Editorial

Canagliflozin lowers blood sugar, but does it also lower cardiovascular risk? Maybe not

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For the last 25 years it has been widely accepted that diabetes mellitus is associated with a twofold or greater risk of clinical atherosclerotic disease (1). Long-standing elevated blood sugar levels, as measured by the hemoglobin A1c level, have been shown to be independent of major cardiovascular risk factors including age, body mass index, systolic blood pressure, serum cholesterol, cigarette smoking, or history of cardiovascular disease (2).

Canagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor approved for treatment of type 2 diabetes that results in decreased resorption of glucose in the S1 segment of the proximal renal tubules causing glucose to be excreted in the urine. SGLT2 inhibitors counteract the increased expression of SGLT2 by diabetic patients who paradoxically have increased glucose reabsorption in the kidneys (3). Canagliflozin is generally well-tolerated and equally effective as metformin at lowering HgbA1c. There is some early evidence that canagliflozin may be synergistic with metformin and that combination metformin/canagliflozin therapy may be a reasonable initial therapy for newly diagnosed patients with type 2 diabetes (4). In addition, canagliflozin appears to be well-tolerated when used with sulfonylureas (5). The most frequent side-effects of canagliflozin are generally minor and consistent with its mechanism of effect including female genital mycotic infections, urinary tract infections, pollakiuria, polyuria, volume depletion, and impaired renal function. Rarely, diabetic patients can experience euglycemic ketoacidosis from SGLT2 inhibition (6-8). Because there is no significant hyperglycemia, recognition of serious metabolic abnormalities can be dangerously delayed (9).

The Canagliflozin Cardiovascular Assessment Study (CANVAS) combined data from two trials analyzing canagliflozin in type 2 diabetic patients with high cardiovascular risk. The trials compared patients on standard diabetic therapy as well as either canagliflozin or a placebo. A recent analysis of the CANVAS data found that the group of patients who were treated with canagliflozin versus placebo had a lower end point HgbA1c, fewer deaths from cardiovascular causes, fewer nonfatal myocardial infarctions, and fewer nonfatal strokes. However, those on canagliflozin had a greater risk of amputation primarily at the level of the toe or metatarsal (10). The increased rate of amputation found in this analysis was an unexpected finding, and the authors did not put forth a hypothesized mechanism. The authors concluded that type 2 diabetic patients with established cardiovascular disease or that are at high risk of cardiovascular disease treated with canagliflozin had a significantly decreased risk of cardiovascular events compared to those who received a placebo.

There are several ethical red flags raised by this study. The patient trials were sponsored by the pharmaceutical company that makes canagliflozin, Janssen Research and Development (11). In addition, the pharmaceutical company funded and the authors used "medical writing support" from a marketing company that advertises that it helps "optimize the impact of your asset or brand every step of the way" (12). This is problematic given that there is good evidence that

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pharmaceutical industry sponsored trials are significantly biased towards the sponsor (13,14). One analysis found that studies sponsored by a pharmaceutical company were four times more likely to have outcomes favoring the sponsor compared to studies with other sponsors (15). Additionally, it seems that the authors have made minimal effort in disclosing these serious conflicts of interest instead of taking a more transparent approach, possibly leaving readers uninformed of potential caveats to the study's results.

Another red flag raised by this study is the lack of statistical correction for factors known to be related to cardiovascular disease. It is unknown if the causative factor in reducing cardiovascular disease in this study was specific to canagliflozin or if the causative factor was simply a lower blood sugar. The authors could have easily shed light on this question by performing an analysis correcting for HgbA1c levels, but this correlation was avoided. It has been well-known for nearly 50 years that there is a strong relationship between diabetes, serum insulin levels, and ischemic heart disease (16). Recent research has found that glycated hemoglobin levels are strongly associated with increased risks of cardiovascular disease and death from any cause (17). The data should have been analyzed by looking at canagliflozin as the independent variable, clinical outcomes as the dependent variables, and correcting for HgbA1c levels. Was this analysis done, but not published because it was not favorable to the study sponsor? We simply do not know.

The study authors used standard errors exclusively when describing their findings and did not provide standard deviations. While this is statistically valid, it is also statistically incomplete. In large studies it has the effect of reducing people to their group identity and masks the significant overlap that exists in most populations. The standard error of the mean in large studies (defined as the sample standard deviation divided by the square root of the sample population minus one) is so narrow it effectively divides patients into binary groups. Thus, it is difficult to determine the likelihood of individual patients seeing a benefit or harm. To apply population studies to individual patients, standard deviations must be provided. Therefore, it is incumbent upon authors to not only give the inferential statistics, i.e., standard errors, but to also give descriptive statistics of sample variation, i.e., standard deviations.

We can conclude with high confidence that canagliflozin compared to placebo, when added to standard therapy for type 2 diabetes, has a reasonably high likelihood of lowering an individual patient's average blood sugar levels. This is an important finding, since many patients prefer to take oral antiglycemic agents, even if it means inferior control of their diabetes. With canagliflozin we have a new agent that likely leads to improved HgbA1c levels without having to resort to injectable medications. This study also reinforces what we already know about diabetes—that it is a risk factor for adverse cardiac and renal events, especially in those with established cardiovascular disease or in those at high risk. The relationship of canagliflozin and amputations is unclear, and potentially a spurious finding. What remains unanswered is whether or not canagliflozin has any unique impact upon cardiovascular or renal disease beyond its effect on lowering blood sugar levels.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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