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No significant benefits for early intensive multifactorial management of type 2 diabetes

The ADDITION-Europe study[1] looked at the effect of early intensive multifactorial management of blood glucose and cardiovascular (CV) risk factors on 5-year CV outcomes in people found to have type 2 diabetes via screening. While there were some small but statistically significant reductions in disease-oriented outcomes (HbA1c, blood pressure [BP], total and LDL-cholesterol) with intensive management compared with usual care, no statistically significant differences were found in any patient-oriented CV outcomes (e.g. CV death, myocardial infarction [MI], stroke).

Action

Patients should continue to be managed according to NICE guidance on type 2 diabetes. This recommends an individualised (rather than intensive) multifactorial approach to management, addressing lifestyle issues, blood glucose, BP and blood lipids as appropriate for the patient. For example, when managing blood glucose, individual targets for HbA1c should be agreed with each patient, taking into account the patient's preferences for care and the balance of likely benefits and harms.

What did this study find?

At five years, there was no statistically significant difference between routine care and intensive treatment in the primary endpoint, a composite of first CV event, including CV mortality, CV morbidity, revascularisation and non-traumatic amputation. The incidence of first CV event was 7.2% in the intensive treatment group and 8.5% in the routine care group (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.65 to 1.05, p=0.12). There were no significant differences in the secondary endpoints (the individual components of the primary endpoint).

Small but statistically significant changes from baseline were seen in some disease-oriented outcomes e.g. mean values for HbA1c (–0.08%, 95% CI –0.14 to –0.02), systolic BP (–2.86 mmHg, 95% CI –4.51 to –1.20), diastolic BP (–1.44 mmHg, 95% CI –2.30 to –0.58), total cholesterol (–0.27 mmol/L, 95% CI –0.34 to –0.19) and LDL-cholesterol (–0.20 mmol/L, 95% CI –0.26 to –0.13).

So what?

This study does not support a case for early intensive multifactorial management of macrovascular and microvascular risk factors in people with type 2 diabetes. As the authors of this study point out, the extent to which the complications of type 2 diabetes can be reduced by earlier detection and treatment remains uncertain. However, the duration of follow-up was only five years and it is possible that reductions in HbA1c, BP and cholesterol could have benefits in the incidence of CV events in the longer-term. NICE guidance on type 2 diabetes should continue to be followed. Further study is needed to determine whether screening patients for type 2 diabetes and early intensive multifactorial management is beneficial.

For more details on this study and its limitations, and how it fits with what we know from other studies, see MeReC Rapid Review No. 4233. More information on type 2 diabetes can be found on NHS Evidence, in a MeReC Bulletin: Improving outcomes in type 2 diabetes and in NPC e-learning materials on type 2 diabetes.

Reference

1. Griffin SJ, et al. Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. Lancet 2011;378:156–67

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

This MeReC Publication is produced by the NHS for the NHS.

SHARP study shows ezetimibe/simvastatin reduces CV events in CKD: but is it better than simvastatin alone?

The SHARP study[1] of ezetimibe plus simvastatin▼* in patients with chronic kidney disease (CKD) found that the combination reduced the risk of major CV events compared with placebo. However, we still do not know if the addition of ezetimibe to simvastatin offers any safety or efficacy advantage over simvastatin alone (at the same or increased dose).

*Note: The MHRA has advised that the black triangle (▼) refers to intensive monitoring being requested only when simvastatin is used in children and adolescents (10–17 years), in line with the licensed paediatric dosing recommendation.

Action

This study provides no reason to change practice with regard to the prescribing of lipid-lowering drugs: simvastatin 40mg/day remains a good first choice in most circumstances. NICE guidance on CKD recommends that the use of statin therapy for the prevention of CV disease in people with CKD should not differ from its use in people without CKD. Ezetimibe has a limited role, according to NICE guidance, for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia in the following circumstances:

- where statins are contraindicated or not tolerated
- in conjunction with a statin where serum total or LDL-cholesterol is not appropriately controlled by initial statin therapy (after appropriate dose titration or because dose titration is limited by intolerance) and when consideration is being given to changing the initial statin therapy to an alternative statin.

Prescribers and prescribing managers should review local prescribing trends for statins and ezetimibe as suggested in the document 'Key therapeutic topics – Medicines management options for local implementation', produced by the NPC as part of the QIPP programme.

What did this study find?

Over a median duration of 4.9 years, fewer participants taking ezetimibe 10mg plus simvastatin 20mg reached the key outcome of a first major atherosclerotic event (non-fatal MI or coronary death, non-haemorrhagic stroke, or arterial revascularisation) compared with those taking placebo (11.3% vs. 13.4%; risk ratio 0.83, 95% CI 0.74 to 0.94, p=0.0021).

So what?

Although the study identified a benefit for ezetimibe plus simvastatin over placebo in patients with CKD, the absence of a simvastatin-alone arm in the study, means that we still do not have any evidence that addition of ezetimibe to simvastatin offers any advantage over simvastatin alone, either at the same dose or at an increased dose, when used in accordance with NICE guidance. This is the case for patients with CKD and for other patients for whom lipid-modifying therapy is appropriate. In addition, the cost of ezetimibe and the ezetimibe/simvastatin combination product is considerably higher than for low cost statin options such as simvastatin alone.

NICE guidance on CKD recommends that the use of statin therapy for the prevention of CV disease in people with CKD should not differ from its use in people without CKD. Treatment decisions should be based on existing risk tables for people with and without diabetes, with the understanding that the Framingham risk tables significantly underestimate CV risk in people with CKD. Statins should be offered for the secondary prevention of CV disease irrespective of baseline lipid values.

For more information on lipid modification see NICE guidance on lipid modification, NHS Evidence and/or the NPC e-learning materials on cardiovascular disease – lipids. For more information on this study see MeReC Rapid Review No. 4270.

Reference

1. Baigent C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377:2181–92

New safety information for dronedarone▼ and varenicline▼

The European Medicines Agency (EMA) has issued/updated safety information regarding dronedarone▼[1] and varenicline▼.[2]

Action
Healthcare professionals who are considering prescribing dronedarone or varenicline should familiarise themselves with the appropriate safety information given by the EMA and follow their recommendations.

Dronedarone: use restricted in atrial fibrillation (AF)
Following a review of its benefit-risk profile, the EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended that dronedarone should only be initiated by a specialist for the maintenance of heart rhythm in patients with paroxysmal or persistent AF and whose normal rhythm has been restored after cardioversion. It should not be used in patients with permanent AF, heart failure or left ventricular systolic dysfunction. Due to an increased risk of liver, lung and CV adverse events, dronedarone should only be prescribed after alternative treatment options have been considered. Patients taking dronedarone should have their treatment evaluated at their next scheduled appointment. Liver function, lung function and heart rhythm should be monitored regularly.

More information is available in Questions and answers on the review of dronedarone. Healthcare professionals should follow NICE guidance on dronedarone for AF, taking into account the additional recommendations from the EMA.

Varenicline: positive benefit-risk balance confirmed
The EMA has confirmed that the benefit-risk balance for varenicline remains positive, despite the results of a recent meta-analysis of CV side effects. The CHMP could not draw robust conclusions from the meta-analysis. Nevertheless, they asked that more information on CV events be included in the medicine's product information. For more details of the meta-analysis and its limitations see MeReC Rapid Review No. 4073.

For more information on these issues see MeReC Rapid Review No. 4090, MeReC Rapid Review No. 4451, NHS Evidence and/or the appropriate e-learning sections of the NPC website.

References
1. EMA. European Medicines Agency recommends restricting use of Multaq. Press release 22/9/11
2. EMA. European Medicines Agency confirms positive benefit-risk balance for Champix. Press release 21/7/11

The National Prescribing Centre (NPC) is responsible for helping the NHS to optimise its use of medicines. NPC is part of the National Institute for Health and Clinical Excellence (NICE), an independent organisation providing national guidance on promoting good health and preventing and treating ill health.

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