Treatment of Type 2 Diabetes With GLP-1 Receptor Agonists Among Patients With CKD

Jakob A. Østergaard1,2 and Mark E. Cooper3

1Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; 2Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark; and 3Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Kidney Int Rep (2022) 7, 2323–2324; https://doi.org/10.1016/j.ekir.2022.09.001 © 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

See Clinical Research on Page 2345

The management of hyperglycemia in individuals with type 2 diabetes and impaired kidney function remains challenging because the pharmacological options are limited especially when estimated glomerular filtration rate (eGFR) is below 30 ml/min per 1.73 m². The effects and safety of GLP-1 receptor agonists in type 2 diabetes have been investigated in several clinical trials, including in patients with moderately and severely impaired kidney function as recruited in the AWARD-7 study1 as well as in those with moderately impaired kidney function as described in the PIONEER-5 study.2 In this issue of Kidney International Reports, Cherney et al.3 have extended our knowledge about the treatment with GLP-1 receptor agonists in type 2 diabetic subjects with renal impairment by performing a post hoc analysis of data from the SUSTAIN and PIONEER trials.

In their analysis of the data from more than 8000 type 2 diabetic subjects in the SUSTAIN and PIONEER studies, the authors compared the glucose-lowering efficacy of subcutaneously and orally administered semaglutide across a broad range of renal impairment. In these study populations the authors found similar effects on glycemic control of semaglutide across subgroups of eGFR varying from chronic kidney disease (CKD) stage 1 to 4. This supplements previous evidence of the efficacy of this particular GLP-1 receptor agonist in those type 2 diabetic patients with impaired kidney function.

The safety of semaglutide was also assessed in this population where side effects from other glucose lowering agents have been reported to be increased. Indeed, more serious adverse effects were reported among patients with eGFR lower than 60 ml/min per 1.73 m² as compared to patients with higher eGFR. It is important to appreciate that the study did not statistically compare the event rates of adverse effects in semaglutide treated patients versus placebo or the active comparator treated patients. Gastrointestinal side effects were common among semaglutide treated patients ranging from 16% to 56% but did not appear to be related to eGFR. Moreover, patients treated with semaglutide tended to more frequently discontinue treatment than patients treated with placebo or an active comparator. In addition, discontinuation of semaglutide treatment occurred more often in patients with lower eGFR as compared to those with a higher eGFR but a similar pattern of increased discontinuation in those subjects with a lower GFR was also seen in patients treated with placebo or the active comparator. Data on mortality were available from the SUSTAIN 6 and PIONEER 6 studies. Although more patients died in the groups with eGFR <60 ml/min per 1.73 m² as one would predict, this increase in mortality was observed in both semaglutide and placebo treated patients.

Treatment with semaglutide induced a loss in body weight across the eGFR subgroups ranging from −2.9% to −8.2% in all the trials except for the PIONEER 5 study in which patients with eGFR ≥60 ml/min per 1.73 m² did not either lose or gain weight during the study. In SUSTAIN 6 and 10 and PIONEER 5 and 6 trials, the authors found a statistically significant interaction between change in body weight and eGFR subgroup with the signal of weight loss being more pronounced in those individuals with lower eGFR. Systolic and diastolic blood pressure decreased in semaglutide treated patients compared with placebo or the active comparator across the trials, with the authors reporting no evidence of an interaction between effects on blood pressure and baseline eGFR.
The post hoc design of the analyses of the SUSTAIN and PIONEER data comes with several limitations, as acknowledged by the authors, including the necessity to interpret the results cautiously because the trials were not designed to specifically compare outcomes among different eGFR subgroups. In this context, for example, baseline hemoglobin A1c differed among the eGFR subgroups. This difference in hemoglobin A1c could influence the treatment effects on glycemic control although the differences appear to have been minor. Nevertheless, the overall conclusion of the study is consistent with an earlier post hoc analysis of data from 8 trials studying once weekly exenatide, including patients with type 2 diabetes and CKD stages 2 and 3.

As in the present report examining semaglutide, the effect of exenatide with regards to reduction in hemoglobin A1c did not differ between certain eGFR subgroups, specifically CKD 2 versus CKD 3 patients. Furthermore, exenatide treatment induced a decrease in systolic blood pressure and body weight, which was similar in the 2 CKD groups.

In conclusion, despite the limitations due to the post hoc design of the study we consider that the data presented affords diabetologists and nephrologists a degree of optimism as reflected by both the safety and efficacy of GLP-1 receptor agonists, thereby representing a viable therapeutic option for the population of type 2 diabetic patients with reduced GFR.

**DISCLOSURE**

All the authors declared no competing interests.

**REFERENCES**

1. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol.* 2018;6:605–617. https://doi.org/10.1016/S2213-8587(18)30104-9

2. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (Pioneer 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7:515–527. https://doi.org/10.1016/S2213-8587(19)30192-5

3. Cherney DZ, Hadjadj S, Lawson J, et al. Hemoglobulin A1c reduction with the GLP-1 receptor agonist semaglutide is independent of baseline eGFR: post hoc analysis of the SUSTAIN and Pioneer programs. *Kidney Int Rep.* 2022;7:2345–2355.

4. Guja C, Frias JP, Suchower L, et al. Safety and efficacy of exenatide once weekly in participants with Type 2 diabetes and Stage 2/3 chronic kidney disease. *Diabetes Ther.* 2020;11:1467–1480. https://doi.org/10.1007/s13300-020-00815-z

**COMMENTARY**

JA Østergaard and ME Cooper: GLP-1 RA in type 2 diabetic patients with CKD