Dear Sir

In our recent UK consensus statement on the management of people with type 2 diabetes, we highlighted the top line results of the 'Researching CV Events with a Weekly INcretin in Diabetes' (REWIND) trial, which had been made available via a press release in November 2018 [1]. These data were subsequently presented at the 79th Scientific Sessions of the American Diabetes Association in June 2019 and simultaneously published in the Lancet [2,3]. Although REWIND has yet to be incorporated into national guidelines, we felt it important to highlight these new data and set them into the context of our consensus view.

The REWIND trial recruited 9,901 people with type 2 diabetes, who had an HbA1c less than 9.5% (90mmol/mol) and an estimated glomerular filtration rate $\geq$ 15mL/min. The mean age at recruitment was 66 years, 45% were female and 69% did not have known cardiovascular disease. Participants received the GLP-1 receptor agonist (GLP-1RA) dulaglutide 1.5mg once weekly or placebo on top of standard of care and the primary end-point was a composite of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal stroke. The primary endpoint was reported in 12% of subjects randomised to receive dulaglutide and 13% of the placebo group, giving a hazard ratio of 0.88 with confidence intervals (CI) between 0.79 and 0.99. Hence, statistically significant superiority of dulaglutide over placebo was demonstrated (P=0.026). For this reason, we would recommend that dulaglutide could be considered as one of the second-line therapies for people with type 2 diabetes and established or at very high risk of cardiovascular disease.

The REWIND trial had the longest median duration of follow-up and a lower placebo event rate than any of the modern era of diabetes cardiovascular outcomes trials. This reflects the entry criteria which led to only 31% of participants having prior cardiovascular disease (defined as previous MI, ischaemic stroke, revascularisation, unstable angina with ECG changes or myocardial ischaemia on imaging or stress test). It is of particular note that the reduction in hazard ratio (0.87, CI 0.74-1.02) was the same in the primary prevention cohort as in those subjects with previous cardiovascular events, showing that the overall result was not driven by benefits in the high-risk subjects. This is in contrast to the cardiovascular outcomes seen with SGLT2-inhibitors, where it appears that benefit is only seen in type 2 diabetes subjects with pre-existing atherosclerotic cardiovascular disease [4].

The beneficial impact of dulaglutide on the primary composite cardiovascular endpoint, irrespective of baseline cardiovascular risk, is worthy of discussion since LEADER, the first cardiovascular endpoint trial to demonstrate superiority of a GLP-1RA appeared to show little benefit in lower risk patients [5]. This outcome was supported by subsequent *post hoc* analyses of LEADER, which defined cardiovascular risk using alternative definitions to the trial inclusion criteria [6,7]. However, in a post hoc analysis of the SUSTAIN 6 cardiovascular outcome trial which examined once-weekly semaglutide versus placebo, there was no significance difference in the improved hazard ratio according to the baseline cardiovascular status (prior MI or stroke versus none; established disease versus risk factors only)[8]. The latter study urged caution due to the low numbers of events (in a trial lasting a median of only 2.1 Years) but it is supported by a recent meta-analysis of all currently published GLP-1RA cardiovascular outcomes trials [9]. In that publication, there was a reduction of cardiovascular events in people with type 2 diabetes both with and without a history of cardiovascular disease, and with lack of statistically significant interaction. The reduction in the hazard ratio for the lower risk cohort was,

however, lower (0.94 versus 0.86) and the CI crossed the line of unity (0.83-1.07) perhaps consistent with a smaller benefit overall.

Whilst REWIND potentially supports the earlier use of GLP-1RAs for primary prevention of cardiovascular disease in people with type 2 diabetes, we believe that it is too early to recommend this as a routine intervention and more data are needed. This view is consistent with guidelines recently updated by the European Society of Cardiology (ESC)[10]. Furthermore, although the relative risk reductions seen in REWIND were the same irrespective of baseline cardiovascular status, the absolute risk reduction was much lower in the lower risk subjects and this will clearly impact on cost-effectiveness analyses when these are eventually performed.

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Yours sincerely

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