Long-term management of atherothrombosis

Keith AA Fox

While clinical trials of specific antithrombotic agents can reduce the risk of vascular events in at-risk patients, understanding the results of these studies is key to optimizing benefit and minimizing risk.

Atherothrombosis and its complications (myocardial infarction (MI), unstable angina, stroke, transient ischaemic attacks (TIAs) and peripheral arterial disease (PAD)) represent the major cause of death and disability in the Western world. Atherothrombosis can reduce life expectancy by approximately 8–12 years in patients over 60 years of age (Peeters et al, 2002) and current models predict that cerebrovascular and ischaemic heart diseases will become the leading causes of morbidity and mortality by 2020, even among emerging nations (Lopez and Murray, 1998), and a major economic burden to society.

The processes underlying atherothrombosis (plaque development, rupture and thrombus formation) are common to different arterial beds and highlight the importance of inflammation, repair mechanisms and thrombosis. An index event in one vascular bed (e.g. TIA or stroke) may presage events in a different arterial bed (e.g. MI or PAD) on account of similar pathophysiology in the arterial wall. Certain conditions increase vascular risk (e.g. diabetes, hypertension or chronic renal disease), as do lifestyle (smoking, diet and exercise) and inherited factors (including gene–environment interactions). Population-based strategies are important in reducing disease prevalence, but in high-risk patients primary and secondary prevention is needed to control hypertension, diabetes, hyperlipidaemia and thrombotic risk.

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ANTIPLATELET AGENTS AND FURTHER ISCHAEMIC VASCULAR EVENTS

During the 1980s, the impact of various antiatherothrombotic therapeutic strategies on vascular risk were systematically evaluated. The first Antiplatelet Trialists' Collaboration (ATC) reviewed the results of 31 clinical trials where antiplatelet treatment (principally aspirin, sulphinpyrazone and dipyridamole) had been used to treat some 29 000 patients with a history of TIA, occlusive stroke, unstable angina or MI (Antiplatelet Trialists' Collaboration, 1988). The analyses revealed that antiplatelet treatment reduced vascular mortality by 15% and non-fatal vascular events (stroke or MI) by 30%.

A further meta-analysis of 174 clinical trials with antiplatelet agents (Antiplatelet Trialists' Collaboration, 1994) included a wider range of patient types, including patients categorized as high and as low risk, and provided unequivocal evidence that antiplatelet therapy reduces the risk of ischaemic vascular disease. This included patients without a prior vascular event but with risk factors present, and suggested that these treatments could reduce total vascular events by about a quarter. Benefit in patients categorized as low risk was not demonstrated, however.

Subsequently, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study (CAPRIE Steering Committee, 1996), conducted in more than 19 000 patients with recent stroke, acute MI or PAD, demonstrated that clopidogrel was superior to aspirin in reducing the risk of vascular events (relative risk reduction (RRR) for composite outcome of ischaemic stroke, MI and vascular death 8.7% (95% confidence interval (CI) = 0.2–16.4; P = 0.043).

The latest meta-analysis to be published by the Antithrombotic Trialists' Collaboration (2002) reviewed 287 antiplatelet studies published before 1997 in 135 000 patients with acute or previous vascular disease or some other risk factor. Overall, antiplatelet therapy reduced the incidence of any serious vascular event by about a quarter, non-fatal MI by a third, non-fatal stroke by a quarter and vascular mortality by a sixth.

ANTICOAGULANT ALTERNATIVES TO ANTIPLATELET AGENTS

An alternative approach to the use of antiplatelet agents is the use of anticoagulant coumarins. For example, the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) study (ASPECT Research Group, 1994) compared the efficacy of anticoagulant (nicoumalone or phenprocoumon) treatment to placebo in a randomized, double-blind trial in 3404 hospital survivors of MI. Anticoagulant treatment led to significant reductions in recurrent MI (hazard ratio 0.47; 95% CI = 0.38–0.59) and cerebrovascular events (0.60; 95% CI = 0.40–0.90) although the effect on mortality was limited. However, major bleeding complications were more common in patients who received anticoagulants compared with those who received placebo (73 *vs* 19 patients). Bleeding complications may be higher in clinical practice than in trial settings and the requirement for well-controlled international normalized ratio (INR) monitoring is a practical limitation. Novel oral antithrombins (ximelagatran) have been tested in atrial fibrillation and acute coronary syndromes and may provide an alternative to warfarin.

COMBINATION THERAPY COMPARED WITH MONOTHERAPY

The Antiplatelet Trialists' meta-analysis in 1994 did not reveal any significant additional benefit from combinations of aspirin with dipyramidole, sulphinpyrazone or ticlopidine. Nevertheless, the second European Stroke Prevention Study (ESPS2) (Forbes, 1998) compared low-dose aspirin, sustained release dipyridamole or a combination of the two agents, with placebo in 6602 patients with prior history of stroke or TIA. ESPS2 demonstrated that while aspirin and dipyridamole were equally effective in stroke and TIA prevention, when used in combination the effects were additive and were significantly more effective than the single agents but no regimen reduced mortality. Nevertheless, this study paved the way for further studies with combination therapy.

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) (Yusuf et al, 2001) compared the efficacy of clopidogrel on top of standard therapy (including aspirin) against standard therapy alone. There was a clear incremental benefit when clopidogrel was used on top of standard therapy (20% RRR in the combination of MI, stroke or vascular death; 95% CI = 0.72–0.90; $P = 0.00009$ at 12 months). There was a small significant increase in major bleeding in the clopidogrel group compared to the placebo group (3.7% *vs* 2.7%) but no significant increase in life-threatening bleeding or haemorrhagic strokes.

THE BENEFIT OF ANTIPLATELET TREATMENT OVER TIME

The CAPRIE study (CAPRIE Steering Committee, 1996), conducted over a 36-month follow-up period, demonstrated that while the benefit of clopidogrel over aspirin appeared at an early stage of treatment, the event rates in the two groups also continued to diverge over time. Similarly, event rates continued to diverge over time in the CURE study (Yusuf et al, 2003) indicating a sustained benefit of antiplatelet treatment over time.

ANTIPLATELET AGENTS IN DIFFERENT PATIENT SUBGROUPS

The ATC meta-analysis (Antiplatelet Trialists' Collaboration, 1994) provided clear evidence that antiplatelet therapy is beneficial in most types of patients at increased risk of occlusive vascular events, including patients with acute MI, stroke, unstable and stable angina and PAD. The ATC meta-analysis also demonstrated that antiplatelet medication provided benefit irrespective of age, sex, blood pressure or the presence of diabetes. Benefits of antiplatelet medication irrespective of age were also seen in ESPS2 (Sivenius et al, 1999).

Risk stratification of the CURE study revealed that clopidogrel therapy was beneficial in low-, intermediate-, and high-risk patients with acute coronary syndromes as stratified by the thrombolysis in myocardial infarction (TIMI) risk score (Budaj et al, 2002) and subgroup analyses showed consistency of benefit across various categories of patients (Yusuf et al, 2001; Bhatt et al, 2002).

ANTIPLATELET THERAPY IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

The use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors such as eptifibatide, tirofiban or abciximab during and after percutaneous coronary intervention (PCI) has been shown to reduce the incidence of ischaemic complications following PCI (Boersma et al, 1999). For example, in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrin Therapy (ESPRIT) trial (O'Shea et al, 2002), 2064 patients scheduled to undergo non-urgent PCI with stent implantation were treated with either eptifibatide or placebo for a period of 24 hours

after surgery. Ischaemic complications were reduced in eptifibatide-treated patients compared with those treated with placebo at all time points investigated up to 1 year where the composite of death or MI had occurred in 8% of eptifibatide-treated patients compared with 12.4% of placebo-treated patients ($P = 0.001$). GPIIb/IIIa inhibitors are, however, limited to short-term treatment; long-term oral therapy has been associated with increased mortality (Cannon, 2003).

The Clopidogrel for the Reduction of Events During Observation (CREDO) (Steinhubl et al, 2002) investigated the effect of peri-procedural and long-term clopidogrel therapy on top of standard therapy including aspirin in the treatment of PCI patients. All patients received clopidogrel for the first 29 days of treatment after which half of the patients continued with clopidogrel while the other half received placebo. Treatment with clopidogrel was associated with a significant 27% RRR ($P = 0.02$) in the combined end point of death, MI and stroke at 1 year. The degree of efficacy observed with clopidogrel was independent of whether patients received GPIIb/IIIa antagonists. The CREDO study also investigated the benefit of initiating clopidogrel treatment with a loading dose (300 mg), given at least 3 hours before the procedure, on event rates over the first 28 days post-procedure. Administration of a loading dose resulted in a non-significant but favourable 18.5% RRR in the combined end point at day 28 with some evidence to suggest that a higher RRR was seen in patients receiving the loading dose more than 6 hours pre-procedure. There was no significant difference in major bleeding.

ANTIPLATELET THERAPY AND THE RISK–BENEFIT RATIO OVER TIME

Bleeding is the major concern associated with any antiplatelet therapy. However, the most recent ATC review (Antiplatelet Trialists' Collaboration, 2002) concluded that in patients with acute or previous vascular disease or some other condition predisposing to high risk of cardiovascular disease the absolute benefits of antiplatelet therapy are substantially outweighed by the absolute risk of major extracranial bleeding unless the absolute risk of bleeding is high (such as among haemodialysis patients) or the absolute risk of a vascular event is low. Studies such as CAPRIE and CURE have demonstrated a very good safety and tolerability profile for clopidogrel treatment over a period of up to 3 years. Analysis of the CURE study data (Peters et al, 2003) indicates that the optimal daily dose of aspirin is probably between 75 and 100 mg as bleeding risk increases with increasing aspirin dose (with or without clopidogrel), without any increase in efficacy with higher aspirin dosage.

THE FUTURE

Ximelagatran is the first in a new class of oral direct thrombin inhibitors currently in development. In the Stroke Prevention using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III) study (Olsson and the Executive Steering Committee on behalf of the SPORTIF III Investigators, 2003) ximelagatran was compared with warfarin in 3407 atrial fibrillation patients over a 12–26-month treatment period. The combined rate of all strokes and systemic thromboembolic events was 2.2% per year in the warfarin group and 1.3% per year in the ximelagatran group, a RRR of 41% ($P = 0.018$).

Most recently ximelagatran has been compared with placebo in the Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patients with rEcent Myocardial damage (ESTEEM) study (Wallentin et al, 2003), a phase II investigation in 1883 patients with MI. ESTEEM showed that ximelagatran significantly reduces the risk of death, recurrent MI or attacks of severe chest pain from 16.3% to 12.7% (all dose groups combined) during 6 months' treatment in combination with aspirin, equating to a RRR of 24% (hazard ratio 0.76; $P = 0.036$) compared with aspirin alone. These results require confirmation in a phase III study.

However, while there was no significant difference between the treatment groups in bleeding or haemorrhage, elevations in serum transaminase levels to more than three times the upper limit of normal were observed in the ximelagatran group in both studies (6.5% of patients in SPORTIF III (0.7% placebo) and 3–9% in ESTEEM (1% placebo)). So, while the results of SPORTIF III and ESTEEM are of considerable interest as ximelagatran, unlike warfarin, does not require INR monitoring, evidence that some patients may experience liver toxicity requires further exploration.

ARE ANTIPLATELET AGENTS BEING PRESCRIBED?

The clinical studies that have been performed with currently available drugs indicate that long-term treatment offers significant risk reduction with few adverse effects. Nevertheless, a study of the gap between evidence and practice (Fox et al, 2003) suggests that hospital characteristics, resources and other geographical factors influence the uptake of evidence-based therapies into clini-

cal practice and that many patients still do not receive therapies recommended by international and national guidelines. This situation requires urgent attention from the medical community.

CONCLUSIONS

The results of numerous clinical studies provide clear evidence that treatment with antiplatelet agents provides a sustained risk reduction for vascular events across a wide range of patients at risk of developing the disease. Antiplatelet agents are an important component of the long-term treatment programme of patients with atherothrombosis. HM

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KEY POINTS

- Atherothrombosis is widespread and has serious health and economic implications.
- Atherothrombosis underlies vascular events in cerebrovascular, cardiovascular and peripheral arteries.
- Antithrombotic therapy reduces the risk of vascular events across a wide range of at-risk individuals.
- In patients at moderate or higher risk, the benefits of antiplatelet therapy outweigh the risks of bleeding.