

Diabetes

Hypoglycaemia risk with combination therapy in type 2 diabetes

A meta-analysis has suggested that the addition of a DPP-4 inhibitor to existing sulphonylurea (SU) therapy is associated with a 50% increased risk of hypoglycaemia in type 2 diabetes patients and one excess case for every 17 patients treated in the first six months. These findings emphasise the importance of following the recommendation to reduce SU dose when commencing a DPP-4 inhibitor.

Placebo-controlled, randomised, double blind trials of type 2 diabetes patients treated with SUs and DPP-4 inhibitors were searched for on Medline, ISI Web of Science, SCOPUS and the Cochrane Central Register of Controlled Trials. Risk of bias in each trial was assessed using the Cochrane Collaboration tool. Two authors screened potentially eligible trials, and approached the authors for relevant data if not included in the text.

Ten studies were eligible for inclusion, covering a total of 6,546 participants. DPP-4 inhibitors and SUs were given to 4,020 of the patients and placebo plus SU to 2,526.

The data from the trials was pooled and subjected to statistical analysis. The addition of DPP-4 inhibitors was associated with a 50% increase in the risk of hypoglycaemia and one excess case for every 17 patients treated in the first six months. The risk ratio (RR) for hypoglycaemia in the DPP-4 plus SU compared with SU plus placebo patients was 1.52 (95% CI: 1.29-1.80). The number needed to harm (NNH) was 17 (95% CI: 11-30) for ≤ 6 months'

treatment, falling to NNH = 15 (95% CI: 9-26) for 6.1-12 months' treatment and NNH = 8 (95% CI: 5-15) for treatment duration > 1 year.

No difference was found between low and high doses of DPP-4 inhibitor, although at the lower dose the increased risk of hypoglycaemia did not achieve statistical significance.

The authors suggest this is quite a powerful meta-analysis in terms of the number of patients and quality of the studies. However, they acknowledge that the studies did use different definitions of hypoglycaemia.

Several recent publications have suggested that the paradigm of diabetes treatment in type 2 diabetes may be focused on more nuanced glycaemic targets and the avoidance of hypoglycaemia, which is now known to be associated with an increasing number of adverse health outcomes.

SUs are associated with as many hypoglycaemic episodes as insulin, and there is increasing evidence that they may be associated with poor long-term outcomes. Their role as a mainstay of future hypoglycaemic treatment is increasingly questioned, but at present GPs will see patients on these drugs every day, and will frequently be adding more medications to go with them.

This paper is a timely reminder to follow the recommendation to reduce the dose of SU when adding DPP-4 inhibitor therapy to reduce the risk of hypoglycaemia.

DR MATTHEW LOCKYER

Salvo F, Moore N, Arnaud M et al. Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis. *BMJ* 2016;353:i2231

Urology

Fracture admissions higher in men on ADT

Androgen deprivation therapy (ADT) in men with prostate cancer is associated with a small but significant increase in fracture risk, a UK study has shown.

Using the Hospital Episodes Statistics database for 2004-2008, the authors identified 8,902 men with prostate cancer who had been admitted to hospital with a fracture. Of these, 3,372 (37.8%) had been treated with ADT and 5,530 (62.2%) had not. There were 228,852 admissions in the background population.

In men aged over 50 with prostate cancer the risk of a fracture resulting in hospitalisation increased from 1.12 per 100 person-years in those who had not been treated with ADT to 1.41 per 100 person-years in those who had.

Compared with the background population, with a risk of 0.58 per 100 person-years, this represents a 2.4-fold relative increase in risk but an absolute risk increase of only 0.83 fracture-related admissions per 100 person-years.

Cohort studies in the United States have shown an increased risk of osteoporotic fracture in men with prostate cancer treated with ADT. However, this study of hospital admissions for fractures in men with prostate cancer is the first of its kind in the UK.

While this increased risk is of statistical significance, the absolute increase is small overall.

The NICE guidance on osteoporosis and fragility fracture¹ recognises ADT as a risk factor, and advises individualised risk assessment of

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fracture risk (using FRAX or Qfracture) for all men commencing ADT for prostate cancer.

I feel it would appear sensible for most men, particularly those aged over 75, to receive calcium and vitamin D supplementation while being treated with long-term ADT. Individualised risk assessment will also allow targeted treatment with bisphosphonates to be given to those men at highest risk.

However, the study authors conclude that all men with prostate cancer should undergo risk assessment 'rather than singling out men on ADT, as all men with prostate cancer have an increased risk of fracture, with men on ADT at slightly higher risk.'

DR JONATHAN REES

Jefferies ER, Bahl A, Hounscome L et al on behalf of the PHONIC collaborative. Admissions to hospital due to fracture in England in patients with prostate cancer treated with androgen-deprivation therapy – do we have to worry about the hormones? *BJU Int* 2016; doi:10.1111/bju.13441

REFERENCE

1 National Institute for Health and Care Excellence. CG146. Osteoporosis: assessing the risk of fragility fracture. NICE. London. 2012

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- Women with bipolar disorder at high risk of relapse after childbirth¹⁵
- AP is a stronger predictor of stroke and death in women¹⁶
- Chemotherapy + hormone therapy boosts survival in advanced prostate cancer¹⁸
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