

EDITORIAL

Antiplatelet therapy and the vascular tree

A Blann



While treatment with aspirin plus clopidogrel may be valid as an adjunct to percutaneous coronary intervention, other issues remain to be addressed before routine combination therapy is recommended for any level of atherosclerosis

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Aspirin is effective in reducing the risk of primary and secondary cardiovascular events, such as myocardial infarction and stroke, and is a mainstay of both the adjuvant treatment of acute coronary syndromes and other cardiovascular disease, with a minor effect on reducing the risk of venous thromboembolism. While this impact is widely believed to be caused by suppression of the platelet, aspirin also has likely desirable non-platelet effects—for example, in inhibiting nuclear transcription initiators such as NF κ B (implicated in the promotion of various genes with pro-inflammatory activity), in protecting low density lipoprotein cholesterol from oxidative modification, and in modulating endothelial dysfunction in atherosclerosis. However, the precise value of these latter mechanisms in vivo and any possible contribution to a reduction in thrombotic events is speculative.

Although low to medium dose aspirin (32.5–75 mg daily) is well tolerated in the majority of patients, the principle adverse effects are gastrointestinal bleeding and haemorrhagic stroke. A meta-analysis of 16 placebo controlled trials of aspirin for cardiac and other indications found that aspirin increased the absolute risk of cerebral haemorrhage by 12 events per 30 000 person-years of follow up. Thus, the possible value of aspirin in reducing thrombosis may be weighed against the risk of bleeding, with the greatest value being in those at highest cardiovascular risk.^{1–3}

HOW VALUABLE IS ASPIRIN?

Despite the positive attributes of aspirin described above, several commentators have expressed other concerns that it may not be broadly valuable.⁴ For example, although recruiting patients with hypertension, the HOT trial reported no protective effect of aspirin on death, cardiovascular death, all cardiovascular events, all strokes, all myocardial infarctions, or silent myocardial infarctions. Aspirin, however, did protect against myocardial infarction but at the cost of an increase in fatal and non-fatal major bleeds, minor bleeds, and total bleeds. There is also some evidence that dual use of aspirin and angiotensin converting enzyme inhibitors in some subgroups of patients may be of dubious value, although this may not be true for low dose

aspirin. An additional possible problem with aspirin is the growing recognition of resistance, reported to be present in 5–10% of patients with stable coronary artery disease.⁵

Clopidogrel inhibits platelet activity by a route independent of that of aspirin—that is, irreversibly inhibiting platelet aggregation by selectively binding to adenylate cyclase coupled adenosine diphosphate receptors on the platelet surface.⁶ One of the first major trials of this agent (CAPRIE) directly compared 325 mg of aspirin daily with 75 mg of clopidogrel daily in approximately 19 000 high risk patients with existing vascular disease (recent ischaemic stroke ($n = 6431$), myocardial infarction ($n = 6302$), or peripheral artery disease ($n = 6452$)). Overall, patients on clopidogrel had a marginally cardiovascular better outcome with a relative risk reduction (RRR) of 8.7% (95% confidence interval (CI) 0.3% to 16.5%, $p = 0.043$) compared to aspirin, with an overall safety and side effect profile at least as good as aspirin.⁷ The fact that clopidogrel and aspirin have different modes of action opens the potential for trials of added efficacy. The CURE trial compared the effects of aspirin alone with a combination of aspirin and clopidogrel in over 12 500 patients with unstable angina or suspected myocardial infarction.⁸ A primary outcome (cardiovascular death, non-fatal myocardial infarction, stroke) occurred in 11.4% of patients on aspirin compared to 9.3% on both agents ($p < 0.001$), although major and minor (but not fatal) bleeding was greater in the combination group. The sub-study in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI-CURE) and the CLASSICS trial provided important data that have led to the combination of aspirin and clopidogrel becoming standard treatment for one month after percutaneous coronary intervention (PCI) with or without stent implantation.^{9–11}

The MATCH trial was a randomised, double blind, placebo controlled trial to compare aspirin (75 mg/day) with placebo in 7599 high risk patients with recent ischaemic stroke or transient

Abbreviations: CAMPER, clopidogrel and aspirin in the management of peripheral endovascular revascularisation; CAPRIE, clopidogrel versus aspirin in patients at risk of ischaemic events; CASPAR: clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease; CLASSICS, clopidogrel aspirin stent international cooperative study; CURE, clopidogrel in unstable angina to prevent recurrent events; CREDO, clopidogrel for the reduction of events during observation; HOT, hypertension optimal treatment; MATCH: management of atherothrombosis with clopidogrel in high-risk patients with recent transient ischemic attack or ischemic stroke; PCI, percutaneous coronary intervention; RRR, relative risk reduction

Correspondence to:
Dr Andrew Blann,
University Department of
Medicine, City Hospital
NHS Trust, Birmingham
B18 7QH, UK; a.blann@
bham.ac.uk

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ischaemic attack and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/day.¹² After 18 months, almost 16% of patients reached the primary end point in the group receiving aspirin and clopidogrel compared with almost 17% in the clopidogrel alone group (RRR 6.4%, 95% CI -4.6% to 16.3%). Life threatening bleeding was higher in the group receiving aspirin and clopidogrel versus clopidogrel alone (96 (2.6%) v 49 (1.3%); absolute risk increase 1.3%, 95% CI 0.6% to 1.9%). Major bleeding was also increased in the group receiving aspirin and clopidogrel, but no difference was recorded in mortality. The authors concluded that adding aspirin to clopidogrel in high risk patients with recent ischaemic stroke or transient ischaemic attack was associated with a non-significant reduction in major vascular events. However, the risk of life threatening or major bleeding was increased by the addition of aspirin.

CLOPIDOGREL PLUS ASPIRIN IN PATIENTS UNDERGOING PCI

More recently, the CREDO trial suggested an incremental benefit of prolonged (one year) use of clopidogrel in addition to aspirin in 2116 patients undergoing elective PCI.¹³ Long term clopidogrel treatment was associated with a 26.9% RRR in the combined risk of death, myocardial infarction, or stroke (95% CI 3.9% to 44.4%; $p = 0.02$; absolute reduction, 3%). Clopidogrel pre-treatment did not significantly reduce the combined risk of death, myocardial infarction, or urgent target vessel revascularisation at 28 days (RRR 18.5%, 95% CI -14.2% to 41.8%; $p = 0.23$). However, in a pre-specified subgroup analysis, patients who received clopidogrel at least six hours before PCI experienced an RRR of 38.6% (95% CI -1.6% to 62.9%; $p = 0.051$) for this end point compared with no reduction with treatment less than six hours before PCI. Risk of major bleeding at one year increased, but not significantly (8.8% with clopidogrel v 6.7% with placebo; $p = 0.07$). The authors concluded that long term (one year) clopidogrel treatment significantly reduced the risk of adverse ischaemic events, and that a loading dose of clopidogrel given at least three hours before the procedure did not reduce events at 28 days, although subgroup analyses suggested that longer intervals between the loading dose and PCI may reduce events.

That these trials have focused on patients with coronary artery disease (CAPRIE, CLASSICS, CURE, CREDO), peripheral artery disease (CAPRIE), or cerebrovascular disease (CAPRIE, MATCH) is unsurprising. However, most patients with advanced atherosclerosis in one such vascular territory generally have disease in another, and those with concurrent disease in all three such territories (coronary, cerebral, and peripheral) are at additional risk of a major cardiovascular event.¹⁴ In this issue of *Heart*, Mukherjee and colleagues present a post-hoc analysis of those patients from CREDO with a high burden of atherosclerosis (that is, of the peripheral and/or cerebral arteries in addition to coronary artery disease, thus: multiple arterial disease).¹⁵ They looked at outcome in 272 patients with multiple arterial disease, of whom 132 received clopidogrel in addition to aspirin, and compared them to those 140 patients on aspirin alone. In the main CREDO trial, the event rate (death/myocardial infarction/stroke) for all patients on aspirin alone was 11.8%, while the current study reports a clearly higher rate of 17.4% for patients with multiple arterial disease, as we would expect. However, while this difference seems large, direct statistical comparison is difficult. Similarly, the main CREDO patients on aspirin plus clopidogrel had an event rate of 8.6%, compared to a rate of 9.2% in the present subgroup analysis of those patients with the most widespread disease. This

modest change suggests that additional long term clopidogrel combination treatment particularly benefits patients with the most widespread disease. This finding is reminiscent of the CAPRIE study, where there was evidence that clopidogrel may be particularly effective at preventing vascular events in patients with peripheral arterial disease compared to those with stroke or myocardial infarction.⁷

RESISTANCE TO ANTIPLATELET EFFECTS

Clopidogrel is clearly recommended for those patients with atherosclerotic vascular disease with a contraindication to aspirin,⁹ and combination treatment is valid as an adjunct to PCI. However, other issues remain to be addressed before routine combination therapy is recommended for any level of atherosclerosis. A developing issue of resistance to the antiplatelet effects of clopidogrel remains.¹⁶ Trials currently in progress (CASPAR, CAMPER) may answer some of the questions of efficacy and safety. For the time being the subanalysis of CREDO data by Mukherjee and colleagues¹⁵ adds further weight to the concept of combination antiplatelet treatment.

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