these agents can be safely continued up to two hours prior to surgery and have been shown to reduce MI in this setting.

It is clear from the CURE trial that patients with unstable angina benefit from treatment with clopidogrel in addition to aspirin. On the basis of this study the Federal Drug Authority in the US and, very recently, the European Medicines Evaluation Agency have licensed clopidogrel for use in unstable angina. What is not clear is the optimal duration of treatment. The most secure data are derived from the trial as a whole. Overall, CURE demonstrated that treating patients for a mean duration of nine months following a non-ST elevation ACS was associated with a 20% relative risk reduction of vascular death, MI or stroke. Patients are at the greatest risk of subsequent adverse ischaemic events in the first few months following their admission with non-ST elevation ACS.

Therefore one would expect the greatest absolute benefit from treatment with clopidogrel during this time period. Examination of the cumulative hazard curves for the primary end point reveals that the greatest divergence of the curves occurs during the first three months of treatment, indicating a greater absolute benefit during this time period. Analysis of the treatment effect of clopidogrel < 30 days and > 30 days after randomisation revealed that the addition of clopidogrel to aspirin in the first 30 days after randomisation prevented 12 adverse events per 1,000 patients (p=0.002) at the cost of three major bleeds (p=0.10) whereas treatment from 30 days to nine months prevented 10 events per 1,000 patients at the cost of one major bleed. This suggests that the benefit is comparable in both treatment phases, but a similar analysis of the benefit before three months and after three months has not been conducted.

Clopidogrel – clinical trials in percutaneous coronary intervention

There have been three major randomised trials (Muller *et al.*, CLASSICS and TOPPS) comparing the use of clopidogrel to ticlopidine post coronary stenting.[34-36] All three of these studies demonstrated that clopidogrel and ticlopidine were equally effective in reducing acute stent thrombosis and other adverse cardiac events. However, the tolerability and side-effect profile of clopidogrel in these studies was significantly better than that of ticlopidine. Clopidogrel in combination with aspirin is now established as the antithrombotic treatment regimen of choice post stenting.

PCI-CURE[37] was a prospectively designed observational study looking at the 2,658 patients in the CURE study who underwent PCI in response to refractory symptoms or adverse events. PCI-CURE aimed to determine whether pre-treatment with clopidogrel followed by long-term therapy was superior to a strategy of no pre-treatment and short-term therapy for only four weeks following PCI. PCI was performed during the initial hospital admission in two thirds of the patients; overall there was a median of 10 days before PCI was performed. About a quarter of patients in each group received open-label pre-treatment with a thienopyridine before PCI and most patients (> 80%) in both groups received an open-label thienopyridine for about four weeks, after which the study drug was restarted for a mean of seven months.

The primary end point, a composite of cardiovascular death, MI or urgent target vessel revascularisation 30 days following PCI, was significantly reduced in patients treated with clopidogrel (4.5% *vs*. 6.4%; relative risk 0.70; p=0.03). The benefit of clopidogrel was clearly apparent during pre-treatment prior to PCI, with significantly fewer patients in the clopidogrel group experiencing a MI (3.6% *vs*. 5.1%; relative risk 0.68; p=0.04). Treatment with clopidogrel between 30 days following PCI and the end of follow-up resulted in a risk reduction similar to that seen in the CURE trial overall (relative risk 0.79; 95% CI 0.53–1.20) but this was not statistically significant.

Further evidence that loading with clopidogrel prior to PCI is of benefit comes from an observational study performed by Berglund *et al*.[38] This study of 1,430 patients compared the effect of pre-treatment with clopidogrel and aspirin on the day prior to PCI with pre-treatment with aspirin alone. Pre-treatment with clopidogrel reduced MI (7.2% *vs*. 4.4%; p=0.24) and the need for percutaneous reintervention (1.2% *vs*. 0.3%; p=0.039). The CREDO study is an ongoing randomised trial of more than 2,000 patients designed specifically to look at the efficacy of clopidogrel loading. It will provide further information on the effect of pre-loading prior to PCI.

Key messages

- The thienopyridines, ticlopidine and clopidogrel irreversibly inhibit platelet activation via the ADP pathway
- The use of ticlopidine is limited by its side-effect profile
- Clopidogrel is an effective alternative antiplatelet agent in patients with cardiovascular disease when aspirin is contraindicated
- The CURE trial showed that patients with non-ST elevation ACS benefit from treatment with clopidogrel in addition to aspirin
- Pre-treatment of patients with clopidogrel prior to percutaneous intervention reduces periprocedural ischaemic events
- The combination of clopidogrel and aspirin is effective in preventing stent thrombosis and is the antithrombotic regimen of choice post stenting

Conclusions

The thienopyridines, and in particular clopidogrel, represent a major advance in antiplatelet therapy. Clopidogrel is an effective alternative to aspirin treatment in patients with cardiovascular disease who have contraindications to aspirin therapy. The CURE trial has provided evidence that addition of clopidogrel to aspirin in patients with non-ST elevation ACS is of benefit, despite a small increase in major bleeding. The optimal duration of therapy in this setting has yet to be defined but evidence from CURE suggests that patients will benefit from nine months' therapy. Whether there is a role for clopidogrel in the treatment of acute ST-elevation coronary syndromes is unknown. The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study and CLARITY-TIMI 28 are investigating this question. The combination of clopidogrel and aspirin is established as the antithrombotic regimen of choice after coronary stent placement and there is now evidence that pre-treatment of patients with clopidogrel prior to PCI is of additional benefit.

References

1. Aukrust P, Waehre T, Damas J, Gullestad L, Solum N. Inflammatory role of platelets in acute coronary syndromes. *Heart* 2001;**86**:605-06.
2. Freedman JE, Loscalzo J. Platelet-monocyte aggregates: bridging throm-

bosis and inflammation. *Circulation* 2002;**105**:2130-2.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71-86.
4. Fox K, Goodman S, Klein W, Brieger D *et al*. Management of acute coronary syndromes. Variations in practice and outcome. *Eur Heart J* 2002;**23**:1177-89.
5. Gum P, Kottke-Marchant K, Poggio E *et al*. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. *Am J Cardiol* 2001;**88**:230-5.
6. Boersma E, Harrington R, Moliterno D *et al*. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002;**359**:189-98.
7. Hollopeter G, Jantzen H, Vincent D *et al*. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 2001;**11**:145-7.
8. Solet D, Zacharski L, Plehn J. The role of adenosine 5'-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001;**111**:45-53.
9. Seyfarth HJ, Koksch M, Roethig G *et al*. Effect of 300 and 450 mg clopidogrel loading doses on membrane and soluble P-selectin in patients undergoing coronary stent implantation. *Am Heart J* 2002;**143**:118-23.
10. Muller I, Seyfarth M, Rudiger S *et al.* Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* 2001;**85**:92-3.
11. Weber A, Braun M, Hohlfeld T *et al*. Recovery of platelet function after discontinuation of clopidogrel in healthy volunteers. *Br J Clin Pharmacol* 2001;**52**:333-6.
12. Patrano C, Coller B, Dalen JE *et al*. Platelet-active drugs: The relationships among dose, effectiveness, and side effects. *Chest* 2001;**119**:39S-63S.
13. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999;**100**:1667-72.
14. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329-39.
15. Bennett CL, Connors JM, Carwile JM *et al*. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000;**342**:1773-7.
16. Salliere D, Kassler-Taub KB, Trontell AE *et al*. Clopidogrel and thrombotic thrombocytopenic purpura. *N Engl J Med* 2000;**343**:1191-4.
17. Andres E, Perrin AE, Alt M *et al*. Febrile pancytopenia associated with clopidogrel. *Arch Intern Med* 2001;**161**:124.
18. Dieter RS. Risk of neutropenia with clopidogrel. *J Am Coll Cardiol* 2000;**36**:1436-7.
19. Gent M, Blakely JA, Easton JD *et al*. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;**1**:1215-20.
20. Janzon L, Bergqvist D, Boberg J *et al*. Prevention of myocardial infarction and stroke in patients with intermittent claudication; effects of ticlopidine. Results from STIMS, the Swedish Ticlopidine Multicentre Study. *J Intern Med* 1990;**227**:301-08.
21. Balsano F, Rizzon P, Violi F *et al*. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter clinical trial. The Studio della Ticlopidina nell'Angina Instabile Group. *Circulation* 1990;**82**:17-26.
22. Hass WK, Easton JD, Adams HP *et al*. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med* 1989;**321**:501-07.
23. Leon MB, Baim DS, Popma JJ *et al*. A clinical trial comparing three antithrombotic drug regimens after coronary artery stenting. *N Engl J Med* 1998;**339**:1665-71.
24. Bertrand M, Legrand V, Boland J *et al*. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998;**98**:1597-603.
25. Urban P, Macaya C, Rupprecht H *et al*. Randomised evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS). *Circulation* 1998;**98**:2126-32.
26. Schomig A, Neuman FJ, Kastrati A *et al*. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. *N Engl J Med* 1996;**334**:1084-9.
27. The CURE Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST segment elevation. *N Engl J Med* 2001;**345**:494-502.
28. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436-43.
29. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med* 1998;**338**:1498-505.
30. The GUSTO IV-ACS Investigators. Effect of the glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001;**357**:1915-24.
31. Fox K, Mehta S, Zhao F *et al*. The risks vs benefits of clopidogrel treatment in ACS patients overall, and those undergoing CABG: the CURE trial. In: *European Society of Cardiology Congress*; 2002.
32. Hongo RH, Ley J, Dick SE, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002;**40**:231-7.
33. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001;**29**:2271-5.
34. Muller C, Buttner HJ, Petersen J, Roskamm H. A randomised comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. *Circulation* 2000;**101**:590-3.
35. Bertrand M, Rupprecht H, Urban P, Gershlick A. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : the clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation* 2000;**102**:624-9.
36. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;**104**:539-43.
37. Mehta SR, Yusuf S, Peters RJG *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527-33.
38. Berglund U, Richter A. Clopidogrel treatment before percutaneous coronary intervention reduces adverse cardiac events. *J Invasive Cardiol* 2002;**14**:243-6.

Issues relating to clopidogrel use in hospital practice

R ANDREW ARCHBOLD, NICHOLAS P CURZEN

Abstract

The spectrum of clinical applications for clopidogrel, either with or without aspirin, has expanded rapidly. Evidence about the use of clopidogrel in stable coronary artery disease comes from the CAPRIE trial. The annual rate of the combined primary end point of ischaemic stroke, myocardial infarction or vascular death was significantly reduced in clopidogrel- compared with aspirin-treated patients.

In CURE, the primary end point (cardiovascular death, myocardial infarction or stroke) occurred in 11.4% of the aspirin-treated patients compared with 9.3% of patients treated with aspirin plus clopidogrel during a mean follow-up period of nine months. This was predominantly due to a significant reduction in non-fatal myocardial infarction in clopidogrel-treated patients.

The PCI-CURE study, an observational study of the 2,658 patients in CURE who underwent percutaneous coronary intervention, showed a significantly lower primary outcome in the clopidogrel group than in the placebo group: this probably reflects a treatment advantage for clopidogrel in the pre-procedure phase.

More up-to-date information on risk analysis is provided by application of the TIMI risk score to the CURE data.

The new ACC/AHA and ESC guidelines on management of patients with unstable angina and non-ST segment elevation MI are briefly discussed.

Cost-effectiveness is one issue relevant to the use of clopidogrel in the UK. Formal cost-effectiveness analyses from the CURE investigators are awaited.

There is evidence of a small improvement in gastrointestinal tolerability for clopidogrel over aspirin, and a decreased frequency of gastrointestinal haemorrhage.

The use of a loading dose of clopidogrel in non-ST segment elevation ACS patients prior to angiography prolongs their bleeding time. If they are then found to need coronary surgery, the timing of surgery poses a dilemma for the cardiac surgeons.

The most appropriate duration of treatment after acute coronary syndrome (with and without PCI) and the degree of additional benefit of clopidogrel when added to other cardioactive agents remain to be defined. Many questions about the extent of the potential clinical applicability of clopidogrel in patients with coronary disease still remain to be answered.

Key words: coronary artery disease, clopidogrel, non-ST segment elevation acute coronary syndrome, percutaneous coronary intervention, guidelines, aspirin, surgical procedures.

Department of Cardiology, St. Bartholomew's Hospital, London.
R Andrew Archbold, Specialist Registrar in Cardiology
Manchester Heart Centre, Manchester Royal Infirmary, Manchester, M13 9WL.
Nicholas P Curzen, Consultant Cardiologist
Correspondence to: Dr N P Curzen
(e-mail: nc@mhc.cmht.nwest.nhs.uk)

Introduction

For cardiologists there was, until recently, little room for uncertainty when prescribing oral antiplatelet agents to patients with vascular disease. The answer was invariably aspirin. Indefinite treatment was recommended, in the absence of contraindications, for all patients with coronary artery disease. In such patients, aspirin reduces non-fatal myocardial infarction (MI) and non-fatal stroke by one third and reduces death from any vascular cause by one sixth.[1] But now clopidogrel has arrived, with large randomised, controlled trials to support its increasingly frequent appearance on our drug charts. Clopidogrel has forced us to rethink our prescribing habits; to which groups of patients should we be prescribing aspirin, clopidogrel, or the two in combination? This article discusses some of the issues pertinent to clopidogrel use in 'real world' hospital clinical practice.

Stable coronary artery disease

Clopidogrel's licence for the secondary prevention of vascular events in patients with established atherosclerotic disease was supported by the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial (CAPRIE).[2] In this double-blind study, a total of 19,185 patients with recent ischaemic stroke, recent MI or symptomatic peripheral vascular disease were randomised to receive aspirin 325 mg/day or clopidogrel 75 mg/day. Over a follow-up period of 1–3 (mean 1.9) years, the annual rate of the combined primary end point of ischaemic stroke, MI or vascular death was significantly reduced (5.32% *vs*. 5.83%; p=0.043) in clopidogrel- compared with aspirin-treated patients. This represented a relative risk reduction of 8.7% (95% CI 0.3–16.5%).

In order to justify the use of clopidogrel in patients with 'sta-

ble' vascular disease, we have to be satisfied that it offers important benefits over aspirin in this setting. It could be argued that the patients recruited to CAPRIE were at higher risk of adverse ischaemic events than stable coronary artery disease patients, two thirds of them having had a stroke within six months or an MI within 35 days. Nevertheless, CAPRIE suggested that clopidogrel is slightly more effective than aspirin in preventing ischaemic stroke, MI or vascular death in the patient group as a whole, and it is interesting to note that when the treatment effect was examined by patient subgroup, significant benefit was gained only in patients with peripheral vascular disease.

So, are cardiologists replacing aspirin with clopidogrel for their patients with stable coronary artery disease? In the main, the answer is no. This is probably a reflection of familiarity of aspirin (to the patient and cardiologist), size of additional benefit and, of course, cost. In the first month after MI, aspirin prevents 40 deaths, strokes or further MIs for every 1,000 patients treated. After the first month, 40 additional events are prevented over the next two years for every 1,000 patients treated, at a drug cost of less than £100 per event avoided.[1] In a population similar to that in CAPRIE, aspirin would be expected to prevent about 19 major clinical events versus 24 with clopidogrel, for each 1,000 patients treated per year.[2] Clopidogrel is considerably more expensive than aspirin. To prevent one event that would have occurred with aspirin, 196 patients would need to be treated for one year with clopidogrel.[3] Most cardiologists, therefore, are reserving clopidogrel for their stable patients who are intolerant of aspirin, though it may be reasonable to switch to or add in clopidogrel in patients who suffer an ischaemic event while taking aspirin. It may also be suitable for those at greatest absolute risk, such as those with two or more cardiovascular risk factors.

The question that we really need to answer – is the combination of aspirin and clopidogrel superior to either agent alone? – has not been addressed in this huge group of patients. It remains to be determined whether the addition of clopidogrel to established aspirin therapy reduces risk in patients with stable coronary disease. This issue is being addressed in the CHARISMA trial (now under way). A novel strategy would be to measure the suppression of platelet activity by aspirin in patients with coronary artery disease and use clopidogrel in 'aspirin non-responders'.

Unstable coronary artery disease

Non-ST segment elevation acute coronary syndromes are associated with considerable morbidity and mortality. Registry data from the UK reveal a rate of death or non-fatal MI at six months of 12.2% and of death, MI, refractory angina or readmission for unstable angina at six months of 30%.[4] It is in this context that clopidogrel has recently been granted a licence for adjunctive therapy in patients with acute coronary syndromes based upon data from the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE).[5] In CURE, some 12,562 patients with an acute coronary syndrome without ST elevation were randomised to receive aspirin alone or aspirin plus clopidogrel. The primary end point (cardiovascular death, MI or stroke) occurred in 11.4% of the aspirin-treated patients compared to 9.3% of the patients in the combined treatment arm (relative risk 0.80 [95% CI 0.72–0.90]; p<0.001) during a mean follow-up period of nine months. This was predominantly due to a significant reduction (5.2% *vs*. 6.7%; p<0.001) in non-fatal MI in clopidogrel-treated patients. Cardiovascular death, MI or stroke, or refractory hospital ischaemia was also significantly lower in the clopidogrel group (16.5% *vs*. 18.8%; relative risk 0.86 [95% CI 0.79–0.94]; p<0.001). Interestingly, the benefit seen in refractory ischaemia was due to a reduction in events during the initial hospitalisation (1.4% *vs*. 2.0%; relative risk 0.68 [0.52–0.90]; p=0.007), with no difference in the rate of subsequent rehospitalisation with unstable angina between the two treatment groups.

Are these data relevant to current UK practice? In the trial centres revascularisation was ischaemia-driven rather than routine, and the study design discouraged early coronary angiography and excluded the use of glycoprotein (GP) IIb/IIIa inhibitors. Despite this, 43.7% of patients underwent coronary angiography. Of these, 13.8% of patients underwent PCI during the initial hospitalisation, 7.4% after discharge and 16.5% of patients underwent CABG. By comparison, in PRAIS-UK only 10% of patients underwent coronary angiography in-hospital and 27% by six months, with PTCA and CABG rates of 4% and 8%, and 2% and 7%, respectively.[4] This level of invasive investigation may no longer reflect current UK practice: even the most conservative-minded UK cardiologist would have referred many of the patients recruited to CURE for early coronary angiography, bearing in mind that half the patients had ST-segment deviation, one third had elevated cardiac enzymes at entry (and presumably more after entry), and one fifth had a history of prior revascularisation.[5]

Can we (and should we) reconcile the low (6.7%) use of GP IIb/IIIa inhibitors with the NICE guidelines, which recommend the use of these agents for high-risk (troponin-positive) patients with unstable angina or non-Q-wave MI and for patients undergoing acute or elective PCI?[6] In practice, we suspect the use of GPIIb/IIIa inhibitors remains relatively low in patients who are managed conservatively in the UK, but CURE provides no outcome data for these patients.

Does CURE indicate to us any subgroups that gain particular benefit from the addition of clopidogrel to aspirin? Intuitively, we might expect the highest risk patients to gain the greatest outcome benefit from the addition of clopidogrel. Similar risk ratios (0.79–0.81) were in fact achieved in patients with and without ST changes, with and without enzyme rises, and with and without post-randomisation revascularisation. Only patients with previous revascularisations (risk ratio 0.55) compared with no previous revascularisations (risk ratio 0.87) seemed to gain particular advantage from the addition of clopidogrel. In each patient group the absolute risk reduction was greater in the higher risk group (ST change 2.8 % *vs*. no ST change 1.7%; enzyme rise 2.4% *vs*. no enzyme rise 2.1%; previous revascularisations 6.2% *vs*. no previous revascularisations 1.3%; post-randomisation revascularisations 2.5% *vs*. no post-randomisation revascularisations 2.0%).

Is nine months of combined therapy really necessary to achieve the clinical benefits? After all, in CURE the outcome curves diverged within 24 hours of treatment (though they continued to diverge over 12 months). The relative risk reduction achieved between 30 days and the end of the study (0.82 [95% CI 0.70–0.95]) was comparable to that achieved at 30 days (0.79 [95% CI 0.67–0.92]). Patients are at high risk certainly up to six months after presentation. One third of patients have an MI, die or have another admission with angina at six months.[4]

Percutaneous coronary intervention

Cardiologists are in universal agreement that clopidogrel should be used in combination with aspirin after coronary artery stenting to prevent stent thrombosis. Ironically, this is not a licensed indication for clopidogrel use. The use of clopidogrel eliminates a number of important problems relating to ticlopidine, the antiplatelet agent previously used in this setting. Ticlopidine use is on a named-patient basis, it causes frequent side effects including rash and gastrointestinal upset which result in early cessation of treatment, but most seriously of all it is associated with a 2.4% incidence of neutropenia, which is severe in 0.8% of patients.[3,7]

Data demonstrating improved tolerability and safety for an alternative agent were therefore particularly welcome. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) randomised 1,020 low-risk patients after successful stenting to one of two clopidogrel treatment groups, or ticlopidine, in addition to aspirin.[8] The primary end point of major peripheral or bleeding complications, neutropenia, thrombocytopenia or early discontinuation of study drug because of a non-cardiac event occurred significantly less frequently (4.6% *vs*. 9.8%; p=0.005) in the clopidogrel-treated patients compared with ticlopidine-treated patients (relative risk reduction 50% [95% CI 31–81%]). Early discontinuation of the study drug was the commonest of these end points. There was no difference in the secondary end point of cardiovascular death, MI or target vessel revascularisation, though the study was not powered to demonstrate efficacy differences. The change in resulting prescribing practice after PCI was rapid, and clinical experience and the subsequent publication of further studies confirmed that clopidogrel was at least as effective as ticlopidine in preventing adverse cardiac events after coronary artery stenting, in higher-risk patients too.[9,10]

This area is becoming confusing, however, for those of us lucky enough to have started using rapamycin-coated stents. We have no clear consensus about how long to continue clopidogrel after their deployment. Is three months long enough, or should it be six months? We know that there is probably a delay in endothelialisation of these devices, so the risk of stent thrombosis is likely to be higher, but we do not know how great the increase is or how long it lasts.

Other questions about the use of clopidogrel after stenting remain outstanding. The PCI-CURE study was designed to test the hypothesis that clopidogrel treatment, in addition to aspirin, *prior to* PCI is superior to placebo in preventing ischaemic events.[11] The secondary objective was to determine whether the continuation of clopidogrel after the standard four-week post-PCI period would result in any additional benefit. This was an observational study of the 2,658 patients in CURE who underwent PCI. The primary outcome (a combination of cardiovascular death, MI or urgent target vessel revascularisation within 30 days of PCI) was significantly lower (4.5% *vs*. 6.4%; p=0.03) in the clopidogrel group compared with the placebo group (relative risk 0.70 [95% CI 0.50–0.97]). The benefit was due to a reduction in the incidence of MI and most probably reflects a treatment advantage from clopidogrel in the pre-procedure phase since more than 80% of patients in both the clopidogrel and placebo arms of PCI-CURE received stents and hence received open-label thienopyridine for four weeks after PCI. The overall reduction in the composite end point was similar to that seen in the CURE trial.

What are the implications of PCI-CURE for real-life practice? The majority of patients referred to our tertiary referral centres for acute coronary syndromes are not receiving clopidogrel on arrival. We administer a 300 mg loading dose of clopidogrel 1–24 hours before their angiogram. It is not yet clear whether this short duration of pre-treatment is sufficient to achieve the clinical benefits demonstrated by pre-treatment in PCI-CURE. Furthermore, it is difficult to know whether such pre-treatment benefits those patients treated prior to angiography with GP IIb/IIIa inhibitors.

To take a broader view of patients with coronary heart disease, significantly fewer patients receiving clopidogrel rather than placebo had an MI or the composite of MI and refractory ischaemia even before PCI.[11] The lower rate of cardiovascular death, MI or urgent target vessel revascularisation was seen as soon as two days after PCI and had reached statistical significance by 14 days. All the subgroups examined showed either a trend or a statistically significant benefit in favour of clopidogrel. Nevertheless, in patients who underwent PCI within 72 hours of randomisation, the reduction in cardiovascular death or MI was not statistically significant (8.5% *vs*. 13.5%; relative risk 0.62 [95%CI 0.37–1.05]); whereas it was significant in the remainder of patients who underwent PCI more than 72 hours after randomisation (8.9% *vs*. 12.3%; relative risk 0.71 [95% CI 0.54–0.92]). Does this mean that 72 hours of pre-treatment with clopidogrel is insufficient? This is doubtful; it is more likely to be a reflection of the smaller numbers within this subgroup.

Additional observational data have shown that pre-treatment with clopidogrel – either started within five days of PCI or a loading dose of 300 mg on the morning of the procedure – is associated with a significant reduction in MI (3.4% *vs*. 12.5%; p=0.0009) and the composite of MI, need for urgent repeat target vessel revascularisation or cardiovascular death during hospitalisation (5.5% *vs*. 14.0%; p=0.03), compared with clopidogrel treatment initiated after stent deployment.[12] Unfortunately, the median duration of pre-treatment was not stated. The question we have posed cannot be answered from the available data but the ongoing CREDO study (due to be presented at the AHA meeting later this year) will provide further information on the effect of clopidogrel pre-loading before PCI. In addition, pharmacological data are consistent with inhibition of platelet aggre-

gation by clopidogrel within hours of a single loading dose.[13,14]

More up-to-date information on risk analysis is provided from application of the Thrombolysis in Myocardial Infarction (TIMI) risk score to the CURE data.[15] Patients (n=12,562) who presented within 24 hours of the onset of symptoms were randomised to receive clopidogrel or placebo in addition to aspirin for 3–12 months. The primary composite outcome of cardiovascular death, MI or stroke increased proportionally with increasing risk according to the TIMI score. In the low-risk group (TIMI score 0–2), the rate of primary outcome for clopidogrel versus placebo was 4.1% *vs*. 5.7% (RR 0.71; 95% CI 0.52–0.97; p<0.04). In the intermediate-risk group (TIMI score 3–4), the corresponding figures were 9.8% *vs*. 11.4%; RR 0.85: 95% CI 0.74–0.98; p<0.03. In the high-risk group (TIMI score 5–7), the corresponding figures were 15.9% *vs*. 20.7%; RR 0.73; 95% CI 0.60-0.90; p<0.004.

Current clinical practice sees a high usage of glycoprotein IIb/IIIa inhibitors given during and after PCI in patients presenting with acute coronary syndromes. How this affects the efficacy of clopidogrel in the short and longer term remains unclear.

Current guidelines

A review of national and international guidelines on the management of patients with vascular disease proves potentially confusing and apparently contradictory (table 1). This, of course, relates to their date of formulation and publication in relation to the publication of relevant clinical trials. Clopidogrel is not referred to specifically in the 1997 European Society of Cardiology (ESC) recommendations for management of stable angina,[16] nor in the recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention,[17] nor in the British Cardiac Society (BCS) guidelines for the management of patients with acute coronary syndromes without persistent ECG ST-segment elevation.[18]

Aspirin remains the antiplatelet agent of first choice in the majority of circumstances. Clopidogrel is recommended by the ACC/AHA for patients with chronic stable angina 'when aspirin is absolutely contraindicated' (class IIa recommendation, level of evidence B).[19] The 2001 update to the AHA/ACC guidelines on secondary prevention recommends 'indefinite aspirin 75–325 mg/day if not contraindicated. Consider clopidogrel 75 mg/day or warfarin if aspirin is contraindicated' and cites CAPRIE as important new trial evidence since the original guidelines in 1995.[20] The ACC/AHA guidelines for the management of patients with acute MI reserve antiplatelet agents other than aspirin (dipyridamole, ticlopidine or clopidogrel) for patients with true aspirin allergy (class IIb recommendation).[21] They correctly observe that there is currently no evidence that other antiplatelet agents have any advantage over aspirin for mortality reduction in the acute treatment of MI.

The current BCS guidelines[18] and The Task Force of the ESC recommendations for the management of patients with acute coronary syndromes without persistent ST segment elevation[22] were both published before CURE. BCS guidelines on 'anticoagulants and antiplatelet agents in vascular disease' are in preparation.

Table 1 Summary of antiplatelet therapy recommendations in 'current' guidelines

	Aspirin	Clopidogrel	Other
Stable angina pectoris			
Management of stable angina pectoris. Recommendations of the Task Force of the ESC (1997)	**	-	-
ACC/AHA guidelines for the management of patients with chronic stable angina (1999)	**	*	-
Secondary prevention			
Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention (1998)	**	-	*
AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease (2001)	**	*	*
Acute (ST elevation) myocardial infarction			
ACC/AHA guidelines for the management of patients with acute myocardial infarction (1999)	**	*	*
Acute coronary syndromes without ST elevation			
Recommendations of the Task Force of the ESC (2000)	**	*	*
BCS guidelines	**	-	-
ACC/AHA guidelines for the management of patients with unstable angina and NSTEMI (2002)	**	**	-
ESC guidelines for the management of patients with unstable angina and NSTEMI (2002)	**	**	-
Percutaneous coronary intervention			
ACC/AHA guidelines for PCI (2001)	**	**	**

Key: ESC = European Society of Cardiology; ACC/AHA = American College of Cardiology/American Heart Association; BCS = British Cardiac Society; NSTEMI = non-ST-segment elevation myocardial infarction.
** = firm recommendation; * = secondary recommendation

The ACC/AHA guidelines on the management of patients with unstable angina and non-ST-segment elevation MI, published in June 2002, have been updated since CURE.[23] Amongst their revised class I recommendations are: 1) the administration of clopidogrel to hospitalised patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (level of evidence A); 2) the administration of clopidogrel for at least one month (level of evidence A) and for up to nine months (level of evidence B) to hospitalised patients in whom an early non-interventional approach is planned; and 3) the administration of clopidogrel for at least one month (level of evidence A) and for up to nine months in patients who are not at risk of bleeding (level of evidence B) in patients for whom PCI is planned.

New ESC guidelines for the management of unstable angina and non-ST elevation myocardial infarction have recently been announced. (They will be published in the November issue of the *European Heart Journal* and will also be published on the ESC website [www.escardio.org].) These guidelines are very similar to the ACC/AHA guidelines. In acute management, a new combination of antithrombotic agents is recommended – a low molecular weight heparin, aspirin and clopidogrel. In long-term management, the guidelines recommend that clopidogrel is used for nine months and aspirin for life.

Other issues

Cost-effectiveness

Ultimately, if we believe that a useful clinical benefit is obtained from an intervention, then patient acceptability, cost-effectiveness and resource allocation become the critical issues that will determine the level of uptake of the intervention. Each additional intervention is likely to result in a smaller absolute reduction in risk. For example, the risk reduction achieved by clopidogrel alone in a smoker with stable coronary artery disease will be greater than that achieved by the addition of clopidogrel to the same patient who has stopped smoking and is already taking aspirin, a statin and an angiotensin-converting enzyme inhibitor.

Most recent interest surrounding clopidogrel has focused upon its use in acute coronary syndromes. For every 100 patients in CURE, the addition of clopidogrel for nine months prevented two additional cardiovascular deaths, or non-fatal MIs or strokes, but caused one additional patient to have a major bleed. Formal cost-effectiveness analyses from the CURE investigators have been conducted and will probably be published within the next 12 months.

A recent article sought to examine the cost-effectiveness of aspirin, clopidogrel or both for the secondary prevention of coronary heart disease.[24] The risk reductions achieved in the Antiplatelet Trialists' Collaboration, CAPRIE and CURE were used in a model that estimated the incidence of coronary disease and mortality in subjects over 35 years of age in the US between 2003 to 2027. However, correspondence regarding the methodology is pending.

Aspirin intolerance

Aspirin intolerance is usually due to one of a range of gastrointestinal side effects. Furthermore, aspirin may cause serious upper gastrointestinal haemorrhage. But is the widely held belief that the gastrointestinal side-effect profile of clopidogrel is superior to that of aspirin correct? One small double-blind, cross-over study in healthy volunteers without gastrointestinal disease demonstrated that, in contrast to 325 mg aspirin, 75 mg clopidogrel did not induce any gastroscopically evident erosions after eight days' treatment.[25] In CAPRIE, which randomised only 'aspirin-tolerant' patients, the occurrence of all gastrointestinal bleeding (1.99% *vs*. 2.66%; p<0.002), hospitalised gastrointestinal bleed (0.74% *vs*. 1.08%; p=0.012), abdominal pain (5.64% *vs*. 7.14%; p<0.001), dyspepsia (5.22% *vs*. 6.10%; p<0.01), gastritis (0.75% *vs*. 1.32%; p<0.001), peptic ulcer (0.68% *vs*. 1.15%; p<0.001) and indigestion, nausea or vomiting (15.01% *vs*. 17.59%; p<0.05) was significantly less in clopidogrel-treated patients compared to aspirin-treated patients, while only diarrhoea occurred more frequently (4.46% *vs*. 3.36%; p<0.001) in patients receiving clopidogrel.[2,26] So there is evidence of a small improvement in gastrointestinal tolerability for clopidogrel over aspirin and a decreased frequency of gastrointestinal haemorrhage. It therefore seems reasonable for us to prescribe clopidogrel both to patients in whom aspirin is contraindicated or poorly tolerated, and to those who have a history of peptic ulceration.

Surgical procedures and bleeding risk

Clopidogrel use has implications for other areas of our practice. The majority of patients who undergo inpatient coronary angiography present with non-ST elevation acute coronary syndromes. Following CURE, an increasing proportion of these patients are started (appropriately) on clopidogrel soon after admission as part of their medical therapy. The remainder receive a loading dose prior to their angiogram, in anticipation of their proceeding on to PCI. However, the bleeding time is approximately doubled in these patients. Thus, when such patients are then found to have coronary artery disease deemed to be surgical, our surgical colleagues face a dilemma regarding the appropriate timing of surgery.

In a study of 247 patients who underwent coronary artery bypass graft surgery (CABG), the incidence of re-exploration for bleeding was significantly higher (9.8% *vs*. 1.6%; p=0.01) in clopidogrel-treated patients (odds ratio 6.9 [95% CI 1.6–30]).[27] Clopidogrel use was also associated with an increased need for packed red cell transfusion (72.6% *vs*. 51.6%; p=0.007), a higher number of packed red cell units (3.0 *vs*. 1.6; p=0.0004) and of cryoprecipitate units transfused (2.4 *vs*. 1.2; p=0.04). A different study reported a similarly increased requirement for blood products and increased rate of reoperation for bleeding (6.8% *vs*. 0.6%; p=0.018) among CABG patients who had received clopidogrel within seven days of surgery compared with patients without such clopidogrel exposure.[28]

Additional data come from CURE.[5] Overall there was no excess of major bleeding after CABG in clopidogrel-treated patients (1.3% *vs*. 1.1%; relative risk 1.26; 95% CI 0.93–1.71). However, in most patients scheduled for CABG, the study medication was discontinued *more than five days* before the procedure and in these patients the rate of major bleeding was actually lower (4.4% *vs*. 5.3%) in clopidogrel-treated patients. In the 912 patients who stopped taking the medication within five days of surgery, the rate of major bleeding was 9.6% in the clopidogrel group and 6.3% in the placebo group (relative risk 1.53; p=0.06).

Our policy is to stop clopidogrel as soon as a surgical opinion is sought for inpatients. Unfortunately, this builds in an inevitable delay in the wait for inpatient CABG surgery and theoretically exposes such patients to a higher risk of an acute cardiac event while they are waiting because the clopidogrel has been withdrawn. The median delay from angiogram to CABG in these circumstances is eight days at the Manchester Heart

Key messages

- Registry data show that patients with non-ST segment elevation acute coronary syndrome have a rate of death, myocardial infarction, refractory angina or readmission for unstable angina at six months of 30%
- New European Society of Cardiology guidelines recommend a low molecular weight heparin, aspirin and clopidogrel in acute management of unstable angina and non-ST elevation myocardial infarction
- They recommend also that clopidogrel is used for nine months and aspirin for life in the long-term management of unstable angina and non-ST elevation myocardial infarction. Controversy surrounds the degree of additional benefit conferred by extending the clopidogrel regimen beyond the first 30 days
- It seems reasonable to prescribe clopidogrel both to patients in whom aspirin is contraindicated or poorly tolerated, and to those who have a history of peptic ulceration
- With the introduction of rapamycin-coated stents, the duration of clopidogrel therapy following PCI in these patients has been extended to between three and six months

Centre. In emergency cases, surgery is performed with appropriate blood product support.

Similar dilemmas are faced in cardiology patients. For example, at St. Bartholomew's Hospital, clopidogrel is stopped for at least seven days prior to the implantation of a pacemaker or implantable cardiovertor-defibrillator (ICD) to minimise the perceived increased risk of haematoma formation. This is based upon evidence that, after discontinuation of clopidogrel, platelet function gradually increases to normal (in the absence of concomitant aspirin) over this time period.[29] In patients who have been revascularised percutaneously prior to proposed ICD implantation, we then have to decide between continuing clopidogrel for the standard four weeks to prevent stent thrombosis and discontinuing the clopidogrel to allow ICD insertion within a reasonable timeframe. It is difficult to allow these patients home during this period, having already justified an ICD for them, so they must wait as inpatients.

Conclusions

Clopidogrel undoubtedly represents a valuable addition to the antiplatelet armamentarium. It is more effective than aspirin in patients with stable vascular disease and its combination with aspirin is superior to aspirin alone in preventing MI and refractory in-hospital ischaemia in patients admitted with non-ST elevation acute coronary syndromes. Its use after coronary artery stenting has simplified life for the interventional cardiologist. The role of clopidogrel in the treatment of patients with (and without) vascular disease, however, remains to be fully defined. Central to this issue are cost-effectiveness, the most appropriate duration of treatment after acute coronary syndromes with and without PCI, and the degree of additional benefit of clopidogrel when added to other cardioactive agents. Many questions will arise concerning the potential expansion of the role of clopidogrel in the future, such as:

- is coronary graft patency prolonged by clopidogrel?
- what is the role of clopidogrel in patients with atrial fibrillation?
- would patients with stable angina or peripheral vascular disease benefit electively from a combination of aspirin and clopidogrel?
- would patients at risk of vascular events, such as those recruited into the Heart Protection Study, benefit from clopidogrel?
- would all patients in these groups be better off on clopidogrel than aspirin?

At present, we can only speculate as to the answers.

References

1. Antiplatelet Trialists' Collaboration. Collaborative overiew of randomised trials of antiplatelet therapy. I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**38**:81-106.
2. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329-39.
3. Clopidogrel and ticlopidine - improvements on aspirin? *DTB* 1999;**37**:59-61.
4. Collinson J, Flather MD, Fox KAA *et al*., for the PRAIS-UK Investigators. Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *Eur Heart J* 2000;**21**:1450-7.
5. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494-502.
6. National Institute for Clinical Excellence. Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. Sept 2000. www.nice.org.uk. Accessed on 15th June 2002.
7. Richardson G, Curzen N, Preston M, Mills PG, Timmis A, Rothman M. Failure to monitor ticlopidine: the case for clopidogrel. *Int J Cardiovasc Intervent* 2000;**3**:29-34.
8. Bertrand ME, Rupprecht H-J, Urban P, Gershlick AH, for the CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS). *Circulation* 2000;**102**:624-9.
9. Taniuchi M, Kurz HI, Lasala JM. Randomised comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. *Circulation* 2001;**104**:539-43.
10. Bhatt DL, Bertrand ME, Berger PB *et al*. Meta-analysis of randomised and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol* 2002;**39**:9-14.
11. Mehta SR, Yusuf S, Peters RJG *et al*., for the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pre-treatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527-33.
12. Assali AR, Salloum J, Sdringola S *et al*. Effects of clopidogrel pre-treatment before percutaneous coronary intervention in patients treated with

glycoprotein IIb/IIIa inhibitors (abciximab or tirofiban). *Am J Cardiol* 2001; **88**:884-6.
13. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. *Circulation* 1999; **100**:1667-72.
14. Gurbel PA, Malinin AI, Callahan KP, Serebruany VL, O'Connor CM. Effect of loading with clopidogrel at the time of coronary stenting on platelet aggregation and glycoprotein IIb/IIIa expression and platelet-leukocyte aggregrate formation. *Am J Cardiol* 2002;**90**:312-5.
15. Budaj A, Yusuf S, Mehta SR *et al*., for the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Investigators. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002,10.1161/01.CIR. 0000029926.71825.E2 (abstract).
16. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 1997;**18**:394-413.
17. Wood D, De Backer G, Faergeman O *et al*. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Eur Heart J* 1998;**19**:1434-503.
18. British Cardiac Society Guidelines and Medical Practice Committee, and Royal College of Physicians Clinical Effectiveness and Evaluation Unit. Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation. *Heart* 2001;**85**: 133-42.
19. Gibbons RJ, Chatterjee K, Daley J *et al.* ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 1999;**33**:2092-197.
20. Smith Jr SC, Blair SN, Bonow RO *et al*. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 2001;**104**:1577-9.
21. Ryan TJ, Antman EM, Brooks NH *et al*. ACC/AHA guidelines for the management of patients with acute myocardial infarction: 1999 update: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Available at www.acc.org. Accessed on 15th June 2002.
22. Bertrand ME, Simoons ML, Fox KAA *et al*. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000;**21**:1406-32.
23. Braunwald E, Antman EM, Beasley JW *et al*. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). 2002. Available at: http://www.acc.org/clinical/guidelines/unstable/unstable.pdf.
24. Gaspoz J-M, Coxson PG, Goldman PA *et al*. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;**346**:1800-6.
25. Fork FT, Lafolie P, Toth E, Lindgarde F. Gastroduodenal tolerance of 75 mg clopidogrel versus 325 mg aspirin in healthy volunteeers. A gastroscopic study. *Scand J Gastoenterol* 2000;**35**:464-9.
26. Harker LA, Boissel J-P, Pilgrim AJ, Gent M, on behalf of the CAPRIE Steering Committee and Investigators. Comparative safety and tolerability of clopidogrel and aspirin. Results from CAPRIE. *Drug Saf* 1999;**21**:325-35.
27. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001;**29**:2271-5.
28. Hongo RH, Ley j, Dick SE, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002;**40**:231-7.
29. Weber AA, Braun M, Hohlfeld T, Schwippert B, Tschope D, Schror K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. *Br J Clin Pharmacol* 2001;**52**:333-6.

Clopidogrel in clinical practice – primary care

KRISHNA KORLIPARA

Abstract

Recent government guidelines have endorsed the need to improve the management of vascular disease, which represents an enormous burden to the UK health service. Antiplatelet agents play a key role in the management of the disease, but are currently underprescribed. Aspirin remains the accepted first-line therapy for this patient group but there is a clear need for other, more effective, antiplatelet regimens, including clopidogrel. Clopidogrel should be considered for secondary prevention in patients with a history of symptomatic atherothrombotic disease (ischaemic stroke, myocardial infarction or symptomatic peripheral vascular disease) and two or more additional risk factors for further events, for those patients who have had an event while taking aspirin and for those who are aspirin-intolerant. In addition, in line with its recently extended licence, clopidogrel may now be considered in combination with aspirin for patients with unstable angina or non-ST elevation myocardial infarction. When deciding on the optimal duration of clopidogrel treatment, GPs should assess each patient's risk of experiencing a further event. The developing role of primary care organisations as service providers for both primary and secondary care should facilitate more consistent pathways of care and prescribing practices across all the health sectors, and in particular vascular disease.

Key words: clopidogrel, aspirin, risk factors, myocardial infarction, stroke, unstable angina.

Introduction

Vascular disease, which includes myocardial infarction (MI), unstable angina (UA), angina of effort, stroke, transient ischaemic attack (TIA) and peripheral vascular disease (PVD), accounts for more than 40% of all deaths in the UK.[1] In 2000, the government endorsed the need for improved management of vascular disease through publication of its National Service Framework (NSF) for Coronary Heart Disease (CHD), with the aim of reducing the incidence of CHD and stroke in people under 75 years of age by 40% by the year 2010. One of the key standards, Standard 3, is to identify all people with established cardiovascular disease and to offer them comprehensive advice and appropriate treatment in order to reduce their risks of further vascular events. By April 2003, every practice should have available clinical audit data that are no more than 12 months old.[2]

Other aspects of vascular disease are addressed in more recent NSFs. For example, the NSF for Older People, published in 2001,[3] sets out standards for preventing stroke and providing prompt access to integrated care services for those who have had a stroke. General hospitals are to have plans in place by April 2002 to introduce specialist stroke services and to have established clinical audit systems for stroke management by April 2003. GPs are to have protocols, agreed with local specialist services, to identify and manage patients at high risk of stroke and to refer patients with TIA by April 2004.[3]

In addition, the NSF for Diabetes[4] stresses that preventing or delaying the onset of diabetes and good management of diabetes will contribute to the achievement of the goals in the NSF for CHD.

Antiplatelet agents, including clopidogrel, play a key role in the management of vascular diseases. This article looks at the issues and prescribing options for clopidogrel in different patient populations within the primary care setting. The optimum duration for clopidogrel use within each patient group and whether it should be prescribed alone or in combination with aspirin are considered in some detail. Finally, the implications of the changing role of primary care organisations (PCOs) for the future management of vascular disease patients are discussed.

Vascular disease – the size of the problem

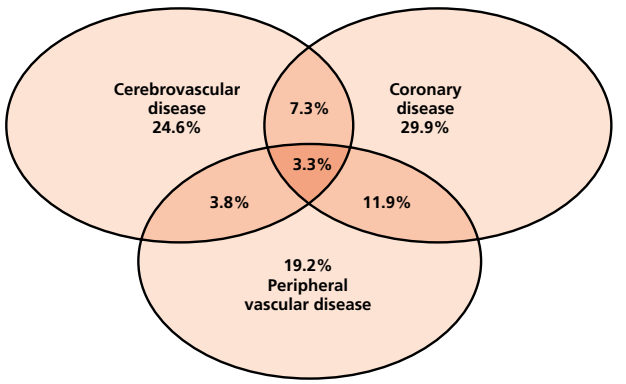
Vascular disease represents an enormous burden to the UK health service, with high annual incidence rates of MI, stroke and PVD (table 1). Moreover, because atherothrombosis plays a key role in the underlying process leading to ischaemic strokes, MI and PVD, the presence of one clinical manifestation substantially increases the chances of developing others. Thus, GPs will commonly see MI patients who have a subsequent stroke or *vice versa* (figure 1), a scenario that is associated with high mortality and morbidity rates. This is confirmed in the literature, for example, in the Oxford Community Stroke Project (OCSP),[5] which followed 675 patients with first stroke for up to 6.5 years. Of those who survived more than 30 days but died within the first six years, 35% of deaths were due to other cardiovascular events.

Pikeview Medical Centre, Albert Street, Horwich, Bolton, BL6 7AN.
Krishna Korlipara, General Practitioner
Correspondence to: Dr K Korlipara
(email: krishna@korlipara.freeserve.co.uk)

Table 1. The impact of vascular disease

Condition	Incidence in the UK	Approx. number per 2,000 patients
Stroke[3]	140,000	4.7
Myocardial infarction (MI)[18]	274,000	9.2
Peripheral vascular disease[19]	23,920	0.8
Unstable angina/non-ST elevation MI[20]	180,000	6.0

Figure 1. Ischaemic co-existence: percentage of patients with co-existing coronary, cerebral and peripheral vascular disease[29]



Similarly, 18% of men and 35% of women who survive an MI suffer a further MI within six years[6] and approximately 8.1% suffer a stroke within five years.[7] As further evidence for the risk of having a second or third vascular event, Criqui *et al*.[8] found that in patients diagnosed with PVD and followed up over a 10-year period, 60% of deaths were due to myocardial infarction and 17% due to a cerebrovascular accident.

These data illustrate the importance of considering antiplatelet therapy for all patients with vascular disease. Aspirin is the accepted and recommended first-line therapy for vascular disease, as advocated by the NSF for CHD. Aspirin was recommended as a result of data from the Antiplatelet Trialists' Collaboration, which showed that aspirin reduced the risk of further serious vascular events by about a quarter.[9] This view was recently reinforced by the Antithrombotic Trialists' Collaboration,[10] which concluded that low-dose aspirin (75–150 mg daily) should be administered routinely for all such patients. Unfortunately, there is plenty of evidence to suggest that there is considerable under-prescribing of aspirin in patients who have experienced vascular events,[11] and there is much that we, as GPs, could do to make a considerable impact on this.

Although aspirin can improve outcomes, the residual risk for patients on aspirin is not negligible: three out of four vascular events still occur despite aspirin therapy.[10] We therefore need to consider prescribing other, more effective, antiplatelet regimens if we are to achieve the government targets. The potential role for clopidogrel in a variety of patient groups is considered below.

Clopidogrel in patients with MI, stroke and PVD

The CAPRIE study[12] showed that long-term administration of clopidogrel was more effective than aspirin in reducing the combined risk of ischaemic stroke, MI and vascular death (relative risk reduction [RRR] 8.7%).

Post-hoc analysis of data from the entire 19,185 CAPRIE population showed a RRR of 19.2% (p=0.008) in favour of clopidogrel for the outcome of first MI alone after recruitment.[13] Reductions were also seen in the outcomes of vascular death and ischaemic stroke (RRR 7.6% and 5.2%, respectively), although these were not statistically significant.[14]

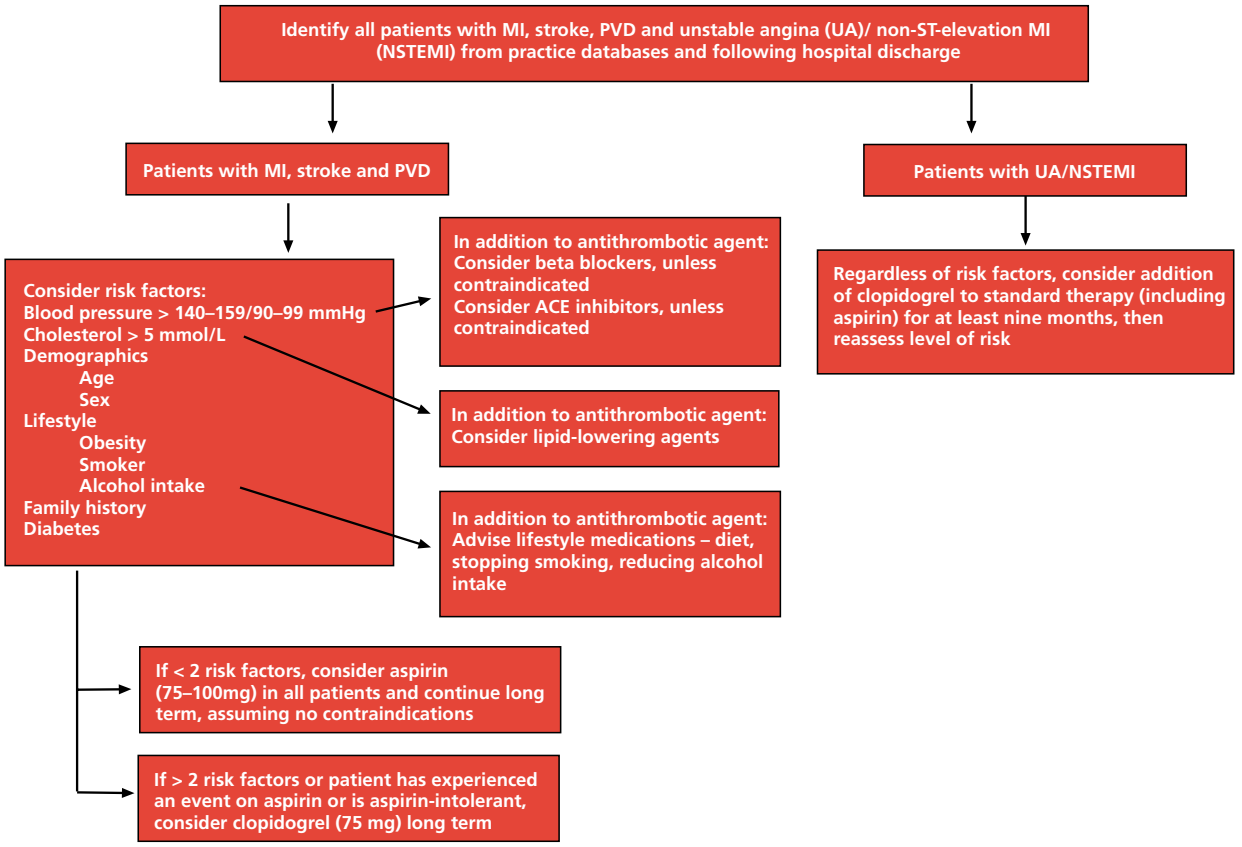
Several *post-hoc* subgroup analyses of the CAPRIE trial data have been performed to determine the benefits of clopidogrel in populations considered to be at particularly high risk of further vascular events. These included patients with diabetes, dyslipidaemia and those who had undergone cardiac surgery. In the first subanalysis,[15] involving 3,866 diabetic patients, the RRR in diabetic patients randomised to clopidogrel was 11% compared with a RRR of 7% in the non-diabetic population. In the subanalysis of 2,204 hypercholesterolaemic patients being treated with lipid-lowering therapy,[16] clopidogrel therapy was associated with a 20.0% reduction in the combined end point of vascular death, MI, stroke and rehospitalisation for ischaemia or bleeding (p=0.026), when compared with aspirin. Clopidogrel was associated with a RRR of 56% in MI alone. The subgroup analysis in 1,480 patients who had undergone coronary artery bypass surgery (CABG) showed clopidogrel therapy to be independently associated with a 31.2% RRR (95% CI 15.8–43.8; p=0.0003) in vascular death, MI, stroke or rehospitalisation for ischaemia or bleeding.[17] Multivariate analysis demonstrated that patients with previous cardiac surgery derived particular benefit from treatment with clopidogrel (p=0.015). Subgroup analyses must be interpreted with caution: the most robust data come from analysis of the trial as a whole.

Which patients should be considered for clopidogrel?

GPs will see on average approximately five stroke patients,[3] nine MI patients,[18] one PVD patient,[19] and six unstable angina/non-ST segment elevation MI (UA/NSTEMI) patients[20] per 2,000 population (table 1). A key issue for GPs is interpreting the clinical evidence to determine which of these patients should receive clopidogrel. It could be argued that any patient who has experienced a vascular event should be given clopidogrel but in practice, given budgetary constraints and the need for a favourable cost/benefit analysis, it is pragmatic to consider those at highest risk of a further vascular event.

Patients at high risk can be identified from those on the practice list who have had either an MI or a stroke or who have estab-

Figure 2. Care pathway for patients with myocardial infarction (MI), stroke, peripheral vascular disease (PVD) or unstable angina (UA)/non-ST elevation MI (NSTEMI)



lished PVD, with or without other additional risk factors. Others can be identified through routine practice audits, which should be reviewed annually, perhaps by a practice nurse or another trained member of the practice team, as part of achieving Standard 3 of the NSF for CHD.[2] Figure 2 shows a suggested care pathway for managing patients at risk of further vascular events, depending on the risk factors present.

Risk factor management

A multitude of risk factors such as hypertension and hypercholesterolaemia, patient demographics (age, sex), lifestyle (obesity, smoking, alcohol intake) and a family history of vascular disease all have an influence on the risk of suffering further serious vascular events. Table 2 shows the proportion of all coronary heart disease that is attributable to five different risk factors in the UK.[21]

Reviewing a patient's risk factors will help to determine their likelihood of suffering further events and could serve as a basis for establishing which patients should receive aspirin and which should be targeted for alternative antiplatelet treatment. As a general guide any patient who has had an MI or stroke or who has PVD should be on long-term aspirin (75–150 mg daily), if there are no contraindications. If patients already on aspirin suffer a further MI or a stroke, they should be started on clopidogrel (75 mg daily). If patients have had a major vascular event such as a stroke or MI or have serious PVD and have at least two additional risk factors, they should be considered for treatment with clopidogrel rather than aspirin to reduce further morbidity and mortality risk. But if

Table 2. Proportion of all coronary heart disease attributable to five different risk factors in the UK[21]

Risk factor	Men (%)	Women (%)	All (%)
Blood cholesterol >5.2 mmol/L	45	47	46
Physical inactivity <12 20 minute occasions in the past four weeks	36	38	37
Blood pressure >140/90 mmHg	14	12	13
Smoking	20	17	19
Obesity: BMI ≥30	5	6	6

a stroke, MI or PVD patient has fewer than two additional risk factors, aspirin (75–100 mg) should be the preferred choice, assuming there are no contraindications.

Patients with type 2 diabetes have a substantially increased risk of cardiovascular complications; at least half of the 33,000 deaths a year attributable to diabetes are caused by cardiovascular disease.[22] The majority of diabetic patients are managed in primary care,[23] where they should be offered effective antiplatelet treatment for the secondary prevention of serious vascular events. Current guidelines[24] suggest that aspirin (75 mg per day) should be given routinely and continued over the long term in patients with diabetes and CHD, stroke or PVD, and that clopidogrel (75 mg daily) could be considered as an alternative to aspirin. Given that patients with type 2 diabetes without a previous MI have as high a risk of developing MI as non-diabetic patients with a previous MI,[25] it could be argued that these two patient groups should be treated in the same way. There are currently no clinical data available to support this argument, but perhaps further studies should be considered to clarify this issue.

In addition to antithrombotic treatment, where appropriate patients should also be considered for antihypertensive and lipid-lowering therapy, together with advice on lifestyle changes – a healthy diet containing plenty of green vegetables, salads and fresh fruit, reduced intake of salt and saturated fats, smoking cessation and regular exercise. The importance of complying with any treatment regimen in order to derive maximum therapeutic benefit should also be emphasised.

Patients who have failed on aspirin or who are aspirin-intolerant

Although aspirin is effective in many patients, GPs will still see a considerable number of patients who have experienced a vascular event while on aspirin. These patients are at a considerably increased risk of further events and could reasonably be considered for clopidogrel therapy.

In practice, the largest group of patients likely to be receiving clopidogrel are those for whom aspirin is contraindicated. This is so despite the fact that the CAPRIE trial[12] excluded aspirin-intolerant patients. However, gastrointestinal adverse events are frequent in patients on aspirin. Aspirin inhibits platelet aggregation by blocking the enzyme cyclo-oxygenase (COX). However, aspirin also inhibits COX in other tissues, including the gastric mucosa. Since COX exerts a protective effect on the gut, inhibiting COX could be the cause of gastric intolerance in patients on aspirin. Clopidogrel, by contrast, does not act on the COX pathway but acts specifically on platelets by interfering with the binding of ADP to its receptors on the platelet surface. Clopidogrel may therefore be associated with fewer gastrointestinal adverse events compared with aspirin.

Unstable angina and non-ST elevation MI

The mortality and morbidity due to UA and NSTEMI is extremely high. These conditions have an annual incidence in the UK of about 180,000 (table 1).[20] This estimate is similar to that obtained by extrapolating from the PRAIS–UK registry, which suggests a presentation rate of 240 per 100,000 population per year.[26] Of these patients, one third will go on to have serious problems: approximately 13,300 will die within six months, 22,000 will die or suffer a secondary cardiovascular event within six months, and 54,000 will die, suffer a secondary cardiovascular event or be readmitted to hospital with UA within six months.[26] The same study concluded that current management is sub-optimal and that the ongoing burden of disease (in terms of death, MI or continuing illness) continues to be high.

Recently, a licence extension based on data from the CURE trial[27] has made clopidogrel available for early and long-term reduction of atherothrombotic events (MI, stroke, death due to vascular causes and refractory ischaemia), in addition to aspirin, in patients with UA or NSTEMI.

GPs will see a number of patients representative of the CURE population (approximately six patients per 2000[20]; table 1). Given the high-risk status of these groups, clopidogrel (75 mg daily) in addition to aspirin should be given to patients presenting with UA/NSTEMI, regardless of the existence of additional risk factors (figure 2).

The PCO perspective

Following recent government reforms in the UK, Primary Care Organisations (PCOs) are now responsible for provision of services across both primary and secondary care, including the allocation of budgets. As such, they are uniquely placed to take a global view of the needs of the community, including social services. PCOs will need to consider the development of integrated pathways of care to facilitate communications between primary, secondary and tertiary health professionals and to ensure optimum assessment and management of high-risk patients. This might include the appointment of primary care specialists with additional training in cardiology to run practice-based or specialist clinics. In addition, the setting up of disease registers and audits of prescribing practices should be considered in order to facilitate sharing of patient information and monitoring of progress across the different health sectors.

It is anticipated that PCOs will act as catalysts to facilitate consistency of care standards and prescribing patterns among all clinicians by providing guidelines and effective formularies. This should ensure that patients receive optimum treatment regardless of where they live. When reviewing formularies, PCOs will need to weigh up, on the basis of current clinical evidence, whether a drug will help to meet the requirements of government guidelines such as the National Service Frameworks (NSFs) for CHD and Older People[2,3] and the expected full NSF for Diabetes. The cost of treatment with clopidogrel is one factor that deserves consideration. Assuming that 200 patients per 100,000 population are eligible for treatment and that uptake rates are 50%, the direct drug cost would be in the region of £50,000 per 100,000 population. Given the government's aims for reducing CHD and stroke, together with the evidence that clopidogrel could contribute towards achieving these targets, the drug should appear on PCO formularies for secondary preven-

tion in patients at risk of cardiovascular or cerebrovascular events. In practice, however, several issues will need to be considered, including whether clopidogrel should be prescribed alone or in combination with aspirin and whether there is an optimum duration of treatment for clopidogrel.

Should clopidogrel be prescribed alone or in combination with aspirin?

Based on evidence from CAPRIE,[12] clopidogrel is licensed as a single agent for secondary prevention of atherosclerotic events in patients with a history of ischaemic stroke, MI or symptomatic PVD. In these populations, therefore, until further evidence is available, clopidogrel should be prescribed alone.

By comparison, the CURE trial[27] assessed the combined antiplatelet action of clopidogrel on top of standard therapy, including aspirin, in patients with UA/NSTEMI. The resulting licence, based on evidence from this trial, is for use of clopidogrel on top of standard therapy (including aspirin) to reduce atherothrombotic events in these patient groups. Concomitant administration with aspirin should be undertaken with caution, since it may increase the risk of bleeding. The majority of bleeds occur early in treatment, within the first 30 days, and the likelihood of bleeding is also dependent on the dose of aspirin used. Patients should be alerted to the symptoms associated with bleeding and followed carefully for any signs of bleeding, especially during the first weeks of treatment.[28]

Patients with symptomatic atherothrombotic disease and more than two risk factors are at increased risk. The only evidence published to date compares clopidogrel against aspirin, rather than in addition to aspirin. This latter comparison is being tested in the CHARISMA study. Until such evidence is published, clinicians will need to make a judgement based upon their analysis of the risk benefit for the individual patient as to whether clopidogrel should be added to aspirin rather than simply replace aspirin in those individuals at particularly high risk.

What is the optimum duration of clopidogrel use?

In the CAPRIE trial, patients receiving clopidogrel or aspirin were followed up for between one and three years (average duration 1.91 years). In clinical practice, it is generally accepted that antiplatelet therapy should be given long term and often for life, although there are no trial data available to support this. The optimum duration of treatment with clopidogrel should therefore depend on the patient's history and level of risk of experiencing a further vascular event.

In the CURE trial, efficacy and safety of both early and long-term use were assessed in patients with UA/NSTEMI. Patients were randomised to either clopidogrel or placebo for 3–12 months (average duration nine months), with therapy initiated within 24 hours of symptom onset. The benefit of clopidogrel on top of standard therapy (including aspirin) was maintained throughout the duration of the trial. The new European Society of Cardiology (ESC) guidelines, announced at the ESC Congress in Berlin in September and due to be published in November, recommend therapy for at least nine months. Since there are no data available on treatment beyond 12 months, GPs should assess patients on an individual basis to determine whether to continue treatment beyond 12 months.

Key messages

- Patients with a history of symptomatic atherothrombotic disease are at high risk of developing further vascular events
- Clopidogrel alone should be given to:
  - Patients who have suffered an ischaemic stroke, MI or symptomatic PVD and who have two or more additional risk factors
  - Patients who have had a major vascular event such as a stroke, MI or PVD while on aspirin, irrespective of other risk factors
  - Patients who are aspirin-intolerant
- Clopidogrel in combination with standard therapy, including aspirin, should be given to:
  - Patients with UA/NSTEMI
- It is necessary for GPs to assess each patient's risk of developing a further vascular event when considering whether to continue clopidogrel treatment
- The developing role of PCOs as service providers across both primary and secondary care should help to facilitate consistent pathways of care and prescribing practices for patients with vascular disease

Conclusions

In primary care clopidogrel is predominantly used for patients with a history of symptomatic atherothrombotic disease (MI, stroke or established PVD) and additional risk factors, those who have had an event on aspirin or who are aspirin-intolerant, and those with UA/NSTEMI. The GP's prime concern is interpreting the clinical evidence to determine how long to continue treatment with clopidogrel. A key factor in this interpretation is regular assessments of the individual patient's risk of suffering a further vascular event. It is anticipated that, in the near future, the provision of better guidelines and effective formularies by PCOs will help to facilitate consistent standards of care and prescribing patterns for patients with vascular disease across both primary and secondary care.

References

1. Department of Health. *White Paper, Saving Lives, CM4386*. London: The Stationery Office, 1999.
2. Department of Health. *National Service Framework for Coronary Heart Disease*. London: The Stationery Office, 2000.
3. Department of Health. *National Service Framework for Older People*. London: The Stationery Office, 2001.

4. Department of Health. *National Service Framework for Diabetes: Standards*. London: The Stationery Office, 2001.
5. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke* 1993;**24**:796-800.
6. *Heart and Stroke Statistical Update*. Dallas: American Heart Association and American Stroke Association, 2002.
7. Loh E, Sutton MS, Wun CC *et al*. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997;**336**:251-7.
8. Criqui MH, Denenberg JO, Langer RD, Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med* 1997;**2**:221-6.
9. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy – I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;**308**:81-106 [published erratum in *BMJ* 1994;**308**:540].
10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71-86.
11. *MediPlus Database*. IMS Health. 2002.
12. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–39.
13. Gent M. Benefit of clopidogrel in patients with coronary disease. *Circulation* 1997;**96**(suppl 8):1-467(abstract 2608).
14. Sanofi-Synthelabo. Data on file. 2001.
15. Bhatt DL, Marso SP, Hirsch AT *et al*. Superiority of clopidogrel versus aspirin in patients with a history of diabetes mellitus [abstract]. *J Am Coll Cardiol* 2000;**35**(suppl A):409.
16. Bhatt DL, Foody JM, Hirsch AT *et al*. Complementary, additive benefit of clopidogrel and lipid-lowering therapy in patients with atherosclerosis [abstract]. *J Am Coll Cardiol* 2000;**35**(suppl A):326.
17. Bhatt DL, Chew DP, Hirsch AT *et al*. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001;**103**:363-8.
18. British Heart Foundation. *Coronary Heart Disease Statistics*. London: British Heart Foundation, 2002.
19. Vascular Surgical Society of Great Britain and Ireland. Critical limb ischaemia: management and outcome – report of a national survey. *Eur J Vas Endovasc Surg* 1995;**10**:108-13.
20. McDonagh M, Bachmann L, Golder S, J K, ter Riet G. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina. *Health Technol Assess* 2000;**4**:1-95.
21. British Heart Foundation. *Coronary Heart Disease Statistics*. London: British Heart Foundation, 2000.
22. British Heart Foundation. *Coronary heart disease statistics: diabetes supplement*. London: British Heart Foundation, 2001.
23. Audit Commission. National report: *testing times, a review of diabetes services in England and Wales*. Abingdon: Audit Commission Publications, 2000.
24. Scottish Intercollegiate Guidelines Network. *Guideline 55: Management of Diabetes*. Edinburgh: SIGN, 2001.
25. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;**339**: 229-34.
26. Collinson J, Flather MD, Fox KAA *et al.* Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK). *Eur Heart J* 2000;**21**:1450-7.
27. The CURE trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494-502.
28. Sanofi-Synthelabo. Plavix® (clopidogrel): Summary of product characteristics, 2001.
29. Coccheri S. Distribution of symptomatic atherothrombosis and influence of atherosclerotic disease burden on risk of secondary ischaemic events: results from CAPRIE. *Eur Heart J* 1998;**19**(suppl 1):1268.