Canagliflozin Slows Progression of Renal Function Decline Independently of Glycemic Effects

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ABSTRACT

Sodium-glucose cotransporter 2 inhibition with canagliflozin decreases HbA1c, body weight, BP, and albuminuria, implying that canagliflozin confers renoprotection. We determined whether canagliflozin decreases albuminuria and reduces renal function decline independently of its glycemic effects in a secondary analysis of a clinical trial in 1450 patients with type 2 diabetes receiving metformin and randomly assigned to either once-daily canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride uptitrated to 6–8 mg. End points were annual change in eGFR and albuminuria over 2 years of follow-up. Glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg groups had eGFR declines of 3.3 ml/min per 1.73 m^2 per year (95% confidence interval [95% CI], 2.8 to 3.8), 0.5 ml/min per 1.73 m^2 per year (95% CI, 0.0 to 1.0), and 0.9 ml/min per 1.73 m^2 per year (95% CI, 0.4 to 1.4), respectively (P<0.01 for each canagliflozin group versus glimepiride). In the subgroup of patients with baseline urinary albumin-to-creatinine ratio ≥30 mg/g, urinary albumin-to-creatinine ratio decreased more with canagliflozin 100 mg (31.7%; 95% CI, 8.6% to 48.9%; P=0.01) or canagliflozin 300 mg (49.3%; 95% CI, 31.9% to 62.2%; P<0.001) than with glimepiride. Patients receiving glimepiride, canagliflozin 100 mg, or canagliflozin 300 mg had reductions in HbA1c of 0.81%, 0.82%, and 0.93%, respectively, at 1 year and 0.55%, 0.65%, and 0.74%, respectively, at 2 years. In conclusion, canagliflozin 100 or 300 mg/d, compared with glimepiride, slowed the progression of renal disease over 2 years in patients with type 2 diabetes, and canagliflozin may confer renoprotective effects independently of its glycemic effects.

Many patients with type 2 diabetes present with hyperglycemia, hypertension, and excess weight, and develop increased albuminuria, all of which increase the risk of micro- and macrovascular complications. Current practice guidelines recommend targeting these risk factors with a range of different drugs.[1] However, despite the many drugs used, many patients do not reach treatment targets and develop potentially preventable micro- and macrovascular complications.

Emerging interest in the role of the kidney in glucose homeostasis has led to the development of sodium-glucose cotransporter inhibitors.[2] These drugs are designed to inhibit sodium-glucose cotransporter 2 (SGLT2), which is located in the S1 segment of the proximal tubule. Previous phase 2 and phase 3 studies have shown that administration of SGLT2 inhibitors augments urinary glucose and sodium excretion and decreases glycated hemoglobin A1c (HbA1c), body weight, and BP in patients with type 2 diabetes.[3,4] Moreover, reductions in albuminuria have been observed after administration of SGLT2 inhibitors.[5,6]

The beneficial effects of SGLT2 inhibitors on multiple cardiovascular and renal risk parameters suggest that SGLT2 inhibitors may confer cardiovascular and renal protection. A recent large clinical trial of the SGLT2 inhibitor empagliflozin demonstrated marked reductions in cardiovascular morbidity and mortality and suggested possible renoprotective effects.[7,8] Whether SGLT2 inhibition slows the progression of kidney function decline independent of its glucose-lowering effect, however, is unknown.

Therefore, the aim of this study was to determine whether SGLT2 inhibition decreases albuminuria and slows the progression of kidney function decline independent of glycemic control by analyzing 2 years of data from a randomized controlled trial comparing canagliflozin and glimepiride.[3]

RESULTS

The study ran from August 28, 2009 until January 30, 2013. As previously reported, 482 patients were assigned to glimepiride, 483 to canagliflozin 100 mg, and 485 to canagliflozin 300 mg. A total of 1161 patients (80.1%) completed the 104-week, double-blind treatment period. At baseline, 230 (15.9%) patients had a urinary albumin-to-creatinine ratio (U_{ACR}) $\geq$30 mg/g. The baseline demographics, clinical and biochemical characteristics, and concomitant medications were similar between the three treatment groups, both in the overall population as well as in the subgroup of patients with $U_{ACR}\geq$30 mg/g (Table 1).

The annual slope of eGFR decline was 3.3 ml/min per 1.73 m^2 per year (95% confidence interval [95% CI], 2.8 to 3.8) in the glimepiride group, 0.5 ml/min per 1.73 m^2 per year (95% CI, 0.0 to 1.0) in the canagliflozin 100 mg group ($P<$0.001 versus glimepiride; Figure 1A), and 0.9 ml/min per 1.73 m^2 per year (95% CI, 0.4 to 1.4) in the canagliflozin 300 mg group ($P=$0.002 versus glimepiride; Figure 1A). Repeated measures analysis showed a least squares mean change in eGFR from

baseline of -5.4 ml/min per 1.73 m^2 (95% CI, -6.2 to -4.5) in the glimepiride group versus -2.7 ml/min per 1.73 m^2 (95% CI, -3.5 to -1.9) and -3.9 ml/min per 1.73 m^2 (95% CI, -4.7 to -3.0) in the canagliflozin 100 and 300 mg groups, respectively (Figure 1A). The eGFR decline was also significantly lower with canagliflozin 100 and 300 mg compared with glimepiride in the subgroup of patients with $U_{ACR}\geq$30 mg/g at baseline (Figure 1B). A sensitivity analysis was conducted using the 4-week follow-up visit (i.e., the first postrandomization visit where eGFR was measured) as a baseline to assess the effect of the acute eGFR outcome of canagliflozin on the subsequent eGFR slope. In the glimepiride group eGFR decline was -2.7 ml/min per 1.73 m^2 per year (95% CI, -3.3 to -2.1), 0.1 ml/min per 1.73 m^2 per year (95% CI, -0.5 to 0.6) in the canagliflozin 100 mg group ($P<$0.001 versus glimepiride), and 0.1 ml/min per 1.73 m^2 per year (95% CI, -0.5 to 0.6) in the canagliflozin 300 mg group ($P<$0.001 versus glimepiride).

In the overall population, the 30% eGFR decline end point was observed in 46 (9.7%) patients in the glimepiride group, 32 (6.7%) in the canagliflozin 100 mg group (hazard ratio, 0.66; 95% CI, 0.42 to 1.04; $P=$0.07), and 43 (9.0%) patients in the canagliflozin 300 mg group (hazard ratio, 0.93; 95% CI, 0.62 to 1.42; $P=$0.75; Figure 2). In the subgroup of patients with $U_{ACR}\geq$30 mg/g, the hazard ratios for the 30% eGFR decline end point were 0.37 (95% CI, 0.15 to 0.90; $P=$0.03) and 0.69 (95% CI, 0.33 to 1.45; $P=$0.33) for the canagliflozin 100 and 300 mg groups, respectively, compared with glimepiride.

U_{ACR} progressively increased over time in the glimepiride group, remained stable in the canagliflozin 100 mg group, and decreased in the canagliflozin 300 mg group in the first year, and then returned to baseline at 2 years (Figure 3A). Relative to glimepiride, canagliflozin 100 mg decreased U_{ACR} by 5.7% (95% CI, -2.3 to 13.1; $P=$0.16) and canagliflozin 300 mg decreased U_{ACR} by 11.2% (95% CI, 3.6 to 18.3; $P<$0.01). In the subgroup of patients with $U_{ACR}\geq$30 mg/g, canagliflozin 100 and 300 mg significantly decreased U_{ACR} over time, by

Table 1. Baseline characteristics of the overall population and a subgroup of patients with $U_{ACR}\geq$30 mg/g

Characteristic	Overall Population			$U_{ACR}\geq$30 mg/g Subgroup		
	Glimepiride (n=482)	Canagliflozin		Glimepiride (n=76)	Canagliflozin	
		100 mg (n=483)	300 mg (n=485)		100 mg (n=76)	300 mg (n=78)
Age, yr	56.3 (9.0)	56.4 (9.5)	55.8 (9.2)	58.5 (8.0)	55.6 (10.2)	55.8 (9.6)
Female, n (%)	219 (45.4)	231 (47.8)	244 (50.3)	28 (36.8)	30 (39.5)	36 (46.2)
HbA1c, %	7.8 (0.8)	7.8 (0.8)	7.8 (0.8)	7.9 (0.8)	7.9 (0.9)	8.0 (0.8)
Diabetes duration, yr	6.6 (5.0)	6.5 (5.5)	6.7 (5.5)	6.9 (4.9)	7.7 (6.6)	8.2 (6.4)
SBP, mmHg	129.5 (13.52)	130.0 (12.40)	129.9 (13.72)	136.7 (12.52)	133.7 (11.79)	133.0 (15.32)
DBP, mmHg	78.9 (8.40)	78.8 (7.98)	79.1 (8.34)	81.7 (9.05)	80.6 (8.98)	80.9 (8.42)
eGFR, ml/min per 1.73 m^2	89.5 (17.5)	89.7 (19.3)	91.4 (19.4)	86.5 (18.5)	91.0 (23.9)	91.1 (23.9)
U_{ACR}, mg/g[a]	8.2 (5.75; 17.98)	8.7 (5.74; 17.52)	8.6 (5.28; 20.64)	60.1 (41.29; 124.91)	56.5 (40.17; 115.49)	75.2 (43.35; 173.11)
ACEI/ARB use, n (%)	303 (62.9)	287 (59.4)	291 (60.0)	49 (64.5)	44 (57.9)	45 (57.7)

Data are mean (SD) unless otherwise indicated. eGFR data at baseline were missing in seven patients in the glimepiride group, six patients in the canagliflozin 100 mg group, and eight patients in the canagliflozin 300 mg group. SBP, systolic BP; DBP, diastolic BP; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]25th and 75th percentile reported.

Canagliflozin Slows eGFR Loss
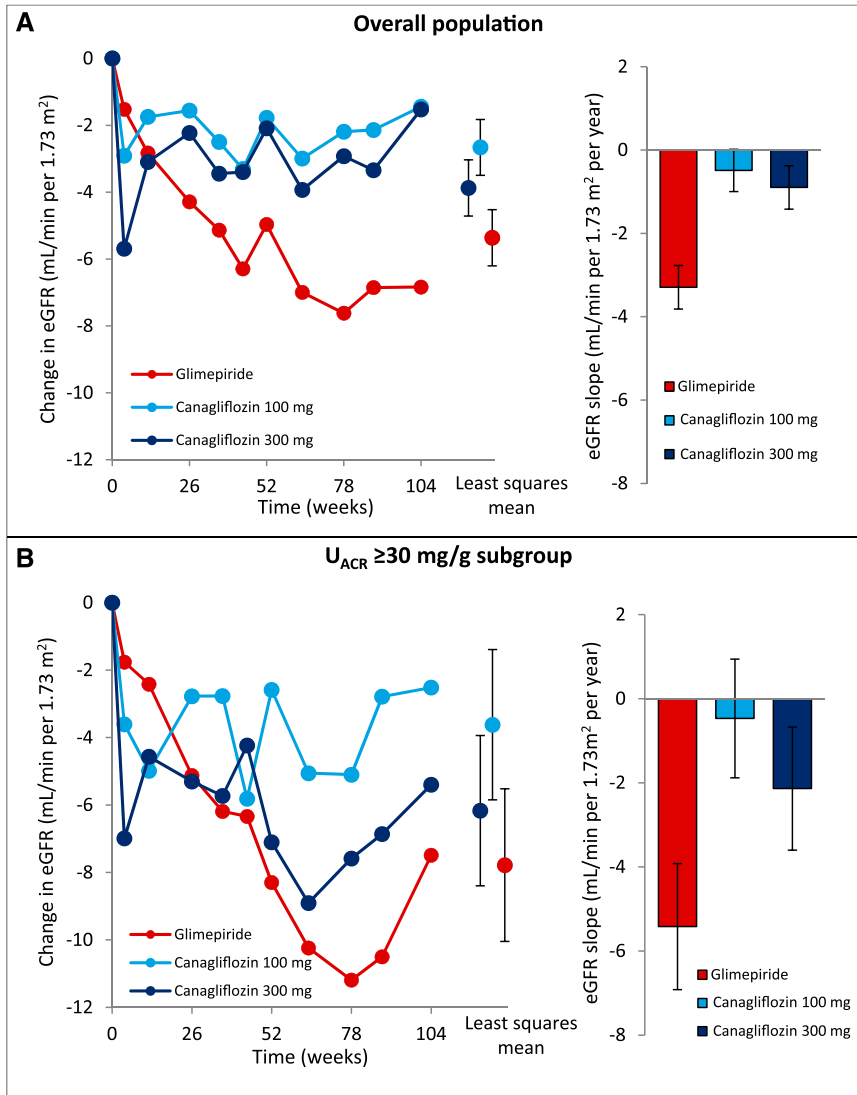
Figure 1. Canagliflozin slows the progression of eGFR decline in patients with type 2 diabetes compared with glimepiride. (A) Changes in eGFR in the canagliflozin and glimepiride treatment arms in the overall population, and the rate of eGFR decline per year. (B) Changes in eGFR in the canagliflozin and glimepiride treatment arms in patients with $U_{ACR} \geq 30$ mg/g, and the rate of eGFR decline per year in patients with $U_{ACR} \geq 30$ mg/g.

31.7% (95% CI, 8.6 to 48.9; $P=0.01$) and 49.3% (95% CI, 31.9 to 62.2; $P<0.001$), respectively, relative to glimepiride (Figure 3B). Effects of canagliflozin on U_{ACR} were consistent regardless of baseline angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (Supplemental Table 1).

Reductions in HbA1c with glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg were 0.81%, 0.82%, and 0.93%, respectively, at 1 year, and 0.55%, 0.65%, and 0.74%, respectively, at 2 years. Changes in systolic BP with glimepiride, canagliflozin 100 mg, and canagliflozin 300 mg were 0.2 mmHg, −3.3 mmHg, and −4.6 mmHg, respectively, at 1 year, and 1.7 mmHg, −2.0 mmHg, and −3.1 mmHg, respectively, at 2 years.
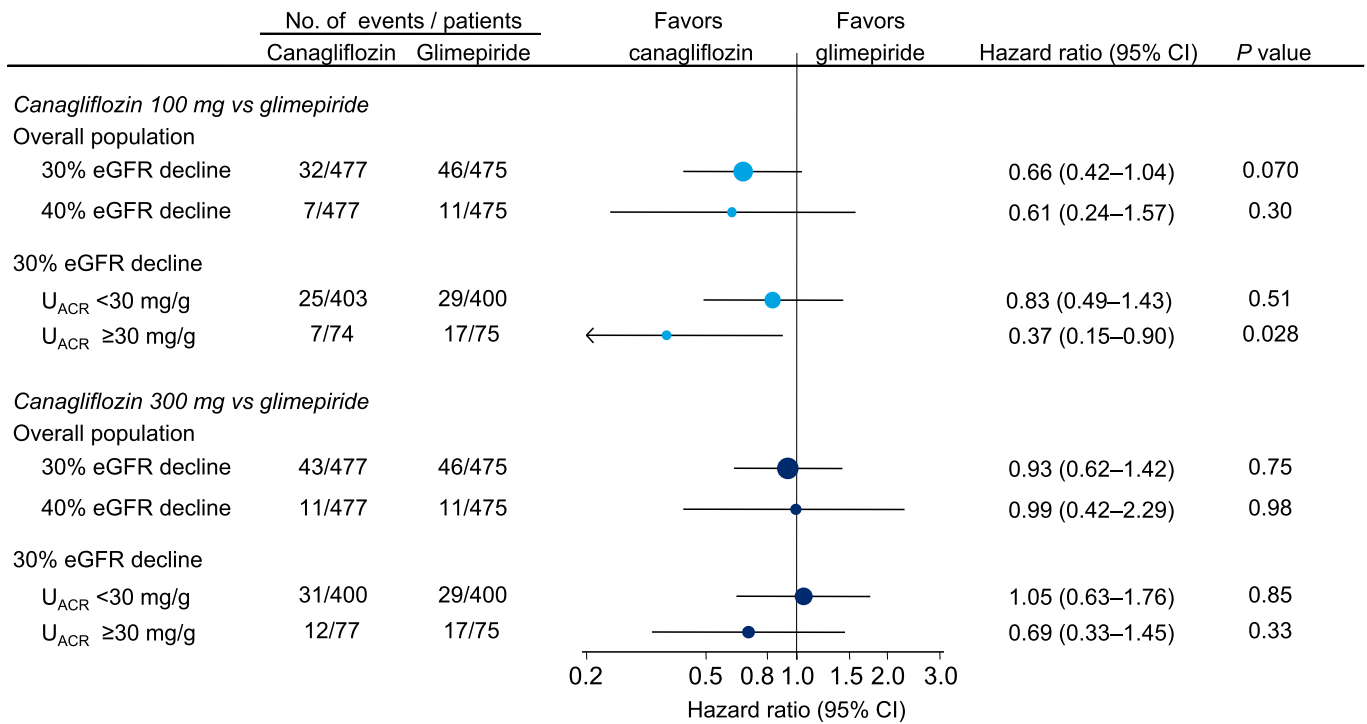
Adjusting the treatment effects of canagliflozin on albuminuria for the differences in HbA1c reductions at 1 and 2 years did not alter the results, nor did adjustment for changes in systolic BP or body weight, or the combined changes in HbA1c, systolic BP, and body weight (Table 2).

With respect to safety, similar proportions of patients across treatment groups experienced adverse events potentially related to kidney function (Table 3). Five patients, all in the canagliflozin groups, experienced an acute renal failure (ARF) or renal failure event. Four of these events were asymptomatic decreases in eGFR that recovered or resolved. One patient, in whom a serious adverse ARF event was reported, died and autopsy revealed a massive pulmonary embolism as a cause of death.

DISCUSSION

This analysis of 2 years of follow-up data from a randomized controlled trial comparing treatment with the SGLT2 inhibitor canagliflozin to glimepiride showed that canagliflozin slows the progression of kidney function decline in patients with type 2 diabetes who are already receiving metformin. In addition, canagliflozin 300 mg significantly decreases albuminuria, particularly in people with increased urinary albumin excretion. The beneficial effects of canagliflozin on kidney function and albuminuria are unlikely to be explained by the modest differential effect on glucose levels, so these findings suggest that SGLT2 inhibitors may be renoprotective, independent of their effects on glycemic control.

As a result of the use of an active comparator arm (glimepiride) in this study, the differences in HbA1c during the trial were modest, and adjustment for changes in HbA1c, BP, and body weight did not alter the results. Although improved glycemic control has been proven to be an important method for reducing the risk of microvascular complications in patients with type 1 and type 2 diabetes on the basis of data from a number of trials,[9–11] these and other trials were not able to show any differences in average kidney function between the treatment arms, despite substantial differences in glycemic control throughout the trials.[12,13] In this study, canagliflozin is superior to glimepiride in preserving kidney function, as defined by eGFR levels, despite smaller between-group differences in glycemic control compared with previous placebo-controlled studies.

	No. of events / patients		Favors canagliflozin	Favors glimepiride	Hazard ratio (95% CI)	P value
	Canagliflozin	Glimepiride				
Canagliflozin 100 mg vs glimepiride						
Overall population						
30% eGFR decline	32/477	46/475			0.66 (0.42–1.04)	0.070
40% eGFR decline	7/477	11/475			0.61 (0.24–1.57)	0.30
30% eGFR decline						
U_{ACR} <30 mg/g	25/403	29/400			0.83 (0.49–1.43)	0.51
U_{ACR} ≥30 mg/g	7/74	17/75			0.37 (0.15–0.90)	0.028
Canagliflozin 300 mg vs glimepiride						
Overall population						
30% eGFR decline	43/477	46/475			0.93 (0.62–1.42)	0.75
40% eGFR decline	11/477	11/475			0.99 (0.42–2.29)	0.98
30% eGFR decline						
U_{ACR} <30 mg/g	31/400	29/400			1.05 (0.63–1.76)	0.85
U_{ACR} ≥30 mg/g	12/77	17/75			0.69 (0.33–1.45)	0.33

Hazard ratio (95% CI): 0.2 0.5 0.8 1.0 1.5 2.0 3.0

Figure 2. eGFR decline >30% or >40% was generally less frequent with canagliflozin compared with glimepiride.
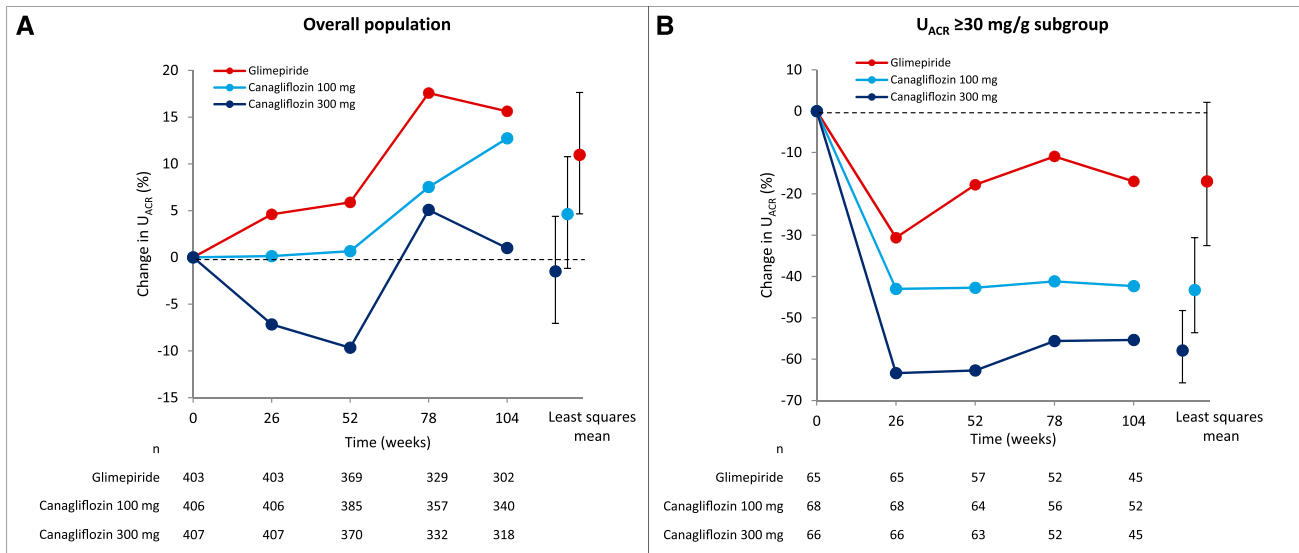
Figure 3. Canagliflozin decreases albuminuria compared with glimepiride. (A) Changes in U_{ACR} in the canagliflozin and glimepiride treatment arms in the overall population. (B) Changes in U_{ACR} in the canagliflozin and glimepiride treatment arms in a subgroup of patients with U_{ACR}≥30 mg/g at baseline.

The magnitude of the reduction in albuminuria with canagliflozin relative to glimepiride was also similar to that previously described with other SGLT2 inhibitors, as compared with placebo. In patients with type 2 diabetes and CKD, empagliflozin decreased albuminuria by approximately 30%, whereas dapagliflozin decreased albuminuria by 33% compared with placebo in patients with type 2 diabetes and micro- or macroalbuminuria treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.[6,14] The albuminuria reduction achieved by empagliflozin was completely reversible 4 weeks after treatment discontinuation, which suggests that albuminuria reduction is mediated

Table 2. Effect of canagliflozin versus glimepiride on albuminuria and eGFR with and without adjustments for covariates

Covariates	Canagliflozin 100 mg Versus Glimepiride		Canagliflozin 300 mg Versus Glimepiride	
	Overall Population	$U_{ACR} \geq 30$ mg/g Subgroup	Overall Population	$U_{ACR} \geq 30$ mg/g Subgroup
eGFR, ml/min per 1.73 m² per year[a]				
None	2.8 (2.1 to 3.5)	5.0 (2.9 to 7.0)	2.4 (1.7 to 3.1)	3.3 (1.2 to 5.4)
ΔHbA1c	2.8 (2.1 to 3.5)	5.0 (2.9 to 7.1)	2.4 (1.7 to 3.1)	3.3 (1.3 to 5.4)
ΔSBP	2.8 (2.1 to 3.5)	5.0 (2.9 to 7.0)	2.4 (1.7 to 3.1)	3.3 (1.2 to 5.4)
ΔBW	2.8 (2.1 to 3.5)	5.0 (2.9 to 7.0)	2.4 (1.7 to 3.1)	3.3 (1.2 to 5.4)
ΔHbA1c; ΔSBP; ΔBW	2.8 (2.1 to 3.5)	5.0 (2.9 to 7.1)	2.4 (1.6 to 3.1)	3.4 (1.3 to 5.5)
eGFR, ml/min per 1.73 m²[b]				
None	2.7 (1.5 to 3.9)	4.2 (1.6 to 7.4)	1.5 (0.3 to 2.7)	1.6 (−1.6 to 4.8)
ΔHbA1c	3.3 (2.1 to 4.5)	4.8 (1.5 to 8.1)	2.1 (0.9 to 3.4)	2.2 (−1.1 to 5.5)
ΔSBP	3.0 (1.9 to 4.2)	4.5 (1.3 to 7.7)	1.9 (0.7 to 3.1)	2.0 (−1.2 to 5.2)
ΔBW	2.8 (1.6 to 4.0)	3.9 (0.7 to 7.2)	1.6 (0.3 to 2.8)	1.4 (−1.9 to 4.6)
ΔHbA1c; ΔSBP; ΔBW	3.7 (2.4 to 5.0)	4.8 (1.5 to 8.2)	2.6 (1.3 to 3.9)	2.2 (−1.2 to 5.6)
Albuminuria, mg/g				
None	−5.7 (−13.1 to 2.3)	−31.7 (−48.9 to −8.6)	−11.2 (−18.3 to −3.6)	−49.3 (−62.2 to −31.9)
ΔHbA1c	−6.2 (−13.5 to 1.7)	−32.3 (−49.2 to −9.7)	−10.9 (−17.8 to −3.3)	−48.6 (−61.6 to −31.2)
ΔSBP	−3.5 (−11.1 to 4.8)	−28.9 (−46.7 to −5.3)	−8.3 (−15.6 to −0.4)	−47.1 (−60.4 to −29.4)
ΔBW	−5.3 (−13.3 to 3.3)	−30.3 (−48.6 to −5.5)	−10.9 (−18.6 to −2.6)	−48.8 (−62.5 to −30.0)
ΔHbA1c; ΔSBP; ΔBW	−5.7 (−13.6 to 2.8)	−28.7 (−47.0 to −4.1)	−9.9 (−17.6 to −1.5)	−46.3 (−60.4 to −27.2)

The least squares mean percent changes (95% CI) from baseline in albuminuria and the least squares mean change (95% CI) from baseline in eGFR over 2 years of follow-up are shown. ΔHbA1c, change in HbA1c; ΔSBP, change in systolic BP; ΔBW, change in body weight.
[a]Expressed as the difference in annual eGFR slope between canagliflozin and glimepiride.
[b]Expressed as the difference in least squares mean eGFR over 2 years of follow-up between canagliflozin and glimepiride.

Table 3. Treatment-emergent kidney-related adverse events during the entire double-blind treatment period

Adverse Event	Glimepiride (n=482), n (%)	Canagliflozin 100 mg (n=483), n (%)	Canagliflozin 300 mg (n=485), n (%)
Total number of subjects with kidney-related adverse events	16 (3.3)	15 (3.1)	16 (3.3)
Blood creatinine increased	5 (1.0)	2 (0.4)	1 (0.2)
GFR decreased	10 (2.1)	11 (2.3)	10 (2.1)
Renal failure	0	1 (0.2)	3 (0.6)
Renal failure acute	0	1 (0.2)	0
Renal impairment	3 (0.6)	0	3 (0.6)

All adverse events are investigator-reported events without adjudication by a separate committee.

through changes in renal hemodynamics.[6] The consistency in results between these studies and the present analysis strongly supports the concept that the reduction in albuminuria has a predominantly glucose-independent mechanism.

What could be the underlying mechanism of any renoprotective effects? Blockade of the SGLT2 transporter inhibits sodium and glucose reabsorption. As a result, the delivery of glucose and sodium is increased in the distal tubule and the juxtaglomerular apparatus, which is sensed as an increase in glomerular perfusion. This leads to a feedback signal that causes afferent arteriolar vasoconstriction, an acute fall in glomerular perfusion and pressure, as well as a diminished extracellular plasma volume and BP.[15] Additionally, these effects reduce atrial natriuretic peptide secretion that may also be important in reducing intraglomerular pressure.[16,17] These effects are clinically manifested as acute reductions in albuminuria and eGFR, followed by stabilization in eGFR in the longer term, and these effects are not observed with other classes of glucose-lowering agents. Thus, SGLT2 inhibitors specifically alter renal hemodynamics and reduce intraglomerular pressure, which could be expected to translate into improved long-term kidney outcomes.

Meta-analyses of large clinical trials have suggested that a 30% reduction in albuminuria might translate into a 30% reduction in the risk of ESRD, assuming no changes in other markers of kidney disease.[18] The effects on eGFR in this study were also similar to those in the placebo-controlled EMPA-REG outcomes trial, where a 55% relative reduction in the risk of ESRD has been reported in a *post hoc* analysis, albeit with a limited number of ESRD cases.[8] These supportive findings will be definitively tested in the ongoing Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (ClinicalTrials.gov identifier: NCT02065791) trial, which is designed to assess whether canagliflozin 100 mg delays or prevents kidney failure or cardiovascular death in patients with type 2 diabetes and established nephropathy.

This study has several limitations. It was not designed nor powered to compare the renoprotective effects of canagliflozin versus glimepiride, so the results should be interpreted as hypothesis-generating. Unfortunately, eGFR was not measured after drug discontinuation in order to verify whether the initial fall in eGFR in the canagliflozin groups was reversible. However, other studies with SGLT2 inhibitors have shown that eGFR returns to baseline values after drug discontinuation.[6,19] In addition, the lack of a placebo arm in this study means that no definitive conclusions can be drawn regarding whether canagliflozin is renoprotective or whether glimepiride worsens the progression of kidney disease. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial showed that lowering HbA1c with a sulfonylurea derivative–based regimen confers renoprotection, suggesting that sulfonylurea derivatives do not accelerate kidney function decline.[20] We note, however, that the rate of eGFR decline in the glimepiride group is higher than what could be expected in a population with preserved kidney function and normoalbuminuria, which may offer an alternative explanation for the beneficial effects of canagliflozin. Also, the effects on albuminuria were particularly marked in people with higher U_{ACR} levels at baseline, and were smaller in those with normal U_{ACR} levels. This is perhaps not surprising, as individuals with high U_{ACR} are more likely to show a reduction in albuminuria compared with people in whom albuminuria levels are already low. Moreover, 61% of all patients received background renin-angiotensin system (RAS) inhibition. Whether the beneficial effects of canagliflozin remain present if all patients receive optimal doses of RAS inhibition remains to be studied, but is likely, since our data showed that the effects of canagliflozin were present regardless of the use of background RAS inhibition. The eGFR course indicates a two-slope model of an acute fall in eGFR, observed after 4 weeks, followed by an attenuation of long-term eGFR decline. eGFR slopes were calculated from baseline in the main analyses instead of using the week-4 eGFR data as baseline to avoid violation of the randomization principle. Finally, eGFR decline was slightly higher with canagliflozin 300 mg versus 100 mg. This may be explained by the larger acute eGFR effects of the 300 mg dose and may also explain why the larger albuminuria reduction in the canagliflozin 300 mg group did not correspond with less kidney function decline.[21,22] A longer follow-up period would be required to completely characterize the effects of canagliflozin on long-term kidney function decline.

In conclusion, in patients with type 2 diabetes, canagliflozin 100 and 300 mg as add-on to metformin slows the progression of disease compared with glimepiride during 2 years of follow-up. Therefore, canagliflozin may offer a novel therapeutic option for patients with type 2 diabetes who are at a high risk of kidney failure.

CONCISE METHODS

Study Design and Participants
The study design has been published previously.[3] In short, this randomized, double-blind, active-controlled trial was conducted in 157 research centers in 19 countries. The study consisted of a 2-week, single-blind, placebo run-in period; a 52-week, double-blind, core treatment period; and a 52-week, prespecified, double-blind, extension treatment period during which patients continued their originally assigned treatment. The 52-week, double-blind, extension period was prespecified to provide a more complete characterization of the efficacy and safety of canagliflozin over 104 weeks of treatment. The prespecified primary efficacy end point was the change in HbA1c from baseline to week 52. The sample size calculation assumed that 277 patients per group would be needed to provide approximately 90% power to show noninferiority of canagliflozin compared with glimepiride for the lowering of HbA1c, with an assumed between-group difference of 0.0% and an SD of 1.0. The primary efficacy results showed that canagliflozin 100 mg was noninferior to glimepiride in reducing HbA1c whereas canagliflozin 300 mg was superior to glimepiride.[3] Eligible patients were between 18 and 80 years of age and had type 2 diabetes with an HbA1c between 7.0% and 9.5% while receiving metformin ≥2000 mg/d (or ≥1500 mg/d if higher doses were not tolerated). Patients with an eGFR of <55 ml/min per 1.73 m^2 (or <60 ml/min per 1.73 m^2 if based on restriction of metformin use in the local label) or serum creatinine concentrations ≥124 μmol/L for men and ≥115 μmol/L for women were excluded. No inclusion or exclusion criteria were specified for albuminuria. Glimepiride was uptitrated if patients met protocol-specified glycemic criteria after ≥2 weeks at the current dose, and uptitration could occur at any time during the study; patients receiving canagliflozin were mock uptitrated. Glycemic rescue therapy was initiated with pioglitazone (where approved) for patients who were at the maximum level of study drug titration and met prespecified glycemic criteria.

The trial was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Ethics committees and institutional review boards approved the research protocol. All patients provided written informed consent before entering the trial. The study was registered with ClinicalTrials.gov (identifier: NCT00968812).

Randomization and Masking
During the run-in period, all patients received single-blind placebo capsules matching the study drug once daily. After the run-in period, patients were stratified according to whether they were taking a stable, protocol-defined dose of metformin before screening versus whether they had undergone dose adjustments in their metformin dose during the run-in period or had discontinued use of a second glucose-lowering drug. Patients were randomly assigned to receive oral, once-daily glimepiride (uptitrated to 6 or 8 mg/d based on the maximum approved dose in the country of the investigational site), canagliflozin 100 mg/d, or canagliflozin 300 mg/d at a 1:1:1 ratio by a computer-generated schedule prepared by the sponsor. Patients and all study personnel (except the safety monitoring committee) were masked to treatment allocation. To allow for masked increases or decreases in the glimepiride dose throughout the double-blind treatment, study drugs were supplied in five levels (levels 1–5).

Procedures
After randomization, patients collected first morning void urine at baseline and weeks 12, 26, 52, 78, and 104 for assessment of U_{ACR}. Urine albumin was measured by a nephelometric assay and creatinine

was measured by a rate-blanked colorimetric assay in a central laboratory (Covance [Indianapolis, IN; Meyrin-Geneva, Switzerland; Singapore]). Serum creatinine and HbA1c were measured at baseline and weeks 4, 12, 18 (HbA1c only), 26, 36, 44, 52, 64, 78, 88, and 104. Serum creatinine was used to calculate eGFR with the Modification of Diet in Renal Disease equation: eGFR = $175 \times (\text{serum creatinine [mg/dl]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$.[21]

Safety was monitored throughout the study by assessing adverse events, laboratory data, vital sign measurements, physical examinations, self-monitoring of blood glucose, and 12-lead electrocardiograms. Reported adverse events were recorded during the trial and analyzed with a standard coding dictionary (*Medical Dictionary for Regulatory Activities*) to classify adverse event terms. Serious adverse events were defined as any adverse event that resulted in death, was immediately life-threatening, required hospital admission or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, was a birth defect, or was an event that jeopardized the patient's health or required intervention.

Outcomes
The main efficacy end point for this *post hoc* analysis was the yearly rate of eGFR decline over the 104 weeks of follow-up. Exploratory efficacy end points were the least squares mean change from baseline in eGFR and U_{ACR} to week 104. The effects on eGFR and U_{ACR} were assessed by comparing mean levels across the treatment period and by assessing the number of individuals who developed a 30% or 40% reduction in eGFR during the study period, as recommended in a recent National Kidney Foundation–sponsored workshop.[22] The effect of the interventions on these end points was assessed in the overall population and in a subgroup that was defined by baseline $U_{ACR} \geq 30$ mg/g (*n*=230). Since all patients had a baseline eGFR >55 ml/min per 1.73 m^2, eGFR subgroups were not examined.

Statistical Analyses
Differences in eGFR and U_{ACR} between randomized groups during follow-up were estimated from repeated measures analysis. Differences between randomized groups in eGFR decline during follow-up were estimated from a mixed-effects model for repeated measures (MMRM). The model included treatment, visit (expressed in time in years since randomization), and treatment-by-visit interaction as factors. The latter was used to estimate the overall between-group difference in eGFR over the course of the study. The MMRM model was also used to calculate the least squares mean change from baseline in eGFR and U_{ACR} over time. For these analyses, baseline eGFR and U_{ACR} were entered as covariates in the model. U_{ACR} was log-transformed before entering in the MMRM analysis to alleviate the skewness of the data. To allow generality for the covariance structure for repeated measures, the variance-covariance matrix was assumed to be unstructured (*i.e.*, purely data-dependent). In the MMRM model, all patients and all data points were included. No patients were excluded due to missing data and no imputation was carried out for missing data.

The effects of randomized treatment on the 30% or 40% eGFR decline end points were estimated from Cox proportional hazard models. Cox proportional hazard models were conducted on the basis of the intention to treat principle. For patients who experienced more than one event during follow-up, survival time to the first 30% or 40%

eGFR decline end point was used in each analysis. Patients were censored at their date of death or, for those still alive at the end of follow-up, the date of their last clinic visit before the termination of this study arm. Patients with unknown vital status were censored when they were last known to be alive. A *P* value <0.05 (two-sided) was considered to indicate a statistically significant difference. Analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC).

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