

Mini Review

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Optimizing Cardiovascular and Renal Outcomes with Canagliflozin- A Focus on CANVAS and CRENDENCE Trials

Tarek Samy Abdelaziz* and Salwa Ibrahim

Department of Renal medicine, Cairo university hospitals, Egypt

*Corresponding author: Tarek Samy Abdelaziz, Department of Renal medicine, Cairo university hospitals, Egypt.

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Abstract

Canagliflozin is one of the sodium glucose cotransporters 2 (SLGT2) inhibitors. In addition to its glucose lowering effect, it has cardiovascular and renal protective mechanisms, through decreasing blood pressure, body weight, diuresis and natriuresis. This has translated into beneficial cardiovascular and renal outcome as compared to placebo in two recent large trials. The most pronounced effects occur in patients with moderate and severe albuminuria.

Introduction

Patients with type 2 diabetes mellitus have an accelerated risk of developing cardiovascular morbidity and mortality. The presence of chronic kidney disease constitutes a significant cardiovascular risk. Certainly, there is a thriving need to mitigate cardiovascular risk without causing insult to the kidneys, especially in patients with type 2 diabetes mellitus where both cardiovascular and renal morbidities exist. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are key medications in primary and secondary prevention of cardiovascular diseases. They act to slow the progression of albuminuria in patients with diabetic nephropathy. ACEI and ARBs delay progression to dialysis and decrease mortality in patients in the predialysis stage [1,2]. However, their use in advanced stages of diabetic nephropathy carries the risk of hyperkalaemia, necessitating cautious and judicious titration of doses especially with accelerated progression of nephropathy [1,2]. Sodium glucose co-transporter inhibitors (SLGT2) are evolving agents that have been recently used for the treatment of type 2 diabetes mellitus. Interestingly, they have proved to exert beneficial cardiovascular effects. The exact mechanisms remain to be fully understood.

Cardiovascular effects of SLGT inhibitors in preclinical studies and clinical studies

Cardiac protection of SLGT2 inhibitors may be attributed to the class effects. The beneficial effects could not be explained solely by the improvement in glycaemic control. Empagliflozin was shown to achieve the most pronounced reduction in cardiovascular morbidity and mortality. In the EMPAREG-OUTCOME trial, a 35 %relative risk reduction of hospitalization due to heart failure and 38% reduction of death due to cardiovascular cause [3]. This relative risk reduction is the higher than cardiovascular risk reduction in the CANVAS study of canagliflozin. This may suggest that empagliflozin has a better cardio-protective profile than other SLGT2 inhibitors. However, since there is no head to head comparison of more than one agent of SLGT2 inhibitors family, this hypothesis lacks robust evidence. Several mechanisms have been proposed to explain the SLGT2 inhibitors effects in reducing cardiovascular morbidity and mortality in patients with type 2 diabetes mellitus [4]. The experimental evidence led to several theories that might explain this striking beneficial effect [5]. Diuresis is one of the most important mechanisms that lead to unloading of the left ventricle. SLGT2 inhibitors can induce

diuresis by natriuretic and osmotic effects. Diuresis induced by SGLT2 does not lead to reflex sympathetic activation, unlike loop or thiazide diuretics. Diuresis leads to reduction in systolic blood pressure [4]. Another important theory is fuel switching of the cardiac myocytes from utilizing fatty acid oxidation as the main fuel to utilizing ketone bodies (B hydroxybutyric acid) especially with empagliflozin. Through different mechanisms, SGLT2 inhibitors can lower the blood pressure.

Cardiovascular outcomes CANVAS and CREDESCENCE

Two large studies, assessing cardiovascular outcomes of canagliflozin, have been recently published. The CANVAS

(Canagliflozin Cardiovascular Assessment Study) and its extension the CANVAS-R (Renal) assessed cardiovascular events as a composite primary outcome, while CREDESCENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) study assessed composite cardiovascular outcome as a composite secondary outcome [6]. Both studies have demonstrated lower rates of cardiovascular events in patients receiving canagliflozin. CANVAS has assured FDA regarding cardiovascular safety of the use of Canagliflozin. Interestingly, a pronounced cardiovascular benefit was observed in patients who received canagliflozin as compared to placebo.

Renal outcomes in CANVAS and CREDESCENCE

Table 1: Summary of main differences between CANVAS and CREDESCENCE.

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	CANVAS	CREDESCENCE
Number of randomised patients	Total 10.142, 4330 in CANVAS and 5812 in CANVAS-R 667 centers-30 countries	4401 patients
Main eligibility	T2DM and either: history of symptomatic atherosclerotic cardiovascular disease or high cardiovascular risk	T2DM: Age ≥ 30 years and albuminuric CKD, receiving either ACE or ARBs
Main exclusion criteria	eGFR less than 30 ml per minute per 1.73 m ² of body-surface area	· Suspected kidney disease due to causes other than diabetes mellitus · History of dialysis or kidney transplantation
Mean follow up	188.2 weeks	2.62 years
Early termination-cause	No	Yes- due to interim analysis favouring Canagliflozin
Cardiovascular outcome	· Composite outcome: death from any cardiovascular cause, non-fatal myocardial infarction or non-fatal stroke: less events in Canagliflozin arm (hazard ratio, 0.86; 95% CI, 0.75 to 0.97; P<0.001 for non-inferiority; P=0.02 for superiority)	· Composite outcome of cardiovascular death or hospitalization for heart failure: 31% reduction in the canagliflozin arm (hazard ratio, 0.69; 95% CI, 0.57 to 0.83; P<0.001), cardiovascular death, · Myocardial infarction, or stroke 20 % less in the canagliflozin arm (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P = 0.01). · Hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001)
Renal outcome	· Progression of albuminuria less in the Canagliflozin arm (hazard ratio of 0.73 (95% CI, 0.67 to 0.79)) · The composite outcome of sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes Less in Canagliflozin arm (hazard ratio of 0.60; 95% CI, 0.47 to 0.77)	· composite of end stage kidney disease, kidney transplantation, or persistent estimated GFR of <15 ml per minute per 1.73 m ² s for at least 30 days ,doubling of the serum creatinine level compared to baseline sustained for at least 30 or death from renal disease: lower by 34% in the canagliflozin an group (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001)
Amputation	Increased risk in canagliflozin arm (hazard ratio of 1.97; 95% CI, 1.41 to 2.75))	Slightly increased in canagliflozin group (hazard ratio,1.11; 95% CI, 0.79 to 1.56), however nonsignificant

The CANVAS and CANVAS R showed improvement in a composite renal outcome due to use of canagliflozin as noted in (Table 1). Participants with very low eGFR (less than 30 ml per minute per 1.73 m² of body-surface area) were excluded from this study, unlike CREDESCENCE. Moreover, the levels of albuminuria in the participants of CANVAS were not as high as CREDESCENCE participants. A post-hoc analysis of the CANVAS data revealed an interesting finding [7]. The effect of canagliflozin was more pronounced in patients with moderate and severe albuminuria; delay in loss of renal function was greater in patients with severe albuminuria [7]. This effect was not due to the mere improvement in glycaemic control, other mechanisms contribute to SGLT2 inhibitors action on the kidney and the heart [6,7]. The CREDESCENCE was a large multicentre study designed to examine the effect of canagliflozin on renal outcomes in patients with diabetes and albuminuria chronic kidney disease [6]. This is one of the limitations of the study, as now it is known that

other phenotypes of diabetic kidney disease exist. Non-albuminuria diabetic kidney disease is currently a recognized phenotype in patients with type 2 diabetes, where progression to end stage renal disease occurs regardless of progression of proteinuria [8]. Patients with non- albuminuric kidney disease were not included in this study. Patients were required to be on stable dose of either ACEI or ARB. Potential renal protective mechanisms of SGLT2 inhibitors, other than improved glycaemic control are decompression of the glomerulus and reduction of blood pressure [1,9].

Risk of lower limb amputation

A major concern in CANVAS was the higher rate of amputation. The main risk factor was history of previous amputation, the highest level of amputation was at the level of toes or metatarsals. In CREDESCENCE, however amputation rate was not significantly higher in patients receiving canagliflozin [6]. The reason for

this discrepancy is not exactly clear, but may be explained by the difference in population, as CANVAS participants had established cardiovascular morbidity or high cardiovascular risk as entry criteria [6,7].

Conclusion

Canagliflozin has been shown to reduce adverse cardiovascular and renal outcomes in patients with T2DM. This was clear from both CANVAS and CREDENCE trials. The most pronounced cardiovascular benefit was reduction of mortality from cardiovascular causes. Renal benefits include regression of proteinuria, slowing proteinuria progression and slowing progression to dialysis. Canagliflozin cardiovascular and renal benefits are more obvious in patients with marked albuminuria and when added on top of ACE or ARBs.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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