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COMMENTARY

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Sodium-glucose cotransporter 2 inhibitors for macroalbuminuria: A new indication

Zachary Bloomgarden[1] | **Yehuda Handelsman**[2]

[1]Department of Medicine, Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, New York

[2]Metabolic Institute of America, Tarzana, California

Correspondence
Zachary Bloomgarden, Department of Medicine, Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, NY 10028.
Email: zbloom@gmail.com

A somewhat underappreciated cause of optimism has been the evidence from the cardiovascular outcome trials of type 2 diabetes (T2D) treatments that all the newer agents appear to improve aspects of renal function.[1] The 2.6-year CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial randomizing 4401 persons with T2D, estimated glomerular filtration rate (eGFR) 30-90 mL/min/1.73m^2 (mean baseline 56), and angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB)-treated macroalbuminuria (>300 mg/g creatinine) to canagliflozin 100 mg daily or placebo showed highly significant reduction in renal disease outcomes,[2] leading the US Food and Drug Administration on 27 September 2019 to add the following indication for the use of the agent: "to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria >300 mg/day." This brief statement indicates a complete about-face from earlier assertions(currently included in the canagliflozin product information[3]) that sodium-glucose transporter (SGLT)2 inhibitors are associated with elevation in serum creatinine and reduction in eGFR. In CREDENCE, the likelihood of doubling of serum creatinine with canagliflozin vs placebo was 4.3 vs 6.1 per 100 patient-years (hazard ratio 0.70 [95% confidence interval 0.59-0.82]), of decline in eGFR to <15 was 1.4 vs 2.2 (0.60 [0.45-0.80]), of cardiovascular death 1.9 vs 2.4 (0.78 [0.61-1.00]), and of heart failure hospitalization 1.6 vs 2.6 (0.61 [0.47-0.80]), with separation of the groups beginning to appear between 12 and 18 months.[2] This new indication highlights the first drug class in nearly 20 years, since the ACEI and ARBs, to slow the progression of chronic kidney disease.

We should ask: What is the implication for the treatment of T2D? Based on this report and similar evidence of renal protection with empagliflozin[4] and dapagliflozin,[5] which patients with diabetes should receive an SGLT2 inhibitor for a renal indication?

In population studies of persons with diabetes, between one sixth and one third have albuminuria levels exceeding 30 mg/g creatinine.[6] Only a minority of these persons have macroalbuminuria: in a Japanese population, 25% and 5% of persons with T2D had micro- and macroalbuminuria';[7] in Ramallah, Palestine, micro- and macroalbuminuria were present in 29% and 5%, respectively;[8]in a population study in Turkey, micro- and macroalbuminuria were present in 43% and 9%, respectively;[9] and in a similar study in Luxembourg, micro- and macroalbuminuria were present in 4% and 1%, respectively.[10] Using data from cross-sectional studies of adults aged 20 years or older with diabetes mellitus participating in US National Health and Nutrition Examination Surveys from 1988 through 2014, the prevalence of microalbuminuria decreased from 16% in 1988-1994 to 11% in 2009-2014, with macroalbuminuria prevalence at 6% and 5% in the two time periods,[11] and another study in Japan analyzed trends in albuminuria prevalence among T2D persons, showing a decline in micro- and macroalbuminuria prevalence from 29% and 13% in 1996, to 16% and 5% in

2014, respectively.[12] In contrast to the declining prevalence of micro- and macroalbuminuria, in the US study the prevalence of eGFR 30-60 and <30 increased from 12% and 1% to 17% and 3% over the time course[11] and in the Japanese study from 2% and 10% to 3% and 21%, respectively.[12]

Thus, depending on the population treated, approximately 5% of persons with diabetes have albuminuria in the range of the new indication. Of >400 million persons having diabetes worldwide,[13] although some will have eGFR <30 and so not be eligible for SGLT2 inhibitor treatment, perhaps 10-15 million having the albuminuria and eGFR characteristics identified in CREDENCE should have such treatment. Beyond these, we do not know whether the larger groups of persons with T2D and eGFR 30-60, either with microalbuminuria or with normoalbuminuria, will also benefit from administration of an SGLT2 inhibitor. Although small studies and post hoc analysis of subgroups from the SGLT2 inhibitor trials seem to suggest benefit in this population,[14] we need to await the results of future studies. In sum, however, as with a recent study showing that persons with heart failure and reduced ejection fraction, regardless of having or not having diabetes, have reduced risk of worsening heart failure and of cardiovascular mortality,[15] CREDENCE, supported by the new Food and Drug Administration indication, opens a new area for SGLT2 inhibitor therapy. Going forward, these agents will become increasingly important, not only in the treatment of diabetes but also in cardiology and in nephrology, representing a major milestone in the medical treatment.

DISCLOSURE

The authors declare no potential conflict of interest.

REFERENCES

1. Bloomgarden Z. The kidney and cardiovascular outcome trials. *J Diabetes*. 2018;10(2):88-89.
2. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295-2306.
3. Canagliflozin prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204042s027lbl.pdf. Accessed Nov 7, 2019.
4. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334.
5. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617.
6. Bloomgarden Z. Sodium-glucose cotransporter 2 inhibitors and renal function-2. *J Diabetes*. 2015;7:295-298.
7. Shikata K, Kodera R, Utsunomiya K, et al. Prevalence of albuminuria and renal dysfunction, and related clinical factors in Japanese patients with diabetes: the Japan diabetes complication and its prevention prospective study 5. *J Diabetes Investig*. 2019. https://doi.org/10.1111/jdi.13116
8. Shahwan MJ, Gacem SA, Zaidi SK. Prevalence of diabetic nephropathy and associated risk factors among type 2 diabetes mellitus patients in Ramallah, Palestine. *Diabetes Metab Syndr*. 2019;13:1491-1496.
9. Fici F, Bakir EA, Beyaz S, Makel W, Robles NR. PAIT-survey-prevalence of albuminuria in patients with diabetes and hypertension in Turkey. *Prim Care Diabetes*. 2018;12(6):558-564.
10. Alkerwi A, Sauvageot N, El Bahi I, et al. Prevalence and related risk factors of chronic kidney disease among adults in Luxembourg: evidence from the observation of cardiovascular risk factors (ORISCAV-LUX) study. *BMC Nephrol*. 2017;18(1):358.
11. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *Jama*. 2016;316(6):602-610.
12. Kume S, Araki SI, Ugi S, et al. Secular changes in clinical manifestations of kidney disease among Japanese adults with type 2 diabetes from 1996 to 2014. *J Diabetes Investig*. 2019;10:1032-1040.
13. IDF diabetes atlas - 8th edition. International Diabetes Federation. http://www.diabetesatlas.org, 2017. Accessed October 17, 2019
14. Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7(11):845-854. https://doi.org/10.1016/S2213-8587(19)30256-6
15. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303