

## Dual antihypertensive therapy in patients at high risk of CV disease

The ACCOMPLISH study<sup>1</sup> suggests that, in patients at high risk of CV disease who require dual antihypertensive therapy to control blood pressure, benazepril (an ACE inhibitor not on the UK market) plus amlodipine may be more effective than benazepril plus hydrochlorothiazide at reducing the risk of CV events.

### Action

Prescribers should continue to follow the NICE clinical guideline for the management of hypertension. The choice between a calcium channel blocker and a thiazide diuretic, either as a first-line treatment or in addition to an ACE-inhibitor, should be based on their likely side-effect profiles, suitability for the individual patient and cost. Patients whose hypertension is complicated by existing cardiovascular (CV) disease, renal disease, or diabetes (type 1 or 2) should continue to be treated according to the respective NICE guidelines for these specific conditions.

### What was ACCOMPLISH?

The ACCOMPLISH study was a double-blind, randomised controlled trial (RCT) of 11,506 patients with hypertension who were at high risk of CV events. The study examined the relative benefits of using benazepril with either amlodipine or hydrochlorothiazide. After a mean follow-up of 36 months, when the trial was stopped early, there were fewer primary-

outcome events (any of: death from CV causes, non-fatal myocardial infarction [MI], non-fatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, or coronary revascularisation) in the benazepril plus amlodipine group compared with the benazepril plus hydrochlorothiazide group (9.6% vs. 11.8%; hazard ratio [HR], 0.80, 95% confidence interval [CI] 0.72 to 0.90,  $P < 0.001$ ). This suggests that 46 people would need to be treated with benazepril plus amlodipine instead of benazepril plus hydrochlorothiazide for about 30 months for one of them to have a CV event prevented. No significant differences were identified between groups with regard to CV death or death from any cause.

Further details of the study can be found in *MeReC Rapid Review Blog No. 250*, which discusses the limitations of the study.

### References

1. Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417–28

## Insignificant benefits for intensive glucose control in type 2 diabetes

Similar to other studies in people with type 2 diabetes, VADT<sup>1</sup> suggests that intensive control of blood glucose does not reduce the risk of CV events or death.

### Action

Management of overall CV risk appears to be most effective for preventing CV events in people with diabetes. NICE guidance should be followed and priority given to lifestyle interventions (i.e. smoking cessation, weight loss, diet modification and increased exercise, as appropriate) and drug treatments to reduce CV risk (i.e. controlling blood pressure, taking a statin, taking metformin and taking aspirin if CV disease is present). While NICE guidance generally advocates setting an HbA1c target of 6.5% for people with type 2 diabetes, it cautions against the use of highly intensive management strategies to achieve levels of less than 6.5%. Moreover, NICE recognises the importance of involving the patient in the setting of their own target level, which may be above 6.5%.

### What was VADT?

VADT was an open-label RCT of 1,791 US military veterans (mean age 60 years) with poorly-controlled type 2 diabetes randomised to intensive or standard glucose control. Over a median of 5.6 years, intensive treatment (median HbA1c 6.9%) with oral hypoglycaemic drugs plus insulin, if necessary, was not associated with a statistically significant reduction in major CV events (a composite of MI, stroke, death from CV causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, or amputation for ischaemic gangrene) compared with less intensive, standard treatment (median HbA1c 8.4%) — HR 0.88, 95%CI 0.74 to 1.05,  $P = 0.14$ . There were no statistically significant differences between treatments for any of the component endpoints, for death from any cause, or for any microvascular outcomes (ophthalmic,

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nephropathic or neuropathic). Patients in the intensive-treatment arm were more likely to suffer hypoglycaemic episodes, including impaired consciousness (9 vs. 3 per 100 patient-years,

$P < 0.001$ ) or complete loss of consciousness (3 vs. 1 per 100 patient-years,  $P < 0.001$ ).

See *MeReC Rapid Review Blog No. 258* for further details, limitations of this study and a discussion of the findings in the context of the other RCT evidence.

#### References

1. Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360. Published early online December 17<sup>th</sup> 2008 (10.1056/NEJMoa0808431)

## Glitazones double the risk of fractures in women

**A meta-analysis<sup>1</sup> found that rosiglitazone and pioglitazone<sup>▼</sup> approximately double the risk of fractures (site not specified) in women, but not men.**

#### Action

Health professionals should heed MHRA warnings and follow NICE guidance regarding the use of glitazones. As well as considering their CV risks, glitazones should not be started or continued in people at higher risk of fractures.

#### What did the study find?

This meta-analysis of ten RCTs of people with type 2 diabetes or impaired glucose tolerance (total  $n = 13,715$ ) found that the odds ratio (OR) for fractures with glitazones compared with control

(placebo or other oral hypoglycaemic drugs) was 1.45 (95%CI 1.18 to 1.79,  $P < 0.001$ ). Five RCTs (11,401 patients) provided data on fractures by gender and found a statistically significant increased risk of fractures among women (OR 2.23, 95%CI 1.65 to 3.01;  $P < 0.001$ ) but not among men (OR 1.00, 95%CI 0.73 to 1.39;  $P = 0.98$ ). It was estimated that if 55 women (mean age 56 years) were treated with a glitazone for one year, one would develop a fracture. Unfortunately, the site of the fracture was not specified in the study.

See *MeReC Rapid Review Blog No. 253* for further details and limitations of this study.

#### References

1. Loke YK, et al. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180(1). DOI:10.1503/cmaj.080486 (Published early online, 10th December 2008)

## Zopiclone or zolpidem increase the risk of road traffic accidents

**A study in Norway<sup>1</sup> found that people prescribed zopiclone or zolpidem had double the risk of road traffic accidents compared with people who weren't prescribed hypnotics, similar to the increased risk seen with nitrazepam.**

#### Action

There would appear to be no perceptible advantage for the use of Z-drugs (zopiclone, zolpidem, or zaleplon) over benzodiazepines in either efficacy, adverse effects, or in causing dependency (see *MeReC Rapid Review Blog No. 164*). Prescribers should follow NICE guidance for the use of Z-drugs in the management of insomnia. After non-drug therapies have been explored, hypnotics should be used in the lowest dose possible for no more than four weeks in the case of benzodiazepines and no more than two weeks with zaleplon or zolpidem, or four weeks with zopiclone. Although there is a common perception that Z-drugs are less likely to have a 'hangover' effect the next day and may reduce the risk of accidents and falls, the clinical evidence to differentiate Z-drugs from benzodiazepines is weak. Patients should be advised that the taking of zolpidem or zopiclone is associated with about double the relative risk of road traffic accidents, and they need to be very cautious about driving the day after taking any hypnotic. Patient information leaflets for all of the Z-drugs warn against driving or operating machinery if drowsiness persists on the day after taking the hypnotic.

#### What did the study find?

This retrospective cohort study found that Norwegian drivers, aged 18 to 69 years, were at increased risk of being involved in a traffic accident if they had been prescribed a hypnotic in the previous week compared with those who had not. Zopiclone or zolpidem use (as indicated by dispensing of a prescription of the hypnotic in the previous 7 days) had a standardised incidence ratio [SIR] of 2.3, 95%CI 2.0 to 2.7, which was similar to that of nitrazepam (SIR 2.7, 95%CI 1.8 to 3.9). Flunitrazepam use was associated with an SIR of 4.0 (95%CI 2.4 to 6.4). Absolute rates of traffic accidents associated with hypnotic prescription were between about 5 and 9 accidents per exposed 1000 person-years in groups treated with hypnotics compared with about 2 per 1000 person-years in the group not exposed to hypnotics.

See *MeReC Rapid Review Blog No. 249* for further details and limitations of this study.

#### References

1. Gustavsen I, et al. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. *Sleep Med* 2008;9:818-22

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