REVIEW ARTICLE

The Use of Canagliflozin in Diabetes Mellitus Type 2 on Renal Outcome: A Systematic Review

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ABSTRACT

Introduction: One of the leading causes of death in patients with diabetes mellitus is Diabetic Kidney Disease (DKD). Canagliflozin is one of the therapeutic options that can be used to mitigate the progression of DKD. However, the limited existing studies have left the data regarding the effects of canagliflozin on the progression of DKD still unclear. Therefore, a comprehensive study on the efficacy and safety of using canagliflozin in patients with DKD is warranted.
Methods: We performed a systematic search in the PubMed, Cochrane Library, ResearchGate, and Springer for randomized, placebo-controlled trials of the treatment of type 2 diabetes mellitus (T2DM) with canagliflozin that were published. A total of 25 journals were identified, and after excluding irrelevant studies, eighteen studies were ultimately included in this systematic review with total participants of 20,047.
Results: Canagliflozin reduces the rate of estimated glomerular filtration rate (eGFR) decline in patients with diabetes mellitus. The reduction of urinary albumin-to-creatinine ratio (UACR) level was greater in canagliflozin group than in the control group, and the progression of albuminuria was slower in the canagliflozin group than in the control group.
Conclusion: The use of Canagliflozin is considered to be one of the effective therapeutic options for kidney protection in patients with diabetes mellitus who are at risk of chronic kidney disease (CKD).

Keywords: Diabetes; kidney disease; canagliflozin;

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from abnormalities in insulin secretion, insulin action, or both (ADA, 2012). One of the leading causes of death in patients with diabetes mellitus is Diabetic Kidney Disease (DKD) (Weir et al., 2020). It is estimated that approximately 840 million people worldwide suffer from Chronic Kidney Disease (CKD), with an estimated 1.2 million deaths in 2017. CKD is diagnosed when the eGFR falls below 60 mL/min/1.73 m² or the UACR equals or exceeds 30 mg/g for 3 months or more (Sanchez et al., 2022).

Unlike cardiovascular diseases (CV), where many cardioprotective drugs are available, the treatment options for inhibiting the progression of kidney disease associated with diabetes mellitus are more limited (Weir et al., 2020). Canagliflozin is one of the therapeutic options that can be used to prevent the progression of DKD. Canagliflozin belongs to the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors developed for the treatment of T2DM by inhibiting glucose reabsorption in the proximal tubules. Additionally, SGLT2 inhibitors (SGLT2i) increase natriuresis, leading to intravascular volume contraction and altering intra-renal hemodynamics, which may positively contribute to changes in blood pressure, body weight, and albuminuria (Lo et al., 2020).

Several studies have shown that the use of canagliflozin in patients with T2DM can reduce the risk of end-stage kidney disease (ESKD) in patients with CKD and type 2 diabetes mellitus. However, the limited existing studies have left the data regarding the effect of canagliflozin on the progression of DKD still unclear. Therefore, there was a need for a comprehensive study on the efficacy and safety of using canagliflozin in patients with DKD.

METHODS

This study was secondary research in the form of a systematic review. A systematic review is a method that involves a structured examination, evaluation, classification, and categorization of findings from previous research (Hariyati, 2010). Therefore, all data variables were obtained from previously published studies. The data, in the form of literature, were collected and managed using

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the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) method. The data in this study were obtained from previous research studies that had been published in the form of research journals, and collected from the PubMed, Cochrane Library, ResearchGate, and Springer databases. The researchers used the keywords "((Diabetes Mellitus type 2) OR (Diabetes Mellitus Type II)) AND (Canagliflozin) AND ((Renal outcome) OR (Renal Disease) OR (Kidney Disease) OR (Kidney Injury) OR (Renal Impairment) OR (GFR) OR (UACR) OR (Mortality) OR (Adverse event))" for data retrieval, which was conducted on January 9, 2023.

We collected data by comparing renal outcomes and safety in patients with diabetes mellitus who received canagliflozin therapy compared to patients who received a placebo and/or standard therapy. We excluded preprints that were yet to undergo peer-review, case reports, reviews, editorials, correspondences, and commentary types of articles. Data extraction was performed by the reviewers and included author first names, study design, study site, sample size, drug administration, eGFR, UACR, albuminuria, adverse events, and mortality outcomes. An evaluation of the risk of bias was also conducted, and for the assessment of RCTs, the Cochrane RoB2 tool was used.

RESULTS

Search Result

In the identification stage, 447 journals were excluded due to duplication with the same titles. A total of 2116 journals proceeded to the screening stage. Among them, 1580 journals had titles and abstracts that did not align with the intended study. Subsequently, 536 journals underwent comprehensive journal screening, resulting in 189 journals lacking full access and 329 journals having study designs and eligibility criteria inconsistent with the intended study. The outcome yielded 18 journals employing the Randomized Controlled Trial (RCT) methodology.

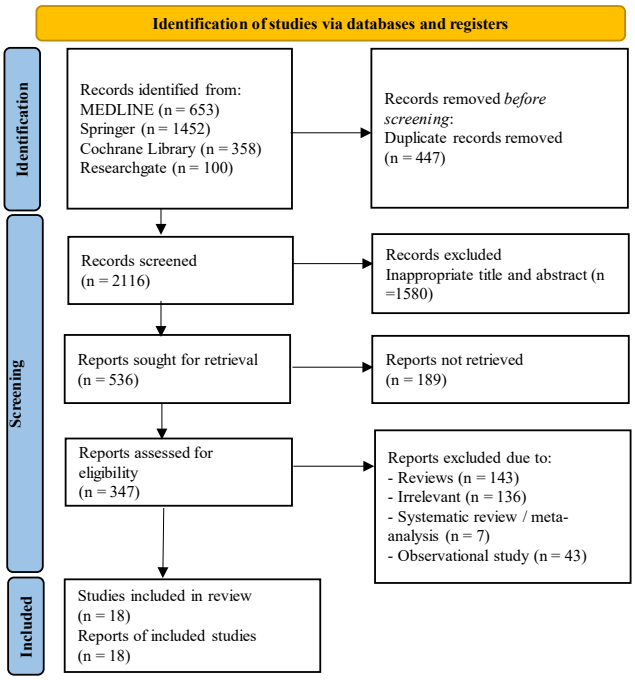

Figure 1. Flowchart of the PRISMA literature selection process.

Characteristic of Involved Study

This review encompassed 18 Randomized Controlled Trials studies (Inagaki et al., 2013, 2016; Schernthaner et al., 2013; Stenlöf et al., 2013; Wilding et al., 2013; Yale et al., 2013; Forst et al., 2014; Qiu, Capuano and Meininger, 2014; Fulcher et al., 2015; Rodbard et al., 2016; Heerspink et al., 2017; Kadowaki et al., 2017; Neal et al., 2017; Perkovic et al., 2018, 2019; Takashima et al., 2018; Oshima et al., 2020; Wada et al., 2022) comprising 20,047 participants with diabetes mellitus who received canagliflozin treatment from various centers. There were 13 international-scale RCTs conducted across more than 5 different countries, while 5 RCTs were conducted in Japan. All study designs were RCTs. The median/mean ages of the subjects exceeded 50 years old in all studies. Additionally, all studies had mean/median eGFR values exceeding 30 ml per minute per 1.73 m^2 of body-surface area.

eGFR

Canagliflozin can reduce the rate of eGFR decline in patients with diabetes mellitus. Five articles reported that the decline in eGFR was slower in the canagliflozin group compared to the control group (Heerspink et al., 2017; Perkovic et al., 2018, 2019; Takashima et al., 2018; Wada et al., 2022). However, two articles reported different findings, indicating a greater decline in eGFR in the canagliflozin group than in the control group (Yale et al., 2013; Fulcher et al., 2015). The most significant reduction in eGFR in the canagliflozin group occurred at the beginning of the intervention and then tended to return to baseline during the treatment period (Yale et al., 2013; Fulcher et al., 2015; Perkovic et al., 2018, 2019). In the study by Wada (2022), a significant difference in the occurrence of a 30% eGFR reduction from baseline was observed at week 104 between the canagliflozin and control groups ($p = 0.029$) (Wada et al., 2022).

UACR

Six articles reported that the reduction in UACR levels was greater in the canagliflozin group than in the control group (Yale et al., 2013; Heerspink et al., 2017; Takashima et al., 2018; Perkovic et al., 2019; Oshima et al., 2020; Wada et al., 2022).

Albuminuria

Four articles reported that the progression of albuminuria (e.g., from normoalbuminuria to micro or macroalbuminuria, or from micro to macroalbuminuria) was smaller in the canagliflozin group compared to the control group (Yale et al., 2013; Neal et al., 2017; Perkovic et al., 2018; Oshima et al., 2020). Meanwhile, albuminuria regression was greater in the canagliflozin group than in the control group (Neal et al., 2017; Oshima et al., 2020).

Adverse Event

Thirteen articles reported that adverse events, as well as serious adverse events, did not show significant differences between the canagliflozin group and the control group (Inagaki et al., 2013, 2016; Schernthaner et al., 2013; Stenlöf et al., 2013; Wilding et al., 2013; Yale et al., 2013; Forst et al., 2014; Qiu, Capuano and Meininger, 2014; Fulcher et al., 2015; Rodbard et al., 2016; Kadowaki et al., 2017; Perkovic et al., 2019; Wada et al., 2022). However, one article reported a significant difference in serious

Tabel 1. Characteristic of involved study

Authors	Study Design	Country	Sample size		Drug Administration	
			Intervention	Control	Intervention	Control
(Forst et al., 2014)	RCT	International	113	115	Canagliflozin 100 mg QD + stable doses of metformin and pioglitazone	Placebo QD + stable doses of metformin and pioglitazone, at week 26 placebo switch to 100 mg of sitagliptin QD
			114		Canagliflozin 300 mg QD + stable doses of metformin and pioglitazone	
(Fulcher et al., 2015)	RCT	International	42	45	Canagliflozin 100 mg QD + sulfonylurea	Placebo + sulfonylurea
			40		Canagliflozin 300 mg QD + sulfonylurea	
(Heerspink et al., 2016)	RCT	International	483	482	Canagliflozin 100 mg tablet orally QD + background therapy metformin	Glimepiride uptitrated to 6–8 mg QD + background therapy metformin
			485		Canagliflozin 300 mg tablet orally QD + background therapy metformin	
(Inagaki et al., 2013)	RCT	Japan	82	75	Canagliflozin 50 mg QD	Placebo
			74		Canagliflozin 100 mg QD	
			76		Canagliflozin 200 mg QD	
			75		Canagliflozin 300 mg QD	
(Inagaki et al., 2016)	RCT	Japan	76	70	Canagliflozin 100 mg QD + standard therapy	Placebo + standard therapy
(Kadowaki et al., 2017)	RCT	Japan	70	68	Canagliflozin 100 mg QD + teneligliptin 20 mg	Placebo + teneligliptin 20 mg
(Neal et al., 2017)	RCT	International	5795	4347	Canagliflozin 100 or 300 mg once a day + standard therapy	Placebo or standard therapy
(Oshima et al., 2020)	RCT	International	2202	2199	Canagliflozin 100 mg tablet orally QD	Placebo
(Perkovic et al., 2018)	RCT	International	5795	4347	Canagliflozin 100 or 300 mg QD + standard therapy	Placebo or standard therapy
(Perkovic et al., 2019)	RCT	International	2202	2199	Canagliflozin 100 mg tablet orally QD	Placebo
(Qiu et al., 2014)	RCT	International	93	93	Canagliflozin 50 mg BID + background metformin	Placebo BID + background metformin
			93		Canagliflozin 150 mg BID + background metformin	
(Rodbard et al., 2016)	RCT	International	107	106	Canagliflozin 100 mg QD, increased to 300 mg if met the criteria + background therapy metformin and sitagliptin	Placebo + background therapy metformin and sitagliptin
(Schernthaner et al., 2013)	RCT	International	378	377	Canagliflozin 300 mg QD	Sitagliptin 100 mg QD
(Stenlöf et al., 2013)	RCT	International	195	192	Canagliflozin 100 mg QD	Placebo
			197		Canagliflozin 300 mg QD	
(Takashima et al., 2018)	RCT	Japan	21	21	Canagliflozin 100 mg tablet orally QD	Standard therapy
(Wada et al., 2022)	RCT	Japan	154	154	Canagliflozin 100 mg tablet orally QD	Placebo
(Wilding et al., 2013)	RCT	International	157	156	Canaglidloin 100 mg tablet orally QD + protocol-specified doses of metformin and sulphonylurea.	Placebo + protocol-specified doses of metformin and sulphonylurea.
			156		Canagliflozin 300 mg tablet orally QD + protocol-specified doses of metformin and sulphonylurea.	
(Yale et al., 2013)	RCT	International	90	90	Canagliflozin 100 mg tablet orally QD + standard therapy	Standard therapy
	RCT	International	89		Canagliflozin 300 mg tablet orally QD + standard therapy	

adverse events between the canagliflozin group and the control group (Neal et al., 2017). Five articles reported no significant differences between the canagliflozin and control groups in the incidence of fractures (Inagaki et al., 2013; Rodbard et al., 2016; Kadowaki et al., 2017; Perkovic et al., 2019; Wada et al., 2022) and amputations (Perkovic et al., 2019). One article reported different results, indicating significant differences in the incidence of fractures and amputations between the canagliflozin group and the control group (Neal et al., 2017).

Mortality

Seven studies are reporting on the incidence of death. There was no significant difference in the number of deaths between the canagliflozin group and the control group (Schernthaner et al., 2013; Stenlöf et al., 2013; Yale et al., 2013; Qiu, Capuano and Meininger, 2014; Neal et al., 2017; Perkovic et al., 2019; Wada et al., 2022). However, there were numerical differences in the two studies indicating that the incidence of death was higher in the intervention group than in the control group (Schernthaner et al., 2013; Wada et al., 2022).

DISCUSSION

DKD is associated with the risk of developing ESKD, which requires kidney replacement therapy, and it is an independent risk factor for cardiovascular disease (CV). The choice of therapy to inhibit CKD progression is more limited (Weir et al., 2020). Canagliflozin is one of the therapy options that can be used to control blood sugar in

Tabel 2. Data extraction of eGFR in the involved study

Reference	eGFR	
	Intervention	Control
(Fulcher et al., 2015)	Canagliflozin 100 mg : mean percent changes from baseline –2.5%	Mean percent changes from baseline –4.7%
	Canagliflozin 300 mg : mean percent changes from baseline –9.6%	
(Heerspink et al., 2016)	Canagliflozin 100 mg :The annual slope of eGFR decline was 0.5 ml/min per 1.73 m^2 per year [95% CI], 2.8 to 3.8) (P<0.001 versus glimepiride)	The annual slope of eGFR decline was 3.3 ml/min per 1.73 m^2 per year
	Canagliflozin 300 mg :The annual slope of eGFR decline was 0.9 ml/min per 1.73 m^2 per year (P=0.002 versus glimepiride)	
	least squares mean change from baseline of −2.7 ml/min per 1.73 m^2	least squares mean change from baseline of −5.4 ml/min per 1.73 m^2
	least squares mean change from baseline of −3.9 ml/min per 1.73 m^2	
(Perkovic et al., 2018)	The mean change in eGFR from baseline - last available data : −1.8 ± 0.2 mL/min/1.73 m^2	The mean change in eGFR from baseline - last available data : –3·9 ± 0.2 mL/min/1.73 m^2
	Baseline - week 13 : mean ± standard error GFR acute decrease of –3.1 ± 0.1 mL/min/1.73 m^2	Baseline - week 13 : mean ± standard error GFR acute decrease of –0.7 ± 0.2 mL/min/1.73 m^2
	week 13 - last available data : mean annual long-term increase of 0.3 ± 0.1 mL/min/1·73 m^2/year	week 13 - last available data: mean annual long-term decline of –0.9 ± 0.1 mL/min/1.73 m^2/year
(Perkovic et al., 2019)	First 3 week : The decline in the estimated GFR (–3.72±0.25 ml per minute per 1.73 m^2)	First 3 week : The decline in the estimated GFR (–0.55±0.25 ml per minute per 1.73 m^2)
	The decline in the estimated GFR (–1.85±0.13 ml per minute per 1.73 m^2 per year)	The decline in the estimated GFR (–4.59±0.14 ml per minute per 1.73 m^2 per year)
	The least-squares mean (±SE) change in the estimated GFR slope (–3.19±0.15 ml per minute per 1.73 m^2 per year)	The least-squares mean (±SE) change in the estimated GFR slope (–4.71±0.15 ml per minute per 1.73 m^2 per year)
(Takashima et al., 2018)	LS mean changes in eGFR at the end of the study were 0.7 mL/min/1.73 m^2 (p = 0.024)	LS mean changes in eGFR at the end of the study were −3.4 mL/min/1.73 m^2 (p = 0.024)
(Wada et al., 2022)	The change from baseline to week 104 (least square mean ± standard error) was −10.39 ± 0.83 mL/min/1.73 m^2	The change from baseline to week 104 (least square mean ± standard error) was −11.49 ± 0.83 mL/min/1.73 m^2
(Yale et al., 2013)	Canagliflozin 100 mg : LS mean percent changes from baseline –9.1% (-3.6 ml/min per 1.73 m^2)	LS mean percent changes from baseline –4.5% (-1.4 ml/min per 1.73 m^2)
	Canagliflozin 300 mg : LS mean percent changes from baseline –10.1% (-3.9 ml/min per 1.73 m^2)	

Tabel 3. Data extraction of UACR in the involved study

Reference	UACR	
	Intervention	Control
(Heerspink et al., 2016)	Relative to glimepiride, canagliflozin 100 mg decreased UACR by 5.7% (95% CI, −2.3 to 13.1; P=0.16) and canagliflozin 300 mg decreased UACR by 11.2% (95% CI, 3.6 to 18.3; P<0.01).	
(Oshima et al., 2020)	Canagliflozin increased the odds of experiencing a >30% reduction in UACR (OR, 2.69; 95% CI, 2.35 to 3.07; P<0.001), and decreased the odds of a ≥30% increase in UACR (OR, 0.41; 95% CI, 0.36 to 0.48; P<0.001) at week 26	
(Perkovic et al., 2019)	Mean of the UACR was lower by 31% (95% CI, 26 to 35) in the canagliflozin group	
(Takashima et al., 2018)	UACR decreased significantly from 139 (67–1506) mg/gCr at baseline to 38 (20–675) mg/gCr at week 52 in the canagliflozin group (p < 0.0001)	unchanged in the control group, with values of 159 (58–1156) mg/gCr and 194 (63–1050) mg/gCr at baseline and week 54 (p < 0.0001)
	The mean changes in UACR were −83 (−266 to −31) mg/gCr (p = 0.004)	The mean changes in UACR were 27 (−11 to 131) mg/gCr (p = 0.004)
(Wada et al., 2022)	The geometric mean change in UACR at week 104 from baseline was −38.8% (95% CI −47.5 to −28.6)	The geometric mean change in UACR at week 104 from baseline was 17.8% (95% CI 1.0–37.3)
	The geometric mean of UACR was 48.0% lower (95% CI 35.4–58.2, P < 0.001) in the canagliflozin group than in the placebo group at week 104.	
(Yale et al., 2013)	Canagliflozin 100 mg : median percent reduction of -29.9%	Median percent reduction of -7.5%
	Canagliflozin 300 mg : median percent reduction of -20.9%	

patients with diabetes mellitus and is considered to have a positive effect on the development of DKD. Based on RCT studies, several studies have shown positive results regarding renal outcomes in the canagliflozin group. There is a positive renal outcome effect in the canagliflozin group, such as a reduction in albuminuria progression, an increase in albuminuria regression, a decrease in UACR levels, and a slower decline in eGFR levels. In some studies, it was found that there was a greater decline in eGFR at the initiation of canagliflozin treatment in participants. The underlying mechanism for this phenomenon may be the renoprotective nature of this class of agents. The effect of canagliflozin on increasing afferent arteriolar tone is by manipulating tubuloglomerular feedback, thereby reducing intraglomerular pressure through parallel and complementary mechanisms with renin-angiotensin system (RAS) blockade. Clinically, this is reflected in the decline in eGFR at the initiation of SGLT2 inhibitor use, followed by stabilization and maintenance of kidney function, as demonstrated in trials of canagliflozin and other agents in its class (Neuen et al., 2018). Therefore, based on the positive results mentioned above, canagliflozin may offer a new treatment option for high-risk type 2 diabetes patients at risk of kidney failure (Heerspink et al., 2017).

Tabel 4. Data extraction of progression and regression of albuminuria in the involved study

Reference	Progression Albuminuria		Regression Albuminuria	
	Intervention	Control	Intervention	Control
(Neal et al., 2017)	89.4 participants with an event per 1000 patient-years	128.7 participants with an event per 1000 patient-years	293.4 participants per 1000 patient-years	187.5 participants per 1000 patient-years
(Oshima et al., 2020)	122 participant (OR, 0.52; 95% CI, 0.41 to 0.66; P<0.001)	214 participant (OR, 0.52; 95% CI, 0.41 to 0.66; P<0.001)	384 participant (OR, 1.85; 95% CI, 1.55 to 2.22; P<0.001)	244 (OR, 1.85; 95% CI, 1.55 to 2.22; P<0.001)
(Perkovic et al., 2018)	new onset albuminuria: 100·4 per 1000 patient-years	new onset albuminuria: 130·8 per 1000 patient-years	NA	NA
	new onset microalbuminuria: 96·7 per 1000 patient-years	new onset microalbuminuria: 127·3 per 1000 patient-years	NA	NA
	new onset macroalbuminuria: 15·1 per 1000 patient-years	new onset macroalbuminuria: 27·6 per 1000 patient-years	NA	NA
(Yale et al., 2013)	Progression of albuminuria from baseline to week 26 was examined was 5.1%	Progression of albuminuria from baseline to week 26 was examined was 11.1%	NA	NA
	Progression of albuminuria from baseline to week 26 was examined was 8.3%		NA	NA

Tabel 5. Data extraction of adverse event in the involved study

Reference	All adverse event		Fracture		Amputation	
	Intervention	Control	Intervention	Control	Intervention	Control
(Forst et al., 2014)	Canagliflozin 100 mg AEs : 79 participant	AEs : 88 participant	NA	NA	NA	NA
	Canagliflozin 300 mg AEs : 87 participant					
	Canagliflozin 100 mg serious AEs : 22 participant	Serious AEs : 27 participant				
	Canagliflozin 300 mg serious AEs : 33 participant					
(Fulcher et al., 2015)	Canagliflozin 100 mg AEs : 11 participant	AEs : 30 participant	NA	NA	NA	NA
	Canagliflozin 300 mg AEs : 18 participant					
	Canagliflozin 100 mg serious AEs : 0 participant	Serious AEs : 4 participant				
	Canagliflozin 300 mgserious AEs : 3 participant					
(Inagaki et al., 2013)	AEs : 37 participant	AEs : 26 participant	NA	NA	NA	NA
	AEs : 34 participant					
	AEs : 38 participant					
	AEs : 34 participant					
(Inagaki et al., 2016)	AEs : 51 participant	AEs : 46 participant	0 participant	1 participant	NA	NA
	Serious AEs : 3 participant	Serious AEs : 1 participant				
(Kadowaki et al., 2017)	AEs : 42 participant	AEs : 32 participant	1 participant	0 participant		
	Serious AEs : 1 participant	Serious AEs : 2 participant				
(Neal et al., 2017)	Serious AEs : 104.3 participants with an event per 1000 patient-years (p = 0.04)	Serious AEs : 120.0 participants with an event per 1000 patient-years (p = 0.04)	All fractures : 15.4 participants with fracture per 1000 patient-years (p = 0.003)	All fractures : 11.9 participants with fracture per 1000 patient-years (p = 0.003)	Amputation of toes, feet, or legs (6.3 participants with amputation per 1000 patient-years (p < 0.001)	Amputation of toes, feet, or legs 3.4 participants with amputation per 1000 patient-years (p < 0.001)
			Low-trauma fracture : 11.6 participants with fracture per 1000 patient-years (p = 0.005)	Low-trauma fracture events 9.2 participants with fracture per 1000 patient-years (p = 0.005)		
(Perkovic et al., 2019)	AEs : 1784 participant	AEs : 1860 participant	67 participant	68 participant	70 participant	63 participant
	Serious AEs : 737 participant	Serious AEs : 806 participant				
(Qiu et al., 2014)	Canagliflozin 50 mg AEs : 33 participant	AEs : 34 participant	NA	NA	NA	NA
	Canagliflozin 150 mg AEs : 38 participant					
	Canagliflozin 50 mg serious AEs : 0 participant	Serious AEs : 1 participant				
	Canagliflozin 150 mg serious AEs : 3 participant					
(Rodbard et al., 2016)	AEs : 43 participant	AEs : 48 participant	0 participant	1 participant	NA	NA
	Serious AEs : 2 participant	Serious AEs : 2 participant				
(Schernthaner et al., 2013)	AEs : 289 participant	AEs : 293	NA	NA	NA	NA
	Serious AEs : 24 participant	Serious AEs : 21 participant				
(Stenlöf et al., 2013)	Canagliflozin 100 AEs : 119 participant	AEs : 101 participant	NA	NA	NA	NA
	Canagliflozin 300 AEs : 118 participant					
	Canagliflozin 100 mg serious AEs : 8 participant	Serious AEs : 4 participant				
	Canagliflozin 300 mg serious AEs : 2 participant					
(Wada et al., 2022)	AEs : 143 (92.9%) participant	AEs : 140 (90.9%) participant	4 (2.6%) participant	9 (5.8%) participant	NA	NA
	Serious AEs : 43 (27.9%) participant	Serious AEs : 33 (21.4%) participant				
(Wilding et al., 2013)	Canagliflozin 100 mg AEs : 106 participant	AEs : 111 participant	NA	NA	NA	NA
	Canagliflozin 300 mg AEs : 114 participant					
	Canagliflozin 100 mg serious AE : 7 participant	Serious AEs : 13 participant				
	Canagliflozin 300 mg serious AEs : 8 participant					
(Yale et al., 2013)	Canagliflozin 100 mg AEs : 71 participant	AEs : 67 participant	NA	NA	NA	NA
	Canagliflozin 300 mg AEs : 66 participant					
	Canagliflozin 100 mg serious AEs : 10 participant	Serious AEs : 16 participant				
	Canagliflozin 300 mg serious AEs : 10 participant					

Tabel 6. Data extraction of mortality in the involved study

Reference	Mortality	
	Intervention	Control
(Neal et al., 2017)	17.3 per 1000 patient-years	19.5 per 1000 patient-years
(Perkovic et al., 2019)	168	201
(Qiu et al., 2014)	0	0
	1	
(Schernthaner et al., 2013)	2	0
(Stenlöf et al., 2013)	1	1
	0	
(Wada et al., 2022)	4	1
(Yale et al., 2013)	1	1
	0	

The incidence of adverse events (AEs) and serious adverse events (SAEs) was similar between the canagliflozin and placebo groups. Overall, the rate of AEs was nearly identical between the two groups (Wada et al., 2022). This indicates that the use of canagliflozin is relatively safe for patients with type 2 diabetes mellitus.

There is an increased risk of fracture and amputation events in the canagliflozin group compared to the control group (Neal et al., 2017). However, in five different studies, no significant difference was found in the incidence of fractures (Inagaki et al., 2013; Rodbard et al., 2016; Kadowaki et al., 2017; Perkovic et al., 2019; Wada et al., 2022). Canagliflozin is associated with an increased risk of fractures, particularly in the upper and lower extremities, driven by a significantly higher rate of fractures in patients at increased risk of cardiovascular disease (CANVAS). Patients in pooled non-CANVAS studies did not experience an increased risk of fractures with canagliflozin treatment. Although the cause of the increased fracture risk with canagliflozin is unknown, small and inconsistent changes in total hip Bone Mineral Density (BMD) (but not BMD at the femoral neck, lumbar spine, or distal forearm) observed with canagliflozin over 104 weeks and the fact that early increases in fractures were observed only in subgroups of patients treated with canagliflozin suggest that extrinsic factors related to canagliflozin, possibly related to falls or other indirect effects of canagliflozin on bone strength, may explain the observed differences in outcomes (Watts et al., 2016). Similar rates of amputations and fractures observed in the canagliflozin and placebo groups are supported by other SGLT2 inhibitor trials (Zinman et al., 2015; Inzucchi et al., 2018; Wiviott et al., 2019), but differ from the findings of the CANVAS Program (Neal et al., 2017). It is still unclear whether the increased risk of lower limb amputations in the CANVAS Program is due to differences in trial populations, protocols, or chance. The overall safety profile in this trial is consistent with known side effects associated with canagliflozin (Perkovic et al., 2019).

There was no significant difference in the number of deaths between the canagliflozin group and the control group. However, there was a numerical difference in two studies showing a higher incidence of death in the intervention group than in the control group (Schernthaner et al., 2013; Wada et al., 2022). It is known that this numerical difference in the number of deaths was not caused by the administration of canagliflozin. In a study conducted by Schernthaner (2013), one death was due to respiratory arrest and cardiac arrest, while the other death was caused by cardiac arrest (Schernthaner et al., 2013). In Wada's (2022) study, one death occurred on the 2nd day of the treatment period, while another death was due to suicide (Wada et al., 2022).

This systematic review utilized recent randomized controlled trials to depict the efficacy and safety of canagliflozin in patients with Type 2 diabetes mellitus regarding renal clinical outcomes. However, variations in sample collection methods, uneven participant numbers, and concomitant therapy differences that can influence the outcomes in each study may also impact the conclusions drawn from this systematic review.

CONCLUSION

The use of canagliflozin is considered to be an effective therapeutic option for kidney protection in patients with diabetes mellitus who are at risk of CKD. This is substantiated by the renal protective effects demonstrated by canagliflozin, including a slowdown in the decline of eGFR values, a reduction in UACR stage, a decrease in the incidence of albuminuria progression, and an increase in albuminuria regression rates. However, conclusions regarding amputation and fracture outcomes remain inconclusive and require further evaluation. The use of canagliflozin in patients with Type 2 diabetes mellitus at risk of DKD is relatively safe, as there were no safety issues identified in the canagliflozin usage safety profile compared to the control group.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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This study did not receive any funding.

AUTHOR CONTRIBUTION

VH developed conceptualization, data curation, writing - original draft, writing - review. SS and PW developed writing - original draft, visualization, writing - review & editing. JP developed manuscript validation, and supervision. All authors approved the final manuscript.

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