thebmj

BMJ 2020;369:m1584 doi: 10.1136/bmj.m1584 (Published 29 April 2020)

EDITORIALS

Check for updates

SGLT2 inhibitors and kidney outcomes in the real world

Observational data from clinical practice favour these drugs over DPP4 inhibitors

Steven M Smith *assistant professor of pharmacy*

Department of Pharmacotherapy and Translational Research and Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, PO Box 100486, Gainesville, 32610-0486, FL, USA

Chronic kidney disease affects 700 million individuals worldwide and contributes to one in 20 deaths annually.[1] Globally, the age standardised mortality rate attributable to CKD has remained virtually unchanged over the past decade, in contrast to most other non-communicable chronic diseases for which these rates have fallen.[1 2] This seemingly intractable problem is driven largely by diabetes.[1] It is thus not surprising that sodium glucose cotransporter 2 (SGLT2) inhibitors have garnered considerable attention following recent clinical trials showing consistent benefits of these glucose lowering drugs on major adverse kidney outcomes.[3-6]

Taken together, current evidence strongly suggests a role for SGLT2 inhibitors in people with or at risk of chronic kidney disease. Yet the key trials left important questions unanswered for clinicians and patients. All were placebo controlled and had highly selected participants, making the results hard to translate to real world use.

In a linked article in *The BMJ*, Pasternak and colleagues report how they sought to answer some of these questions in a cohort study using pooled national registry data from Scandinavia (doi:10.1136/bmj.m1186).[7] They used propensity scores to match new users of SGLT2 inhibitors (n=29 887) or dipeptidyl peptidase 4 (DPP4) inhibitors (n=29 887) between 2013 and 2018. The primary outcome was a composite: first occurrence of renal replacement therapy, hospital admission for renal events, or death from renal causes. In the primary analysis, SGLT2 inhibitor initiation, compared with DPP4 inhibitor initiation, was associated with 3.6 fewer events per 1000 person years, equating to a 58% (95% confidence interval 47% to 66%) lower risk of the primary outcome over a mean follow-up of 1.4 (SGLT2 inhibitors) to 2.0 (DPP4 inhibitors) years. This difference was primarily driven by lower rates of renal replacement therapy and hospital admission with SGLT2 inhibitor use, whereas no difference was seen in the rates of death from renal causes. Subgroup analyses found consistent benefits for SGLT2 inhibitor initiators across sex, age groups, and individual drugs, but greater risk reduction in patients with cardiovascular disease and patients with chronic kidney disease.

The results from this well designed study are qualitatively consistent with previous clinical trials and smaller observational studies, and adds new evidence that SGLT2 inhibitors seem preferable to DPP4 inhibitors in patients at risk of developing or worsening diabetic kidney disease. Evidence is mixed regarding whether DPP4 inhibitors prevent progression of diabetic kidney disease, but they do not worsen it. The protective effect of SGLT2 inhibitors seems to occur independent of improved hyperglycaemic control and probably independent of other effects shared by DPP4 inhibitors (such as reduced blood pressure or weight loss). And although SGLT2 inhibitors appeared particularly beneficial in people with cardiovascular disease or chronic kidney disease, it is perhaps more informative that these drugs were associated with a lower risk of development and progression of diabetic kidney disease in patients without these overt comorbidities, who have largely been excluded from clinical trials. Most patients in the study did not have diagnoses of cardiovascular disease, and only around 3% had diagnosed chronic kidney disease (although measuring the disease from diagnosis codes is notoriously inaccurate and many more patients probably had some degree of the disease[8]).

Despite this study's strengths, the results should be interpreted with some caution. Sensitivity analyses supplemented with clinical data suggested a modest degree of unmeasured confounding in the primary analysis. Additional unmeasured confounding is possible; any such confounder would, however, need to be associated with both the treatment and outcome by a risk ratio of 1.8-fold (based on Sweden data) or 2.0-fold (Denmark) for the confidence intervals to include null results.[9]

Overall, the findings by Pasternak and colleagues add to the impressive track record for SGLT2 inhibitors. Additional pragmatic comparative effectiveness trials in real world settings and more diverse populations could add further support for broader access to these drugs, not only in high income countries but also in lower income countries where the burden of kidney disease is disproportionately high.[1]

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The author declares the following other interests: research funding received from the National Institutes of Health (US) and service on the Board of Directors for Consortium for South-eastern Healthcare Quality (US

ssmith@cop.ufl.edu

non-profit; unpaid position). *The BMJ* policy on financial interests is here: https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf

Provenance and peer review: Commissioned; not peer reviewed.

1 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;395:709-33. 10.1016/S0140-6736(20)30045-3 32061315

2 GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1736-88. 10.1016/S0140-6736(18)32203-7 30496103

3 Perkovic V, Jardine MJ, Neal B, etal. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;380:2295-306. 10.1056/NEJMoa1811744 30990260

4 Perkovic V, de Zeeuw D, Mahaffey KW, etal . Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018;6:691-704. 10.1016/S2213-8587(18)30141-4 29937267

5 Mosenzon O, Wiviott SD, Cahn A, etal . 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;7:606-17. 10.1016/S2213-8587(19)30180-9 31196815

6 Wanner C, Inzucchi SE, Lachin JM, etal. EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med* 2016;375:323-34. 10.1056/NEJMoa1515920 27299675

7 Pasternak B, Wintzell V, Melbye M, etal . Use of sodium-glucose co-transporter 2 inhibitors and risk of serious renal events: Scandinavian cohort study. *BMJ* 2020;369:m1186.

8 Brück K, Stel VS, Gambaro G, etal. European CKD Burden Consortium. CKD Prevalence Varies across the European General Population. *J Am Soc Nephrol* 2016;27:2135-47. 10.1681/ASN.2015050542 26701975

9 VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017;167:268-74. 10.7326/M16-2607 28693043