Canagliflozin and Renal Outcomes in Diabetic Nephropathy

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Published in:
New England Journal of Medicine

DOI:
10.1056/NEJMc1909687

Publication date:
2019

medical marijuana for symptom relief receive little or no guidance from medical professionals.

With the increasing use of medical marijuana, it is time for regulations to standardize and monitor these substances. Currently, there is no state or national database to report adverse effects; the MedWatch program of the Food and Drug Administration is only accepting reports related to the approved product Epidiolex, a cannabidiol.[5] Packaging changes to prevent such extremely concentrated formulations and a central agency for reporting, research, and regulation are overdue.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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DOI: 10.1056/NEJMc1907013

Figure 1. Liquid Marijuana Packaging and Syringe.
The liquid marijuana product used by the patient was obtained from a local medical marijuana dispensary. The syringe contains the amount remaining after 2 days of use.

Canagliflozin and Renal Outcomes in Diabetic Nephropathy

TO THE EDITOR: The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial reported by Perkovic et al. (June 13 issue)[1] exemplifies a deficiency in the pharmaceutical regulatory system — that is, sponsors are not required to ascertain whether the results of canagliflozin therapy and those of more cost-effective diuretic therapy might be similar. In this trial, canagliflozin, a drug with diuretic properties, was administered to patients with diabetic kidney disease, nearly all of whom were receiving a renin–angiotensin–aldosterone system (RAAS) inhibitor. In the placebo group, however, fewer than half the patients were taking diuretics.

In a seminal study that established the renoprotective effect of RAAS inhibition in patients with diabetic kidney disease, 84% of the patients in both the losartan and placebo groups received diuretics during the treatment period.[2] Diuretics may augment the renoprotective effects of RAAS inhibitors by potentiating their antihypertensive

and antiproteinuric actions.[3] A clinical trial comparing canagliflozin added to RAAS inhibition with a generic thiazide diuretic added to RAAS inhibition in patients with diabetic kidney disease and otherwise controlled hyperglycemia could help to determine whether the renoprotective qualities of canagliflozin are anything more than those of an expensive diuretic.

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Dr. Leslie reports having been an employee involved in the development and safety monitoring of sodium–glucose cotransporter 2 (SGLT2) inhibitors at Bristol-Myers Squibb, Janssen, and Pfizer; being an inventor on patent US8,518,895B2, entitled "Method for Treating Hyponatremia Employing an SGLT2 Inhibitor and Composition Containing Same," and patent US8,791,077B2, entitled "Method for Treating Hyperuricemia Employing an SGLT2 Inhibitor and Composition Containing Same" — both currently assigned to AstraZeneca; and owning stock in Bristol-Myers Squibb, Eli Lilly, and Pfizer. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1909687

TO THE EDITOR: The CREDENCE trial showed a lower risk of kidney failure and cardiovascular events among patients who received canagliflozin than among those who received placebo. The systolic blood pressure and glycated hemoglobin levels were higher than the recommended targets, especially in the placebo group. Previous studies have established that blood pressure control and diabetes control both improve renal outcomes.[1,2] To conclude that canagliflozin decreases the risk of kidney failure, the trial would have had to involve patients with proper blood pressure and diabetes control that was similar in the two groups.

Given that canagliflozin has diuretic properties, it is not surprising that patients in the canagliflozin group had lower systolic blood pressure than those in the placebo group.[3] Differences in medication to control blood pressure during the intervention were not reported in the trial. In fact, control of blood pressure alone could account for the better outcomes in the canagliflozin group than in the placebo group.[1]

The CREDENCE trial did not show the significant increase in the rate of amputation seen by the CANVAS (Canagliflozin Cardiovascular Assessment Study) investigators.[4] The design of the CREDENCE trial involved the selection of patients at low risk for amputation. The exclusion of high-risk patients may have biased the results toward lower rates of amputation. In conclusion, we find the CREDENCE trial design and methods to be biased and potentially misleading.

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DOI: 10.1056/NEJMc1909687

TO THE EDITOR: Ever since the outcomes of the CANVAS Program[1] were reported, the finding of a significantly higher incidence of lower-limb amputations in the canagliflozin group than in the placebo group has aroused concerns. This finding did not occur with either empagliflozin or dapagliflozin.[2]

In the CREDENCE trial, Perkovic et al. found a nonsignificant but higher number of amputations among patients receiving canagliflozin at a dose of 100 mg daily than in those receiving placebo (70 vs. 63 amputations; hazard ratio, 1.11; 95% confidence interval, 0.79 to 1.56). Although the authors suggest that this finding is

reassuring for physicians prescribing canagliflozin, we disagree.

The main differences between the CREDENCE trial and the CANVAS Program are that the latter had two treatment groups (canagliflozin at a dose of 100 mg and canagliflozin at a dose of 300 mg) and a larger number of patients than the CREDENCE trial (10,142 vs. 4401). Different doses are unlikely to explain the differing results, since the subgroup analysis in the CANVAS Program did not show an interaction between dose and amputation risk.[3]

However, the total number of amputations in the CANVAS Program was higher than that in the CREDENCE trial (187 vs. 133).[1] Therefore, because of the larger number of events, safety outcomes in the CANVAS Program are more reliable, and safety issues regarding canagliflozin remain unresolved.

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DOI: 10.1056/NEJMc1909687

TO THE EDITOR: The CREDENCE trial showed a greater reduction in the estimated glomerular filtration rate (GFR) among patients with type 2 diabetes and chronic kidney disease who received canagliflozin than among those who received placebo. However, because the estimated GFR corrects the serum creatinine level for population variation in muscle mass rather than for individual variation,[1] a comparison of treatments with respect to changes in the estimated GFR over time is valid only if the treatment has no effect on muscle mass.

Unfortunately, there are reasons to believe that canagliflozin does affect muscle mass. Canagliflozin can stimulate gluconeogenesis,[2] which uses amino acids from muscle protein for synthesis of new glucose molecules. This process causes loss of muscle mass,[3] which may explain the loss of lean body mass that has been observed in response to treatment with canagliflozin.[4] Also, because dialysis is usually initiated according to the estimated GFR rather than the serum creatinine level corrected for individual variation in muscle mass,[5] the renoprotective effect of canagliflozin described by Perkovic et al. may have been in whole or in part the consequence of loss of muscle mass. Studies or analyses that control for change in muscle mass may provide definitive answers.

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DOI: 10.1056/NEJMc1909687

THE AUTHORS REPLY: Leslie and Gerwin suggest that the benefits of canagliflozin may be due to a diuretic effect. Diuretics have not been shown to prevent kidney failure. The benefits observed in the CREDENCE trial were also consistent, regardless of baseline diuretic use, so we think it is unlikely that the diuretic effect explains the benefits of canagliflozin.

Isreb et al. ask whether benefits in the CREDENCE trial may have resulted from between-group differences in blood pressure or glucose control. Pooled analyses of intensive blood pressure and glucose lowering have not shown clear renal benefits, so these are also unlikely explanations, particularly given the modest differences between the two groups. The trial protocol encouraged investigators to deliver the best guideline-based care to patients according to blood

pressure and glucose and lipid levels. None of these interventions (i.e., the use of diuretics and intensive blood pressure and glucose lowering) has been shown to have benefits of the magnitude observed in the CREDENCE trial, despite multiple trials.

We disagree with the assertions by Lima et al. and Isreb and colleagues regarding amputation. Patients in the CREDENCE trial were at higher risk for amputation than those in the CANVAS Program. A history of amputation is predictive of subsequent amputation[1] and was more common in the CREDENCE trial than in the CANVAS Program (in 5.3% of patients vs. 2.3% of patients).[2] Also, the rate of amputation among patients receiving placebo in the CREDENCE trial was substantially higher than that among patients receiving placebo in the CANVAS Program (11.2 per 1000 patient-years vs. 3.4 per 1000 patient-years). As a result, more amputations were observed in the placebo group of the CREDENCE trial than in the placebo group of the CANVAS Program (63 vs. 47). Thus, the two trials had similar power to detect an increased risk, but the results were clearly different ($P=0.02$ for heterogeneity). We think the CREDENCE trial provides reassurance that the increase in amputation risk observed in the CANVAS Program is very unlikely to be seen among patients such as those in the CREDENCE trial who received treatment according to our protocol.

Post and colleagues ask whether weight loss may influence the estimated GFR values. In studies of SGLT2 inhibitors in which body composition was assessed, weight loss was driven mostly by decreases in fat mass, with much smaller decreases in lean and muscle mass.[3,4] Furthermore, weight loss in the CREDENCE trial occurred almost entirely in the first 6 months, after which weight remained stable, yet the difference in the estimated GFR slope was observed throughout the full trial period. Thus, although small changes in muscle mass may have a minor influence on the creatinine-based estimated GFR values in the CREDENCE trial, the magnitude of change in the estimated GFR slope and the time profile for the changes seen with canagliflozin cannot be explained by the small changes in weight.

We think the benefits seen with canagliflozin in the CREDENCE trial are clear and important.

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Since publication of his article, Dr. Perkovic reports receiving fees for consulting and scientific presentations related to canagliflozin from Mitsubishi Tanabe Pharma and Mundipharma. No further potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1909687

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