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New from NICE: Important changes in the use of clopidogrel and MR dipyridamole

Clopidogrel* is now recommended by NICE with no limits on duration of treatment in people who have had an ischaemic stroke. Modified-release (MR) dipyridamole plus aspirin is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated. This and other changes in NICE guidance on clopidogrel and MR dipyridamole for the prevention of occlusive vascular events have been introduced in technology appraisal guidance 210,[1] which replaces previous NICE guidance from 2005.

*Treatment with clopidogrel should be started with the least costly licensed preparation.[1] In current practice, this means generic clopidogrel.

What are the implications of the new guidance?
Health professionals should follow this guidance[1] for people who have had an occlusive vascular event or who have established peripheral arterial disease. Here is our **summary of the practical implications of these changes:**

After an ischaemic stroke:

- Clopidogrel is now recommended, with no specified limit on duration of treatment
- MR dipyridamole plus aspirin is now recommended after an ischaemic stroke **only** if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to two years
- MR dipyridamole alone is recommended after an ischaemic stroke **only** if aspirin or clopidogrel cannot be used as above because they are contraindicated or not tolerated, again with no limit on duration of treatment.

After a transient ischaemic attack (TIA):

- Treatment with MR dipyridamole plus aspirin is still recommended for people who have had a TIA, but now there is no recommended limit on the duration of treatment
- MR dipyridamole monotherapy is recommended after TIA **only** if aspirin is contraindicated or not tolerated, again with no limit on duration of treatment
- No recommendations are made about the use of clopidogrel after a TIA because it is not licensed for this indication.

After a myocardial infarction (MI):

- Recommendations about aspirin as the treatment of choice post MI is not affected by this new guidance
- Clopidogrel is recommended for people who have had an MI, only if aspirin is contraindicated or not tolerated. This guidance[1] should be considered alongside existing NICE guidance, which gives details on the use of clopidogrel in combination with aspirin in people who have had an MI (see CG48), and in people with unstable angina or non-ST-segment-elevation MI (NSTEMI, see CG94).

Peripheral arterial disease (PAD) or multivascular disease:

- Clopidogrel is now recommended for patients with PAD or multivascular disease.

Treatment with clopidogrel should be started with the **least costly licensed preparation.[1] In current practice, this means generic clopidogrel**. Although not discussed in the guidance, aspirin monotherapy would seem to be the logical choice if both clopidogrel and MR dipyridamole were contraindicated or not tolerated.

People currently receiving clopidogrel or MR dipyridamole, either with or without aspirin outside the revised recommendations, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.[1]

This guidance does not apply to people with atrial fibrillation (AF). NICE guidance on prophylaxis of stroke in people with AF is given in CG36. More information on managing AF can be found in the NPC eLearning materials on atrial fibrillation. It also does not apply to those who need treatment to prevent occlusive events after coronary revascularisation or carotid artery procedures.

All information was correct at the time of publication (March 2011)

See MeReC Rapid Review No. 2353 for further details, particularly the background to these changes. More information can be found in the NPC eLearning materials on stroke, the NPC eLearning materials on post MI and the NPC eLearning materials on antiplatelets.

References
1. NICE. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events. Review of Technology Appraisal Guidance 90. Technology appraisal guidance 210. December 2010

Does eplerenone▼ have a role in mild heart failure?

The EMPHASIS-HF study[1] (n=2,737) found that adding eplerenone▼ to recommended therapy for heart failure (HF) with left ventricular systolic dysfunction (LVSD) reduced the risk of a composite of death from cardiovascular (CV) causes or hospitalisation for HF compared with placebo in patients with mild symptoms. However, this was in a very specific patient group (e.g. with additional CV risk factors, recent CV hospitalisation) and the results may not be applicable to all patients with 'mild symptoms'. Furthermore, the study gives no information on whether spironolactone (an alternative and considerably less expensive aldosterone antagonist) would have performed as well, better or worse than eplerenone in this patient population.

Action

Health professionals should continue to follow the recently updated NICE guidance on the management of HF. **ACE inhibitors and beta-blockers licensed for heart failure** should be considered as first-line treatments in patients with HF due to LVSD, using clinical judgement to decide which drug to start first. Adding an aldosterone antagonist (spironolactone or eplerenone) can be considered as a second-line option, and while there is currently no head-to-head comparative evidence, there appears to be little difference between the two in terms of effectiveness. Specialist advice should be sought before offering any second-line treatment.

We discuss this study in more detail in MeReC Rapid Review No. 2359. Information on managing HF can be found in the NPC eLearning materials on HF.

References
1. Zannad F, et al. Eplerenone in patients with systolic heart failure and mild symptoms. NEJM 2011;364:11–21

Observational study suggests candesartan may be preferable to losartan▼* in heart failure

A Swedish observational study[1] (n=5,139) has suggested that patients with HF have improved survival when they are treated with candesartan compared with losartan▼*. This study has limitations (e.g. there was no control arm) but it highlights the possibility that there may be some differences between individual angiotensin 2 receptor antagonists when they are used in people with HF.

* The black triangle has been reinstated for Cozaar▼ (losartan) specifically for the new indication of heart failure.

Action

Clinicians should continue to follow NICE recommendations that an ACE inhibitor is the first choice renin-angiotensin system (RAS) drug in HF. An angiotensin 2 receptor antagonist (A2RA) licensed for HF can be considered if the patient has intolerable cough with an ACE inhibitor; or it can be used in combination with an ACE inhibitor and a beta blocker in certain patients on specialist advice, if the patient remains symptomatic despite optimal therapy with an ACE inhibitor and beta blocker. Despite this study's limitations, any change from candesartan to losartan in patients with HF, requires caution.

Further details

This study provides no information about the comparative effects of losartan or candesartan in hypertension or other indications, but A2RAs are not recommended by NICE as first choice RAS drugs for any indication. Prescribing managers should review local prescribing trends for RAS drugs as suggested in the document 'Key therapeutic topics 2010/11 – Medicines management options for local implementation' produced by the NPC as part of the NHS 'Quality, Innovation, Productivity and Prevention (QIPP)' programme. This document highlights the productivity opportunity in using ACE inhibitors in preference to A2RAs and for careful consideration of switching from A2RAs to ACE inhibitors in some selected patients. However, despite this study's limitations, it would seem appropriate to exercise caution when considering whether to change from candesartan to losartan in patients with HF, even after a careful medication review.

This study is discussed in more detail in MeReC Rapid Review No. 2396.

References
1. Eklind-Cervenka M et al. Association of candesartan vs losartan with all-cause mortality in patients with heart failure. JAMA 2011;305:175–82

Getting better value from the NHS drug budget

A BMJ article[1] proposes innovative ways of restructuring healthcare prescribing to get better value for money from the NHS drug budget, and encourages pharmaceutical companies to research more innovative medicines. It suggests that more efficient use of the most cost-effective medicines could save the NHS more than £1 billion per year.

What actions can be taken now?

In view of current financial constraints within the NHS, it is important that health professionals continue to review and amend prescribing practices and policies to ensure that drug budgets are used efficiently without compromising quality of care. Although, some of the financial and regulatory recommendations in this paper[1] would require high level policy decisions, it gives recommendations on choice of medicines, many of which mirror those already in the NHS QIPP programme. An initial document prepared by the NPC and Department of Health, updated in February 2011, includes recommendations covering 15 therapeutic topics. This is available for download from the NPC website. In addition, NICE has issued guidance on medicines adherence, which is an important consideration when trying to reduce wastage of medicines.

MeReC Rapid Review No. 2294 gives details of the specific recommendations made in this article and the NPC's opinion on some of these. Further information on getting better value from the NHS drug budget can be found in the QIPP document and in the appropriate therapeutic NPC eLearning materials.

References

1. Moon JC, et al. Getting better value from the NHS drug budget. BMJ 2010; 341:c6449

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