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Is canagliflozin effective in lowering the risk of all-cause mortality in adults with type 2 diabetes compared to the placebo?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "canagliflozin is effective in lowering the risk of all-cause mortality in adults with type 2 diabetes compared to the placebo?"

STUDY DESIGN: A systematic review of three English language, primary, double-blind, randomized controlled trials published from 2013 to 2019.

DATA SOURCES: All primary studies were published in peer reviewed journals and selected through PubMed and Cochrane databases comparing canagliflozin vs. placebo.

OUTCOMES MEASURED: All-cause mortality, defined as death of patient within the study interval and expressed as number of death/ total participants over the study time interval.

RESULTS: The search yielded a total of 20 articles. Three studies were ultimately included in the EBM review after exclusion of other irrelevant studies. Neal et al. showed no statistically significant reduction in all-cause mortality rate, 17.3 vs. 19.5 participants with an event per 1000 patient-years between the intervention vs. placebo groups, respectively (HR 0.87; 95% CI 0.74 to 1.01; P = 0.24). In the Perkovic study, all-cause mortality rate was also similar between both groups, 29.0 vs. 35.0 per 1000 patient-years (HR 0.83; 95% CI 0.68–1.02; P not given) for the intervention and placebo groups, respectively. Likewise, all-cause mortality rate was shown to be the same, 1.1 % in both the placebo and the treatment arms in Yale et al. study.

CONCLUSIONS: The results of all three studies demonstrated that canagliflozin is not effective in lowering the risk of all-cause mortality in adults with type 2 diabetes compared to the matched placebo. Due to the potential heterogeneity among the included studies, the results of this analysis should be confirmed with new and larger trials in the future to better evaluate all-cause mortality over a longer follow-up period.

KEY WORDS: Type 2 diabetes, canagliflozin, safety outcome

INTRODUCTION

Type 2 diabetes is a complex, chronic condition in which the body does not produce enough insulin and/or is unable to use insulin properly, leading to high levels of sugar in the bloodstream and causing a variety of serious complications, such as cardiovascular disease, vision loss, kidney disease and death. This disease, thus, has been a major concern for healthcare providers working in any field.[1-3] Poorly controlled blood sugar and chronic hyperglycemia are detrimental to the body and associates with high mortality and morbidity due to the risk for developing cardiovascular disease is twofold in these patients.[1] Moreover, type 2 diabetes can be caused by several factors, including overweight and obesity, sedentary lifestyle, insulin resistance, and genetics.[1-3] Random plasma glucose tests, fasting plasma glucose tests, or HbA1c are often used to confirm the diagnosis. Patients may be asymptomatic or present with blurred vision, altered mental status, weakness, paresthesia, nausea, vomiting, anorexia, polydipsia, or polyuria.

Per the CDC, 34.2 million Americans have diabetes.[4] It is estimated that the prevalence of type 2 diabetes mellitus will continue to rise, specifically 25 to 33 percent of American adults could have diabetes by 2050, either diagnosed or undiagnosed, with the majority of them being 45-64 years old.[4] Moreover, the increasing management costs of type 2 diabetes and its complications has conferred a large economic burden on the U.S. healthcare system in recent years.[4] The total estimated cost of diabetes in the United States was $327 billion in 2017, according to the American Diabetes Association.[5] Of the spending spent on direct costs in 2017, hospital inpatient care and prescription medications to treat diabetes make up the largest components of the total spending cost.[5] Furthermore, in 2016, there were 7.8 million hospital discharges were reported with diabetes as a listed diagnosis among US adults aged 18 years or older per the CDC.[4]

Optimal glycemic control is required to restrain the developing of serious complications in patients with type 2 diabetes, and this can be accomplished through carbohydrate counting, lifestyle modification and medications. Existing medications such as metformin, sulfonylureas (glyburide, glipizide), thiazolidinediones (rosiglitazone), alpha-glucosidase inhibitor (acarbose), incretin mimics: GLP1 receptor agonists (exenatide, liraglutide), DPP-4 inhibitors (sitagliptin, linagliptin), serum glucose co-transporter 2 inhibitor (dapagliflozin, canagliflozin), other: glucagon suppression and insulin, lower blood glucose either by enhancing insulin secretion or by improving insulin sensitivity. Most patients with type 2 diabetes will eventually maintain on a combination of different medications to achieve optimal glycemic control.[1-3] However, deciding on an optimal treatment choice is a major challenge for healthcare providers, especially after inadequate treatment with metformin monotherapy, due to the constantly rising number of available antidiabetic medications. While the standard treatment options such as insulin, sulfonylureas, and DPP4 inhibitors all effectively lower blood glucose, these medications have not been associated with improvements in survival rate for type 2 diabetes patients.[6] Conversely, the use of canagliflozin, a SGLT2 inhibitor, has been shown to have favorable effects in reducing the risk of serious cardiovascular complications and kidney disease,[1,3] but whether or not canagliflozin, can produce similar effect on all-cause mortality is undetermined.

SGLT2 inhibitors have been recommended by clinical guidelines as potential pharmacological approaches for second-line therapy following metformin failure or intolerance.[6] Canagliflozin, a SGLT2 inhibitor, decreases reabsorption of glucose at the proximal tubules in the kidneys, leading to greater urinary excretion, subsequently reducing in plasma glucose concentration, in individuals with hyperglycemia. Canagliflozin at a daily dose of 100 or 300 mg has received authorization in the U.S. for use in patients with type 2 diabetes, while its current

placement in the treatment algorithms is in second or third line of therapy.[6] Also, there have been many favorable reports from multiple systematic reviews and meta-analyses about the effects of canagliflozin in reducing fasting blood sugar, lipid profile, blood pressure, HbA1C and body weight.[7] Furthermore, empagliflozin, another SGLT2 inhibitor has shown benefits in the prevention of CV events and all-cause mortality in patients with CVDs from the EMPA-REG trial.[8] It is, therefore, suggested that canagliflozin has the potential to lower the risk of all-cause mortality in adults with type 2 diabetes.

OBJECTIVE

The objective of this study is to determine whether or not "canagliflozin is effective in lowering the risk of all-cause mortality in adults with type 2 diabetes compared to the placebo?"

METHODS

The search for articles was performed using PubMed and Cochrane databases. Key words used to acquire literature included "type 2 diabetes", "canagliflozin" and "safety outcome". All the full-text studies published in English language and peer-reviewed journals from 2009 to 2019, were included in the review. Inclusion criteria was based on studies that were randomized, placebo-controlled, their relevance to my clinical questions and that the outcomes of the studies mattered to patients (POEMs). Exclusion criteria consisted of articles published before 2009, those that were not published in peer-reviewed journal and those that were not RCTs/prospective intervention studies, or secondary study design. Statistics reported included p-values, relative risk reduction (RRR), absolute risk reduction (ARR), and numbers needed to treat (NNT). Table 1 expresses the specific demographics, inclusion, and exclusion criteria of each trial used in this review.

Three double blind, randomized control trials were selected to create this evidence-based medicine review. The populations of all selection of studies included patients >18yo with type 2 diabetes. The intervention assessed in these studies was varying doses of canagliflozin in comparison to the placebo in type 2 diabetic patients. Outcome studied was the efficacy of canagliflozin in lowering the risk of all-cause mortality in adults with type 2 diabetes.

OUTCOME MEASURED

The primary outcome measured in all three studies was all-cause mortality of the patient. Mortality was defined as death of the patient within the study interval. All three studies expressed all-cause mortality result as number of death/ total participants over the time interval.

RESULTS

The search yielded a total of 20 articles. Three studies were ultimately included in the EBM review after exclusion of other irrelevant studies. All three randomized, placebo-controlled trials presented in this review involved data presented as an intention to treat analysis. The results regarding to the outcome measured were recorded as dichotomous data in all three studies. All participants in each study were randomly assigned to either the experimental group receiving canagliflozin, or the control group receiving a placebo. There was no clinically significant difference at baseline with regards to demographic characteristics in each trial. The ratio between the comparison and intervention group was 1:1 in all the studies. However, compared the population among each study, there are a differential proportion of enrolled cases with established CVD; for instance, 50% of patients enrolled in CREDENCE trial (Perkovic et al.), 66% of patient in CANVAS (Neal et al.), and 55% of patient in Yale et al. study had established CVD. While the CREDENCE trial had enrolled patients with chronic kidney disease and was required to be on ACE/ARB (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker) inhibitor

therapy, the other two studies did not have ACE/ARB inhibitor therapy as one of the inclusion criteria. It is also noted that while both Neal et al. and Perkovic et al. studies excluded only NYHA class IV patients, the Yale et al. study excluded both NYHA class III – IV patients.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Neal (2017)[1]	Double blind RCT	10142	63±8	Patients 30 yo or older with type 2 DM, HbA1c ≥7.0% - ≤10.5% and/or with established CVD or GFR ≥30	Patients with type 1 DM, having MI, UA, revascularized or CVA within 3 months screen, or history of NYHA Class IV heart failure	408	Canagliflozin 100 mg daily PO, at week 13 and after canagliflozin dose varies, 100 – 300 mg
Perko-vic (2019)[2]	Double blind RCT	4401	63±9	Patients 30 yo or older with type 2 DM, HbA1c ≥6.5% - ≤12.0% and/or with established CVD or GFR 30-89 -On an ACEi or ARB at the maximum labeled dose	Patients with type 1 DM, or renal disease that required treatment with immunosuppressive therapy or a history of chronic dialysis or renal transplant or NYHA Class IV heart failure	40	Canagliflozin 100 mg daily PO
Yale (2013)[3]	Double blind RCT	272	68±8	Patients 25 yo or older with type 2 DM and stage 3 CKD and were either not on antihyperglycemic agent (AHA) therapy or were on a stable AHA regimen prior to the week–2 visit	Patients with type 1 DM, having MI, UA, revascularized or CVA within 3 months screen or history of NYHA class III- IV heart failure or patients with renal disease required immunosuppressive therapy, dialysis or transplant	35	Canagliflozin 100 mg or 300 mg daily PO

The Neal et al. study in 2017 compared canagliflozin to placebo in diabetic patients with high-risk cardiovascular disease. Participants received 100 mg of canagliflozin by mouth once a day for 12 weeks. Starting from week 13, there was an optional increase to 300 mg or matching placebo. All participants finished a 2-week, single-blind, placebo run-in period. The study comprised a total of 10,142 participants. A total of 9734 participants (96.0%) completed the trial. The mean follow-up was 188 weeks. The all-cause mortality rate was not significantly different between the groups, 17.3 vs. 19.5 participants per 1000 patient-years for the intervention vs placebo groups, respectively (HR 0.87; 95% CI 0.74 to 1.01; P = 0.24; Table 2). The statistical significance was defined as $p<0.05$. The absolute risk reduction (ARR) of this study was calculated to be 0.22% and the relative risk reduction (RRR) was 11%. The number needed to treat (NNT) was determined to be 455; hence the effect of the study was small (Table 3).

In the Perkovic et al. study published in 2019, there were 4,401 patients with diabetes and albuminuria randomized to canagliflozin 100 mg or placebo. A total of 4361 participants (99.1%) completed the trial. Participants received a canagliflozin dose of 100 mg daily or placebo. All participants must receive a stable dose of an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker for at least 4 weeks before randomization. At the trial conclusion a median follow-up was 2.6 years. The study was halted at 2.6 years due to early achieving prespecified efficacy criteria with canagliflozin. Secondary outcomes of this study including all-cause mortality were planned for sequential hierarchical testing. Between groups, there was a non-statistically significant difference for CV death outcome so subsequent outcomes including all-cause mortality was not formally tested. At the termination of the trial, the all-cause mortality was reported as, 29.0 vs. 35.0 per 1000 patient-years (HR 0.83; 95% CI 0.68–1.02; P not given) for the intervention and placebo groups, respectively (Table 2). The author did not provide an estimation

of precision for all-cause mortality outcome. The ARR of this study was calculated to be 0.6% and the RRR was 17.1%. The calculated NNT was determined to be 167 which showed a small treatment effect. This difference is hence not clinically significance (Table 3).

In Yale et al. study, all subjects either received canagliflozin 100 or 300 mg or placebo daily. This 52-week, randomized, double-blind, placebo-controlled, phase 3 study consisted of an antihyperglycemic agent adjustment period; a 2-week, single-blind, placebo run-in period; a 26-week, double-blind, core treatment period; and a 26-week, double-blind, extension period. Of the 272 randomized subjects, 269 received ≥1 dose of study drug and were included in the ITT analysis population. A total of 35 (12.9%) subjects discontinued before the week 26 visit, with fewer discontinuations in the canagliflozin 300 mg group compared with the canagliflozin 100 mg and placebo groups. A smaller proportion of subjects treated with canagliflozin 100 or 300 mg received glycemic rescue therapy before the week 26 visit compared with those treated with placebo (4.4, 3.3 and 14.3%, respectively). Baseline demographic and disease characteristics were similar across the groups. All-cause mortality rate was 1.1% in both the placebo and the treatment arms (Table 2). The calculated ARR and RRR of this study were both 0 (Table 3). Thus, there is no significant difference in the reduction of all-cause mortality risk observed with canagliflozin relative to the placebo. The author did not provide an estimation of precision for all-cause mortality outcome. In brief, the treatment effect of this study is small. The results of all three studies are summarized in Table 2. This data was reported as the number of deaths during the study interval. This information was presented in dichotomous form as those that died and those in the study that did not. Through this comparison the “control event rate” (CER) was determine as those receiving placebo who died and the “experimental event rate” (EER) as those administered canagliflozin who died. Using these numbers, the relative risk reduction and the absolute risk reduction were calculated. The numbers

need to treat was then computed to find out how many people would have to be treated with canagliflozin in order for one person to be positively affected.

Table 2. Patient Mortality and p-value

Study	Canagliflozin	Placebo	P-value
Neal et al.[1]	17.3	19.5	0.24
Perkovic et al.[2]	29	35	Not given
Yale et al.[3]	1	1	Not given

Table 3. Efficacy of Treatment, Canagliflozin vs. Placebo

Study	CER	EER	RRR	ARR	NNT
Neal et al.[1]	1.95%	1.73%	11%	0.22%	455
Perkovic et al.[2]	3.5%	2.9%	17.1%	0.6%	167
Yale et al.[3]	1.1%	1.1%	0%	0%	undefined

DISCUSSION

This review aims to compare the results of the three RCT trials and provide healthcare workers with information regarding the efficacy of canagliflozin in reducing the risk of all-cause mortality outcomes in type 2 diabetes adults. Patients with diabetes are at high risk of developing serious complications despite having adequate glycemic control and especially after the failure or intolerance of metformin.

The CANVAS (Neal et al.) trial showed that type 2 diabetics with CVD had a lower risk of death from CV causes but no significant difference in lowering the risk of all-cause mortality compared to the placebo. Similarly, the CREDENCE trial (Perkovic et al.) demonstrated the CV benefits of canagliflozin in diabetics with chronic kidney disease but no significant reduction in all-cause mortality rate. Similarly, Yale et al. study also did not show statistically significant result

in all-cause mortality outcome. The three studies included in this review were large randomized and strictly controlled trials with high rates of drug adherence and close monitoring of adverse events, so it is reasonable to draw a conclusion based on these studies that canagliflozin does not provide any benefit in lowering the risk of all-cause mortality in adults with type 2 diabetes. However, there were some differences in the follow-up periods among the trials, for example, CREDENCE was conducted for 2.62 years whereas the median follow-up for the CANVAS trial was 2.4 years and Yale et al. study was 26 weeks. It is possible that more prolonged drug administration can influence and produce different study outcomes than given for a smaller follow-up duration.

In addition, the studies chosen for this review did have certain limitations that need to be considered when interpreting the findings. First, none of the included studies were designed explicitly to assess all-cause mortality outcomes of SGLT2 inhibitors, even though all trials intended to evaluate the safety of SGLT2 inhibitors in patients with type 2 diabetes. Moreover, participants were not screened for subclinical atherosclerotic vascular disease in all three studies so those with asymptomatic CV disease may have not been included in the cohort; this can affect the generalizability of this study. In addition, the involved trials had a broad range of clinical characteristics among them, such as comorbid conditions, disease duration, and follow-up duration, which will undoubtedly lead to heterogeneity. Factors such as patient's comorbid conditions, and lifestyle can impact the results of the study. Third, the Perkovic et al. study was terminated early at a planned interim analysis, which may have limited the power for some secondary outcomes of this study including the all-cause mortality and may impact the effect sizes. Lastly, there were some differences in the exclusion criteria among each study such as various classes of heart failure patients or chronic kidney disease, so it is not known whether the findings

can be generalized to such population. These limitations mentioned above may impair the power of this study. Future long-term study is, thus, warranted to enhance generalizability and validity of the use of canagliflozin in reducing all-cause mortality among adults with type 2 diabetes.

CONCLUSION

In summary, this EBM review evaluated the effects of canagliflozin in reducing the risk of all-cause mortality outcomes in patients with type 2 diabetes compared to matched placebo, and the results demonstrated that patients treated with canagliflozin experienced no significant difference in all-cause mortality lowering effects compared to the placebo. Due to the potential heterogeneity among the included studies, the results of this analysis should be confirmed with new and larger trials in the future to better evaluate all-cause mortality over a longer follow-up period. Discrepancies between study can be reduced by setting stricter inclusion and exclusion criteria. Having patients with similar co-morbid conditions and medical histories could strengthen the study although this might cause a decrease in the sample size. Furthermore, only canagliflozin has been investigated in this study and therefore we cannot generalize the same effect for all SGLT2i. Since the prevalence rates of type 2 diabetes continue to rise, the use of canagliflozin should continue to be studied. The benefits and risks of these medications must be considered carefully before prescribing by clinicians, keeping in mind the most important goal, that is, what is best for the patients.

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