Guest editorial

Kevin Fernando
GPwSI Diabetes and Medical Education, North Berwick

Semaglutide and SUSTAIN-6: Another step towards the holy grail of type 2 diabetes management?

Cardiovascular (CV) disease remains the leading cause of death in people with type 2 diabetes. Overall, the risk of CV disease is around double in people with type 2 diabetes compared to those without the condition, independent of conventional risk factors (Emerging Risk Factors Collaboration, 2010). Therefore, mitigating CV risk in these people remains a key priority for all diabetes healthcare professionals. Indeed, a recent position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) explicitly stated that "comprehensive CV risk reduction should be a major focus of therapy" (Inzucchi et al, 2012).

Since the rosiglitazone debacle, the US Food and Drug Administration (FDA) has mandated pharmaceutical companies to prove the CV robustness of new diabetes medications. This can be achieved by including individuals at high CV risk in phase III trials, or by undertaking a CV safety trial. This may be followed by a dedicated CV outcomes trial. Over the last 12 months, we have had two positive CV outcome trials, in which the study drug has demonstrated superiority to placebo in reducing major adverse coronary events (MACE).

The EMPA-REG OUTCOME trial (Zinman et al, 2015) demonstrated that the sodium–glucose cotransporter 2 inhibitor empagliflozin reduced the primary MACE composite endpoint (CV death, non-fatal myocardial infarction [MI] and non-fatal stroke) by 14%. This was mainly driven by a significant reduction in CV mortality. In June this year, the LEADER trial (Marso et al, 2016a) demonstrated that the glucagon-like peptide-1 (GLP-1) analogue liraglutide reduced the primary MACE endpoint by 13%, and this was driven by both CV mortality and MI benefits.

Incredibly, in September 2016, at the EASD Annual Meeting, we were presented with a third positive CV safety trial. SUSTAIN-6 (Marso et al, 2016b) was a non-inferiority trial exploring the safety of an as yet unlicensed once-weekly GLP-1 analogue, semaglutide, in 3297 people with type 2 diabetes at high CV risk. As such, the trial was not designed to prove superiority. However, it demonstrated a statistically significant 26% reduction in the primary MACE endpoint. On this occasion, benefits were mainly driven by a significant reduction in non-fatal stroke; there were actually no significant reductions in CV death or MI. Like LEADER, benefits were seen later in the trial, at around 18 months, suggesting underlying regression of atherosclerosis as a possible mechanistic explanation.

With respect to microvascular outcomes, there were significant improvements seen in new or worsening nephropathy (a pre-specified secondary endpoint) with semaglutide. However, worryingly, a significant worsening of diabetic retinopathy complications (another pre-specified endpoint) was noted. Interestingly, this worsening of retinopathy was observed very early in the trial, and the authors postulate whether this was related to rapid glucose lowering, a phenomenon previously observed in people with type 1 diabetes. A direct effect of semaglutide, however, cannot be excluded.

In terms of side-effects, as predicted, there was an increased incidence of gastrointestinal symptoms in the semaglutide arm, with the majority occurring early in the trial. There were similar rates of pancreatitis and pancreatic cancer in the two arms. However, as the study participants were followed-up for just 2.1 years, meaningful conclusions about differences in pancreatic cancer rates are not possible.

Of note, there was an increase in pulse rate of 2 bpm in the semaglutide group. This has previously been observed with other GLP-1 analogues and is thought to be caused by activation of the autonomic nervous system. In contrast, the ELIXA trial (Pfeffer et al, 2015), which explored the CV safety of lixisenatide, demonstrated the non-inferiority of lixisenatide to placebo, but there was no significant difference in heart rate between the active and placebo arms.

Additionally, as in LEADER, in SUSTAIN-6 there was more intensification of diabetes medications in the placebo group than in the semaglutide group. Might the positive results of the trial just reflect the adverse effects of these other diabetes therapies, rather than an effect of semaglutide *per se*?

On the basis of SUSTAIN-6, semaglutide is likely to be approved by the FDA. However, as outlined above, and like all good research, the study raises many more questions than answers. Have we finally achieved the holy grail of diabetes management – a reduction in the risk of CV disease and mortality? With further CV outcome studies due to complete almost annually until 2020, we are tantalising close to this answer. ■

References

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David Kerr is away. He will return for issue 1 next year.