

DRUG UPDATE

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SECONDARY PREVENTION OF STROKE AND TIA

Secondary prevention of stroke or TIA consists of antiplatelet or anticoagulation therapy, depending on the aetiology of the event. The mainstay of antiplatelet therapy is aspirin, with the addition of modified-release dipyridamole for the first two years following an event. Clopidogrel should only be used in individuals who have true aspirin hypersensitivity or are unable to tolerate aspirin despite acid suppressant therapy. Modifiable risk factors should be managed in accordance with current NICE guidance.

What are they?

Stroke or transient ischaemic attack (TIA - defined as a neurological disturbance of a presumed vascular cause) may present with signs of motor, sensory or cortical dysfunction such as hemianopia.¹

Secondary Prevention

Current National Institute for Health and Clinical Excellence (NICE) guidance recommends the combination of modified-release (MR) dipyridamole and aspirin for people who have had an ischaemic stroke or TIA for a period of two years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care including aspirin.²

Evidence from the recently published ESPRIT study (n = 2,739)³ demonstrated that combinations of aspirin (30-325 mg daily) and dipyridamole (200 mg twice daily) were associated with a lower incidence of vascular events than aspirin alone. The composite primary endpoint of combined vascular events was 16% in the group taking aspirin alone and 13% in the combination group. This reflects an absolute risk reduction of 1% per year or a number needed to treat (NNT) per annum of 100. Mean follow up was 3.5 years suggesting the 2 years of combination therapy currently recommended by NICE may have to be revised.³

Patients should be counselled about the side effects of dipyridamole which tend to occur early after initiating treatment and may disappear with continued treatment.⁴ Clopidogrel alone is only recommended for people who are genuinely intolerant of low-dose aspirin (i.e. proven hypersensitivity to aspirin-containing medicines, or history of severe dyspepsia induced by low-dose aspirin) and have experienced an occlusive vascular event or have symptomatic peripheral vascular disease.² The comparative, blinded, CAPRIE study evaluated the efficacy of clopidogrel and aspirin for vascular disease over almost two years (n = 19,185).⁵ The annual risk of ischaemic stroke, myocardial infarction (MI) or vascular death was 5.32% and 5.83% in the clopidogrel (75 mg daily) and aspirin (325 mg daily) groups, respectively (p = 0.043).⁵ The 0.51% absolute benefit of

clopidogrel over aspirin equates to an NNT of 196 and a cost per event prevented of £89,970. In patients with aspirin-induced dyspepsia, addition of a proton pump inhibitor is a more cost-effective alternative to monotherapy with clopidogrel. The recently published CHARISMA study compared combination treatment of clopidogrel and aspirin with aspirin alone in patients with multiple risk factors for vascular disease or symptomatic cardiovascular disease.⁶ Overall there was no statistically significant reduction in vascular events in the combination group compared with aspirin (p = 0.22). However, there was a significantly higher risk of moderate bleeding associated with combination therapy (number needed to harm NNH = 80).⁶ Similarly in the MATCH study, combination treatment was reported to increase the risk of life-threatening bleeding when compared with clopidogrel alone (NNH = 77).⁷

Anticoagulants reduce the risk of recurrent vascular events in patients who have AF with a recent TIA or minor ischaemic stroke from 17% to 8% per year (placebo vs. anticoagulant, respectively) compared with a reduction from 19% to 15% per year (placebo vs. aspirin, respectively).⁸ The risk of major bleeding complications with warfarin is 2-3%^{8,9} per year, compared with 0.9% per year with aspirin.⁸ The decision to anticoagulate must take into account the possible risks and benefits in each individual.

Modification of Risk Factors

Lipid Lowering

The national targets for total cholesterol (TC) and LDL cholesterol are < 5 mmol/L and 3 mmol/L respectively (or a 30% reduction, whichever is greater).¹⁰ Recent guidelines for lipid-lowering treatment in certain groups suggest achieving a TC of < 4 mmol/L and LDL cholesterol < 2 mmol/L, or a 25% reduction in TC and a 30% reduction in LDL, whichever attains the lowest value.¹¹ However, the benefits in terms of reduced mortality and cost-effectiveness of lowering to targets below 5 mmol/L of TC have yet to be demonstrated in this group. A recent statement from the Department of Health reiterates that targets for TC and LDL remain at 5 mmol/L and 3 mmol/L, respectively.¹²

Hypertension

Current NICE guidelines recommend a blood pressure target of 140/90 mmHg or less, with treatment recommendations that include:¹³

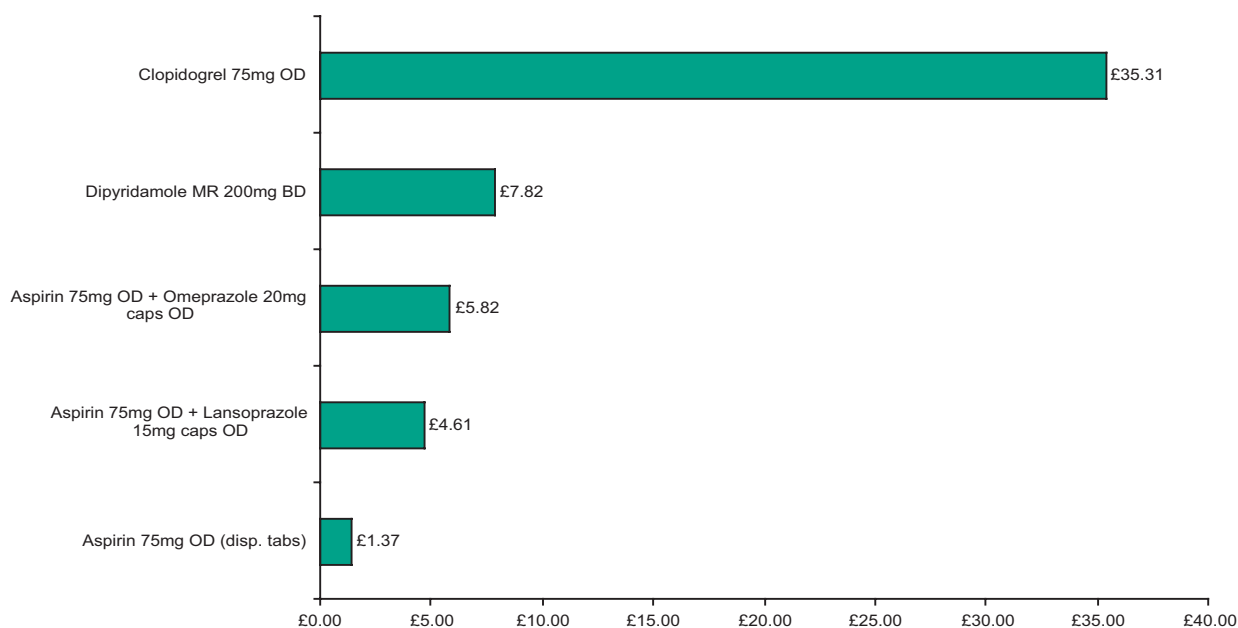
- ❑ Patients < 55 years – initial treatment with an ACE inhibitor.
- ❑ Black patients and patients ≥ 55 years – thiazide diuretic or calcium channel blocker.
- ❑ Beta blockers are no longer preferred as routine initial therapy (See NICE guidance for further details¹³).
- ❑ AT2 antagonists can be considered an option for patients with intolerance to ACE inhibitors.

How much does it cost?

Smoking cessation

The excess mortality risk due to coronary heart disease falls by half after one year of smoking abstinence.¹⁴ The risk of stroke for those formerly smoking < 20 cigarettes per day, falls to pre-smoking levels within five years.¹⁵ Nicotine replacement therapy and bupropion are recommended for smokers who express a desire to stop smoking.¹⁶ Other lifestyle modifications e.g. regular exercise may also be of benefit.

Cost of 28 days treatment (Drug Tariff January 2007)



REFERENCES

1. Bath PMW et al. ABC of arterial and venous disease. Acute stroke. *BMJ* 2000;320:920-3. (R)
2. National Institute for Health and Clinical Excellence. Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events. *Technology Appraisal* 90; May 2005. (G)
3. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT). *Lancet* 2006;367:1665-73. (RCT)
4. Boehringer Ingelheim Ltd. Persantin Retard 200mg. Summary of product characteristics July 2004. www.medicines.org.uk (last accessed 16/01/07)
5. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39. (RCT)
6. Bhatt DL et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *New Engl J Med* 2006;354:1706-17. (RCT)
7. Diener HC et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH). *Lancet* 2004;364:331-7. (RCT)
8. European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-62. (RCT)
9. Evans A et al. Secondary stroke prevention in atrial fibrillation: lessons from clinical practice. *Stroke* 2000;31:2106-11. (CT,O)
10. Department of Health. Coronary heart disease: national service framework for coronary heart disease - modern standards and service models. March 2000. (G)
11. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91(Suppl 5):v1-4. (G)
12. Professor Roger Boyle - Department of Health. National policy on statin prescribing. November 2006.
13. National Institute for Health and Clinical Excellence. Hypertension. Management of hypertension in adults in primary care. *Clinical Guideline* 34; June 2006. (G)
14. Edwards R. The problem of tobacco smoking. *BMJ* 2004;328:217-9. (R)
15. Wannamethee SG et al. Smoking cessation and the risk of stroke in middle-aged men. *JAMA* 1995;274:155-60. (O)
16. National Institute for Health and Clinical Excellence. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation. *Technology Appraisal Guidance* No. 39 March 2002. (G)

KEY RCT - randomised controlled trial, CT-controlled trial, G-guidelines, R-review, O-open label

Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH

Tel: 0191 232 1525 Fax 0191 260 6192

E-mail: nyrdtc.di@ncl.ac.uk Website: www.nyrdtc.nhs.uk

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