Incretin-based drugs and the kidney in type 2 diabetes

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Liraglutide and renal outcomes in type 2 diabetes

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To the Editor

In reporting the results of the secondary analysis of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, Mann et al. (Aug. 31 issue)[1] provide details on the previously reported prespecified composite renal outcome that was 22% lower with long-term use of the human glucagon-like peptide 1 (GLP-1) analogue liraglutide than with placebo.[2] That result was driven by a 26% reduction in new-onset persistent macroalbuminuria.

Continuous data on the urinary albumin-to-creatinine ratio indicate that liraglutide slowed albuminuria progression at month 12, which was maintained until the trial ended. Yet the relative contribution of liraglutide-related improvement in variables otherwise associated with a reduction in albuminuria — namely, the glycated haemoglobin level, blood pressure, weight, and lipid levels[3,4] — remains insufficiently analysed.

The considerable difference in the glycated haemoglobin level (approximately 1.0 percentage point up to month 6, followed by approximately 0.4 percentage points until the trial ended) between the liraglutide group and the placebo group[2] is probably relevant, and dedicated exploratory analyses should determine glucose independence (i.e., effects beyond glycaemic control).[4] The current exploration across glycated haemoglobin tertiles at month 6 is not fully convincing in this regard. To increase the clinical relevance of the "headline" finding indicating a drug-specific benefit of liraglutide, and to increase mechanistic insight, the results should account for representative changes versus placebo with respect to the glycated haemoglobin level, blood pressure, body weight, lipid levels, and estimated glomerular filtration rate (GFR).

Such a statistical approach was used recently in assessing the effects of the sodium–glucose cotransporter 2 (SGLT2) inhibitor empagliflozin in the EMPA-REG OUTCOME trial. An exploratory analysis of that trial characterized the effect of individual risk factors on the overall change in the urinary albumin-to-creatinine ratio.[5]

References

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The authors reply

Tonneijck et al. comment on the potential contributions of differences between liraglutide and placebo with respect to glycated haemoglobin levels, body weight, blood pressure, lipid levels, and estimated GFR in the reduction in renal outcomes observed in the LEADER trial. Our trial was not a mechanistic trial; therefore, we can only speculate about potential mechanisms driving the results. Furthermore, mediation analyses in a trial with many potential time-varying confounders are not easily performed. As detailed in the Supplementary Appendix, available with the full text of our article at NEJM.org, the difference between liraglutide and placebo with respect to the main renal outcome was not altered in a major way in subgroups of patients who had large or small changes in the glycated haemoglobin level. To be conservative, we used the largest difference in the glycated haemoglobin level between the liraglutide and placebo groups for the latter subgroup analysis — namely, at 6 months. Results were not materially different in patients with small or large changes in blood pressure and body weight (see the Supplementary Appendix of our article); differences in serum lipid levels and the estimated GFR between the groups were small throughout the trial. Nevertheless, we performed additional analyses of the risk of the composite renal outcome, with adjustments in a time-dependent manner for the change from baseline in the glycated haemoglobin level, body weight, and systolic blood pressure, separately and together (Table 1). The hazard ratios in these analyses were similar to our previously reported results. Although we agree that improvements in the glycated haemoglobin level, body weight, and systolic blood pressure contribute to decreases in albuminuria,[1] our analysis suggests that the effects of liraglutide may go beyond glucose control and, as we speculated in the article, anti-inflammatory effects in the kidney might contribute.[2]

Table 1. Composite renal outcome with adjustment for change from baseline in glycated haemoglobin level, body weight, and systolic blood pressure*

Outcome	Liraglutide (N=4668)	Placebo (N=4672)	Hazard ratio (95% CI)#
	number (percent)		
Composite renal outcome	268 (5.7)	337 (7.2)	0.78 (0.67-0.92)
Adjusted for glycated haemoglobin level	268 (5.7)	337 (7.2)	0.78 (0.67-0.92)
Adjusted for body weight	268 (5.7)	337 (7.2)	0.79 (0.67-0.93)
Adjusted for systolic blood pressure	268 (5.7)	337 (7.2)	0.80 (0.68-0.94)
Adjusted for glycated haemoglobin level, body weight, and systolic blood pressure	268 (5.7)	337 (7.2)	0.78 (0.66-0.93)

*The composite renal outcome consisted of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level and an estimated glomerular filtration rate of 45 mL/min/1.73 m2 or less, the need for continuous renal-replacement therapy (end-stage renal disease), or death due to renal disease. CI denotes confidence interval. #Hazard ratios were estimated with the use of a Cox regression analysis with changes from baseline in the glycated haemoglobin level, body weight, and systolic blood pressure as time-dependent covariates and corresponding baseline values as covariates.

References

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