

Prescribing clopidogrel with aspirin

Introduction

Aspirin and clopidogrel are antiplatelet agents with different modes of action; aspirin acts through inhibition of platelet cyclooxygenase and suppression of thromboxane, whereas clopidogrel acts by blocking a receptor for adenosine diphosphate. There is evidence that, used separately, aspirin and clopidogrel are both effective in preventing further thromboembolic events in people who have established cardiovascular disease – stroke, coronary heart disease (CHD), or peripheral vascular disease.¹ Since its launch, clopidogrel has been used as an alternative agent to aspirin to prevent atherothrombotic events in high-risk patients. In Wales during the year to July 2007, approximately £9 million was spent on 250,000 dispensed items for clopidogrel.² In view of its associated costs compared to aspirin, clopidogrel is generally reserved for use in patients who have hypersensitivity to aspirin.[†] More recently, clopidogrel has been used as add-on therapy to aspirin in the treatment of acute coronary syndrome (ACS) and also in patients undergoing percutaneous coronary intervention (PCI), for example stenting or angioplasty. The use of the combination in patients undergoing PCI should be guided by local protocol, usually led by tertiary care centres. A discussion of the evidence for such use is beyond the scope of this document.

The possibility of combining aspirin and clopidogrel for more stable cardiovascular disease, to give added benefit, appears attractive. However, studies have shown that combining their effects could also increase the risk of adverse effects, in particular the risk of bleeding. This document discusses these studies and the implications for practice. It adds to information given in the previous WeMeReC Bulletin on prescribing clopidogrel (Vol. 11 No.1, February 2004).

The evidence

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which set out to test the hypothesis that combining these drugs gives added benefit, was greeted enthusiastically and widely publicised. The study has been promoted to encourage greater use of combination therapy.³ However, there is a concern that the results have been extrapolated too far and outside the context of the study by some clinicians.^{4,5} The study compared the combination of clopidogrel and aspirin with aspirin alone, for 3 to 12 months (median duration 9 months), in patients admitted with ‘high risk’ non-ST-segment elevation ACS. The results suggested some benefit from the combination; a reduction in the risk of the composite primary endpoint of death from cardiovascular causes, non-fatal MI or stroke was reported (NNT 48, see table), compared with aspirin monotherapy.⁶ Closer examination of this study suggests that maximum benefit is seen within the first three months after an ACS event. Beyond this time it is possible that the increased risk of haemorrhage could result in more harm than benefit, as pointed out in the Summary of Product Characteristics (SPC) for clopidogrel.⁷ Studies in patients suffering acute myocardial infarction (AMI), including the very large CLOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), suggest benefit from short-term combined treatment with clopidogrel and aspirin (mean duration 15 days in COMMIT), but have not looked at longer-term effects.⁸ An explanation of the effect seen in CURE could be that where absolute risk of AMI is very high the added benefit of combining the drugs outweighs the risks. As an individual’s risk subsequently declines and CHD becomes ‘stable’ then any added benefit is outweighed by increased risk of haemorrhage.⁵

[†] See WeMeReC Bulletin Vol.11 No.1, February 2004 for a more detailed discussion of the use of clopidogrel in patients who are unable to take aspirin.

The potential for harm resulting from the less conservative interpretation of CURE and overenthusiastic use of the combination has been reinforced by two recent, large, randomised-controlled studies. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study was conducted in a broad population of patients at high risk of a cardiovascular event; patients with either clinically evident, or multiple risk factors for, cardiovascular disease. It showed that clopidogrel and aspirin together were no more effective than aspirin alone at preventing further cardiovascular events, but that the combination causes an excess of bleeding complications.⁹

Similarly the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study compared the use of clopidogrel alone with the combination of clopidogrel and aspirin after stroke or transient ischaemic attack (TIA) and showed significant potential for harm, with no added benefit over clopidogrel alone in preventing further cardiovascular events.¹⁰ A Cochrane review, looking at these combination studies as a whole, concluded that in patients at high risk of cardiovascular disease who do not present acutely, there is only weak evidence of benefit, and the hazards of treatment almost match any benefit obtained.¹¹

What are the implications for practice?

Clopidogrel is currently licensed for use in combination with aspirin for the prevention of atherothrombotic events in patients suffering from non-ST segment elevation ACS (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following PCI; or ST segment elevation AMI (STEMI), in medically treated patients eligible for thrombolytic therapy.⁷

The National Institute for Health and Clinical Excellence (NICE) has issued guidance on the use of clopidogrel in combination with low-dose aspirin following STEMI. It advises that patients treated with the combination during the first 24 hours after a myocardial infarction should continue this treatment for at least four weeks. Thereafter, standard treatment, including low-dose aspirin should be given, unless there are other indications to continue dual antiplatelet therapy.¹²

Although it is licensed for ACS without ST-segment elevation, the point at which to stop the combination of clopidogrel and aspirin following such an ACS event is controversial. NICE has clarified its advice to the NHS in England and Wales and state that this combination should be used for 12 months after an episode of high-risk ACS.¹³ Commentators have expressed concern that there is little evidence of benefit after three months but clear evidence that risk of harm continues.^{5,14} Furthermore, a recently published national guideline for Scotland advises that the aspirin and clopidogrel combination should only be continued for three months in patients with non-ST-segment elevation ACS.¹⁵ Certainly, people with stable disease 12 months or more after an ACS event should be reviewed and have combination therapy changed to a single agent; in most cases aspirin is appropriate.* A particular concern in the NHS is that it can be difficult to implement 'stopping rules'. One suggested approach is to advise patients being discharged from hospital of a date for stopping clopidogrel and to add this date to prescription instructions.

The evidence from the studies discussed above does not support the use of clopidogrel with aspirin to prevent cardiovascular events following stroke or (TIA), as combined they clearly show potential for more harm than benefit. Furthermore, in patients who have stable cardiovascular disease the combination of aspirin and clopidogrel should not be used in preference to a single agent. For single-agent use, low-dose aspirin is likely to be more cost-effective, since it is much cheaper than clopidogrel and has very similar benefits and risks; it is preferred in suitable individuals, unless there is evidence of aspirin hypersensitivity.¹³

* As stated in the introduction, a discussion of the use of aspirin with clopidogrel in patients undergoing or having undergone PCI (including stenting and angioplasty) is beyond the scope of this document and should be guided by local protocol.

References

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TABLE 1. Summary of studies guiding combined use of clopidogrel and aspirin (excluding angiography/angioplasty/stent studies)

Study	Population Studied	Duration	Primary outcome	Relative risk reduction (RRR) [95% CI] Absolute risk reduction (ARR) Number needed to treat (NNT)	Significant adverse effects: haemorrhage events	Relative risk increase (RRI) [95% CI] Absolute risk increase (ARI) Number needed to harm (NNH)
CURE⁶ Aspirin (75mg to 325mg daily) plus placebo or clopidogrel 75mg daily	12,562 patients within 24 hours of admission with ACS without ST-elevation (most had enzyme changes or other ECG abnormalities – ‘high risk’). Mean age 64 years, 38% women	Median follow-up 9 months (from 3 to 12 months)	Composite: MI, stroke or vascular death	20% RRR [10% to 28%] p<0.001 11.4% vs. 9.3% ARR 2.1% NNT 48, 9 months	Major bleeding = substantially disabling bleeding, intraocular bleeding leading to loss of vision, or needing transfusion ≥2 units blood	38% RRI [13% to 67%] p=0.001 2.7% vs. 3.7% 1% ARI NNH 100, 9 months
CHARISMA⁹ Aspirin (75mg to 162mg daily) plus placebo or clopidogrel 75mg daily	15,603 patients with clinically evident ‘stable’ cardiovascular disease – CHD, stroke or PVD – (78%) or multiple risk factors Median age 64 years, 30% women	Median follow-up 28 months (range not stated)	Composite: MI, stroke, or vascular death	7% RRR [-5% to 17%] p=0.22 7.3% vs. 6.8% ARR not significant	Severe or moderate bleeding* = bleeding leading to transfusion, fatal bleeding, intracranial haemorrhage or bleeding needing inotropic support [*Calculated from: Letters. NEJM 2006;355:419-421]	46% RRI [22% to 73%] p<0.001 2.6% vs. 3.8% 1.2% ARI NNH 84, 28 months
MATCH¹⁰ Clopidogrel 75mg daily plus placebo or aspirin 75mg daily	7,599 patients with recent stroke or TIA (within 3 months) plus at least one additional risk factor (e.g. diabetes – 68%) Mean age 66 years, 37% women	Full 18 months treatment and follow-up	Composite: MI, stroke, vascular death or rehospitalisation for ischaemic episode	6.4% RRR [-4.6% to 16.3%] p=0.24 16.7% vs. 15.7% ARR not significant	Life threatening bleeding or major bleeding = fatal bleeding, drop in Hb ≥50g/l, significant hypotension with need for inotropes, intracranial haemorrhage, transfusion ≥3 units, loss of vision	137% RRI [80% to 210%] p<0.0001 1.9% vs. 4.5% 2.6% ARI NNH 39, 18 months
COMMIT⁸ Aspirin (162mg daily) plus placebo or clopidogrel 75mg daily	45,852 patients within 24 hours of suspected AMI Mean age 61 years, 28% women	Treatment continued for up to 4 weeks in hospital (mean 15 days in survivors)	Composite: Death, reinfarction or stroke	9% RRR [3% to 14%] p=0.002 10.1% vs. 9.2% ARR 0.9% NNT 111, 15 days	Life threatening bleeding or major bleeding = haemorrhagic stroke and major non-cerebral bleeding	RRI not significant [mean 15 days]