Breaking news in cardiovascular outcome trials; empagliflozin and stroke; and glycaemic variability in type 1 diabetes

Too busy to keep up to date with the latest research? In this new series, Lori Berard, a Nurse Manager from Canada, selects the latest papers of interest to diabetes nurses.

Canagliflozin impacts CV and renal events in type 2 diabetes

Neal B et al (2017) *N Engl J Med* **377**: 644–57

This paper integrates the analysis of two very similar cardiovascular (CV) outcome trials using canagliflozin: CANVAS and CANVAS-R. These trials included a total of 10 142 participants with type 2 diabetes with CV disease/risk (65% secondary prevention and 35% primary prevention).

The primary outcome of composite of death from CV causes, nonfatal myocardial infarction or nonfatal stroke was reduced by 14%. These trials also demonstrated a possible benefit of canagliflozin with respect to the progression of albuminuria and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy or death from renal causes. The results must be balanced, however, against the unexplained increase in amputations (6.3 vs 3.4 participants per 1000 patient-years).

Reduction in hypoglycaemia with insulin degludec

Marso S et al (2017) *N Engl J Med* **377**: 723–32

In keeping with the 2008 US Food and Drug Administration guidance for the CV safety of new diabetes agents, insulin degludec required a CV outcome trial. Marso et al compared 100 U/mL insulin degludec with the active comparator 100 U/mL insulin glargine. It is important to note that, unlike other trials, the US Food and Drug Administration also mandated target HbA_{1c} levels and fasting blood glucose targets.

The DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular) trial involved patient self-titration of insulin. This double-blind trial included 7637 patients, 85.2% with established CV disease, moderate chronic kidney disease, or both.

The primary composite outcome in the time-to-event analysis of the first occurrence of an adjudicated major adverse CV event met the non-inferiority hypothesis. The mean HbA_{1c} in each group at 24 months was 58 mmol/mol (7.5%), but the mean fasting plasma glucose level was significantly lower in the degludec than the glargine group. Severe hypoglycaemia occurred in 187 patients (4.9%) on degludec and 252 (6.6%) on glargine, a statistically significant reduction of 40%. There was no difference in the rate of generalised adverse events.

This study demonstrated the CV safety and reduction in severe, as well as nocturnal severe, hypoglycaemia of insulin degludec.

No increased cerebrovascular events with empagliflozin

Zinman B et al (2017) *Stroke* **48**: 1218–25

The 14% reduction in three-point major adverse CV event endpoints in the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was driven primarily by the 38% reduction in CV death. A question remained, however, about the increased rate of nonfatal stroke.

Zinman et al investigated cerebrovascular events and found that the numeric difference in stroke between empagliflozin and placebo in the modified intention-to-treat analysis was primarily driven by 18 patients in the empagliflozin group, with a first event >90 days after the last intake of the study drug; there were only three cases in the placebo group. When they looked at stroke rate ≤90 days after the last dose of drug, the hazard ratio for stroke with empagliflozin vs placebo was 1.08 (95% confidence interval, 0.81–1.45; P=0.60). In this population, there was therefore no difference in stroke rate. The authors also investigated the role of increased haematocrit and large decrease in systolic blood pressure, finding no association. They conclude that in this population, there was no significant difference in the risk of cerebrovascular events with empagliflozin vs placebo.

Type 1 glycaemic variability and microvascular outcomes

Lachin et al (2017) *Diabetes Care* **40**: 777–83

The role of glycaemic variability in the development of diabetes complications has been an area of speculation and investigation. The Diabetes Control and Complications Trial demonstrated the benefit of intensive vs conventional therapy in reducing the development and progression of microvascular complications, primarily related to HbA_{1c} reduction. In this paper, the authors took a retrospective look at the data from quarterly seven-point glucose profiles to assess the role of glucose variability in the development/progression of microvascular complications. They concluded that within-day variability does not have an apparent role in microvascular complication development beyond the role of the mean glucose. ■