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A key message on intensive blood pressure control in type 2 diabetes from ACCORD

The ACCORD blood pressure trial[1] concluded that intensive blood pressure (BP) control to a systolic target of less than 120mmHg, compared with a target of less than 140mmHg, did not significantly reduce the rate of a composite outcome of fatal and non-fatal major cardiovascular (CV) events in patients with type 2 diabetes at high CV risk. Adverse effects were more common in the intensive BP control group. This study adds to the evidence that over-intensification of treatment in type 2 diabetes provides limited or no overall benefit, and may increase the risk of adverse events.

Action

Health professionals should continue to follow NICE guidance on the management of type 2 diabetes. This guidance recommends that in patients with type 2 diabetes, BP should be reduced to below 140/80mmHg (below 130/80mmHg if there is kidney, eye or cerebrovascular damage). Health professionals may wish to consider the implications of the ACCORD BP trial, with respect to the risk and benefits of intensifying BP control, especially if aiming for BP targets below the standard target levels set by NICE.

What does this study claim?

People with type 2 diabetes are at increased CV risk, which is reduced by improving BP control. The ACCORD study was designed to assess the effect of intensive treatment of blood glucose on CV outcomes in 10,251 patients with type 2 diabetes who were at high risk for CV disease. From within this cohort of patients, two other trials evaluated the effect of intensifying either systolic BP control (ACCORD BP trial)[1] or lipid-modification therapy (ACCORD lipid trial), in people with type 2 diabetes.

The ACCORD BP trial[1] followed up 4,733 patients with type 2 diabetes at high risk for CV disease for a mean of 4.7 years. It concluded that BP control to a systolic blood-pressure target of less than 120mmHg (intensive therapy), as compared with less than 140mmHg (standard therapy), did not significantly reduce the rate of a composite outcome of fatal and non-fatal CV events. However, a small but statistically significant difference was seen in the rate of total stroke between groups (0.32% per year intensive therapy vs. 0.53% per year standard therapy, hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.39 to 0.89, P=0.01).[1] There were significantly more serious adverse events attributed to antihypertensive treatment in the intensive therapy group, compared with the standard-therapy group (3.3% vs. 1.3%, P<0.001, number needed to harm [NNH] 50 over 5 years).[1] These events included hypotension, hyperkalaemia, and bradycardia or arrhythmia.[1]

More details about the ACCORD BP trial[1] and its place in the management of diabetes can be found in MeReC Rapid Review Blog No. 1296. More information on the management of type 2 diabetes can be found on the type 2 diabetes floor of NPCi.

Reference

1. The Accord Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. New Engl J Med 2010; published online March 14th (10.1056/NEJMoa1001286)

All information was correct at the time of publication (June 2010)

Insulin use may increase mortality in type 2 diabetes

A large observational study[1] in Canada found a statistically significant association between all-cause mortality and exposure to insulin in people with type 2 diabetes. There was an almost three-fold increased risk in the highest exposure group (>1 vial of insulin/month), compared with never-users. This dose-response relationship was also seen in the secondary outcomes of CV and non-vascular mortality.

Action

NICE guidance on the management of type 2 diabetes recommends that patients should be involved in setting their individual glycated haemoglobin (HbA1c) target, which may be above the general target of 6.5% (48mmol/mol). NICE recommends adding a second oral drug when patients are unable to reach their agreed target by lifestyle modification or monotherapy with an oral hypoglycaemic agent (usually metformin). Insulin therapy is an option where the HbA1c does not fall below 7.5% (59mmol/mol), or another agreed higher target. Health professionals may wish to consider the implications of the present study, and others we have blogged, in their discussion with patients about risks and benefits of intensifying glycaemic control, setting of individual HbA1c targets, and the use of insulin in type 2 diabetes.

What does this study claim?

The ACCORD, ADVANCE and VADT randomised controlled trials (RCTs) did not identify a consistent significant benefit of intensive glycaemic control in the treatment of type 2 diabetes with regard to cardiovascular (CV) outcomes and mortality. Indeed, the ACCORD study, which compared treatments that aimed to achieve HbA1c levels of less than 6.0% (42mmol/mol) with those of between 7.0% (53mmol/mol) and 7.9% (63mmol/mol) was stopped early because of an increased risk of death in the intensive treatment arm. It is unclear whether insulin use was associated with the increased mortality risk seen in the intensive treatment arm of the ACCORD study (see Blog No.1021 on the post-hoc analysis of ACCORD).

This cohort study compared rates of all-cause mortality in more than 12,000 newly treated people with type 2 diabetes exposed to various levels of insulin. The study found a statistically significant dose-related association between all-cause mortality and insulin exposure level. After adjusting for confounders, the risk of dying varied from 75% higher in the lower exposure group to 179% higher in the highest exposure group, compared to the non-exposed group (low exposure HR 1.75, 95%CI 1.24 to 2.47; moderate exposure HR 2.18, 95%CI 1.82 to 2.60; high exposure HR 2.79, 95%CI 2.36 to 3.30). A similar dose-response relationship was seen for the secondary outcomes of CV mortality and non-vascular mortality; both increased with increasing exposure to insulin.

Observational analyses always have the potential for some residual confounding bias. However, the authors of the paper point out that the magnitude of the excess mortality with insulin is so great that, according to their calculations, this could only be explained by an imbalance in baseline HbA1c of 10% — a value which they considered improbable.

Further information about this study[1] and its place in the management of diabetes can be found in MeReC Rapid Review Blog No. 1279. More information can be found on the type 2 diabetes floor of NPCi.

Reference

1. Gamble J–M, et al. Insulin use and increased risk of mortality in type 2 diabetes: a cohort study. Diabetes, obesity and metabolism 2010;12:47–53

Concomitant use of clopidogrel and PPIs: MHRA updates warning

In light of evidence recently reviewed by the MHRA, the previous advice (to avoid all proton pump inhibitors [PPIs] unless absolutely necessary) is no longer considered necessary.[1] Nevertheless, as a precaution, the MHRA advises that the concomitant use of clopidogrel with omeprazole or esomeprazole should be discouraged unless considered essential. The current evidence does not support extending this advice to other PPIs which can be considered if specifically indicated.

Action

As we suggested in a previous MeReC Rapid Review blog, this provides an excellent opportunity to review patients taking clopidogrel and a PPI to see if both are still appropriate. Options to consider may include stopping either the clopidogrel, if it is being used outside NICE guidance or beyond the recommended period, or reviewing the PPI, or both (see the antiplatelet floor on NPCi for more information). If the original reason for using clopidogrel was due to gastrointestinal (GI) intolerance on aspirin alone, switching to aspirin plus a PPI would seem a reasonable approach.

What do the MHRA advise now?

This most recent evidence reviewed by the MHRA suggests that prescribers should consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel.[1] However, because it is not possible to completely exclude a possible class-effect interaction with these PPIs on the basis of available data, the potential risk of a slight reduction in efficacy of clopidogrel should be weighed against the potential GI benefit of the PPI. Other GI therapies such as H2-receptor antagonists (except cimetidine) or antacids may be more suitable in some patients. Doctors should check whether patients who are taking clopidogrel are also buying over-the counter omeprazole and consider whether other medicines for gastro-protection would be more suitable. Pharmacists should check whether patients buying omeprazole are also taking clopidogrel.

Concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel should be discouraged as these are expected to have a similar effect to omeprazole and esomeprazole (examples include fluvoxamine, fluoxetine, moclobemide, fluconazole, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine, and chloramphenicol).

More detailed information and advice can be found in the April 2010 Drug Safety Update by the MHRA. Further information on the use of clopidogrel is available on the antiplatelet floor of NPCi.

Reference

1. MHRA: April 2010 Drug Safety Update

NICE: no specific recommendations now on choice of tool for use in CV risk estimation

NICE has reissued its guideline on cardiovascular risk assessment and lipid modification (CG67), removing the recommendation to use a specific method for risk estimation (based on the Framingham equation). QRISK is an alternative method that can now be considered. All other recommendations in the guideline are unchanged.

Action

The decision on which cardiovascular disease (CVD) risk assessment method to use in the NHS in England and Wales should be made locally using the method best suited to local requirements. Both Framingham-based methods and QRISK can be considered. Where a Framingham-based method is chosen, previous NICE recommendations relating specifically to the use and modification of this equation are still appropriate. Specific recommendations relating to use and modification of the Framingham risk equation has been moved to appendix D of the NICE guideline and page 13 of the quick reference guide. Education, training and support may be required locally to ensure consistent, optimal use of whichever risk estimation method is locally chosen.

NICE suggests further research is conducted to validate the many different tools to assess CVD risk and assess their relative performance and ease of use. NICE are continuing to monitor this area and we will blog any important changes they make to their recommendations.

NICE recommendations apply to the NHS in England and Wales. In Scotland, SIGN Guideline 97 (February 2007) specifically recommends the use of ASSIGN for the estimation of CV risk.

More information on the assessment of CV risk can be found on the cardiovascular disease — risk assessment floor of NPCi.

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