


Renal haemodynamic and protective effects of renoactive drugs in type 2 diabetes: Interaction with SGLT2 inhibitors

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Abstract

Diabetic kidney disease remains the leading cause of end-stage kidney disease and a major risk factor for cardiovascular disease. Large cardiovascular outcome trials and dedicated kidney trials have shown that sodium-glucose cotransporter (SGLT)2 inhibitors reduce cardiovascular morbidity and mortality and attenuate hard renal outcomes in patients with type 2 diabetes (T2D). Underlying mechanisms explaining these renal benefits may be mediated by decreased glomerular hypertension, possibly by vasodilation of the post-glomerular arteriole. People with T2D often receive several different drugs, some of which could also impact the renal vasculature, and could therefore modify both renal efficacy and safety of SGLT2 inhibition. The most commonly prescribed drugs that could interact with SGLT2 inhibitors on renal haemodynamic function include renin-angiotensin system inhibitors, calcium channel blockers and diuretics. Herein, we review the effects of these drugs on renal haemodynamic function in people with T2D and focus on studies that measured glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) with gold-standard techniques. In addition, we posit, based on these observations, potential interactions with SGLT2 inhibitors with an emphasis on efficacy and safety.

KEYWORDS

calcium channel blockers, diabetic kidney disease, diuretics, RAS inhibitors, renal haemodynamic function, SGLT2 inhibition, type 2 diabetes humans

1 | DIABETIC KIDNEY DISEASE: A ROLE FOR IMPAIRED GLOMERULAR FUNCTION

Diabetic kidney disease (DKD), characterized by increased urinary albumin excretion and/or impaired glomerular filtration rate (GFR), is a common complication of type 2 diabetes (T2D).¹ DKD is the leading cause of kidney failure and a major risk factor for cardiovascular disease

(CVD).² The pathogenesis of DKD is complex and multifactorial, and is associated with risk factors such as hyperglycaemia, obesity, hypertension as well as dyslipidaemia, as reviewed in detail elsewhere.²⁻⁴ Despite optimal treatment with intensive glycaemic control and inhibitors of the renin-angiotensin system (RAS), residual risk for remains high, as shown in the STENO-2 trial.⁵ Glomerular hyperfiltration has long been proposed to be a major contributing factor in the pathogenesis of DKD⁶ and numerous studies reported on the association between whole-kidney hyperfiltration and onset and progression of albuminuria.⁷⁻⁹ In contrast, large-sized studies that estimated GFR did not

[Correction added on 20 February, after first online publication: The reference citations have been updated.]

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TABLE 1 Renal outcomes of large trials with SGLT2 inhibitors, RAS blockers and CCB in people with T2D

Trial	Year	Treatment arms	Patient population	Number of patients	Median follow-up	Renal outcome
SGLT2 inhibitors						
EMPA-REG OUTCOME ¹⁹	2015	Empagliflozin vs placebo	T2D with established CVD	7020	3.1 years	Secondary: composite (macroalbuminuria, dScr, ESKD, renal death); HR 0.61; 95% CI 0.53-0.70
CANVAS Program ²⁰	2017	Canagliflozin vs placebo	T2D who had or were at high risk for atherosclerotic CVD	10 142	3.6 years	Secondary: composite (macroalbuminuria, dScr, ESKD, renal death); HR 0.58; 95% CI 0.50-0.67
DECLARE-TIMI ²¹	2018	Dapagliflozin vs placebo	T2D who had or were at high risk for atherosclerotic CVD	17 160	4.2 years	Secondary: composite (>40% decrease in eGFR to <60 mL/min per 1.73 m ² , ESKD, renal death); HR 0.53; 95% CI 0.43-0.66
CREDESCENCE ²³	2019	Canagliflozin vs placebo	T2D + nephropathy	4401	2.6 years	Composite (dScr, ESKD, renal death); HR 0.66; 95% CI 0.53-0.81
RAS inhibitors						
FACET ⁴⁷	1997	Amlodipine vs fosinopril	Hypertensive T2D	380	3.5 years	Albuminuria change from baseline: Fosinopril -8%; 95% CI -11 to -5
MICRO-HOPE ⁴⁸	2000	Ramipril vs placebo	T2D ± microalbuminuria	3577	4.5 years	Overt nephropathy; RRR 24%; 95% CI 3-40
IDNT ⁴⁹	2001	Irbesartan vs amlodipine vs placebo	T2D + nephropathy	1715	2.6 years	Composite: (dScr, ESKD, death from any cause); RR 0.80; 95% CI 0.66-0.97) vs placebo; RR 0.77; 95% CI 0.63-0.93) vs amlodipine
IRMA-2 ⁵⁰	2001	Irbesartan vs placebo	T2D + microalbuminuria	590	2 years	Time to onset of diabetic nephropathy: 150 mg; HR 0.61; 95% CI 0.34-1.08 300 mg; HR 0.30; 95% CI 0.14-0.61
RENAAL ⁵¹	2001	Losartan vs conventional therapy	T2D + nephropathy	1513	3.4 years	dScr; RRR 25%; 95% CI 8-39 ESKD; RRR 27%; 95% CI 11-42
BENEDICT-A ⁵²	2004	Trandolapril vs verapamil vs combination vs placebo	Hypertensive T2D	1204	3.6 years	Time to onset of microalbuminuria: Trandolapril monotherapy; HR 0.47; 95% CI 0.26-0.83 Trandolapril + verapamil; HR 0.39; 95% CI 0.19-0.80
BENEDICT-B ⁵³	2011	Trandolapril vs trandolapril/verapamil	Hypertensive T2D + microalbuminuria	281	4.5 years	Trandolapril normalized albuminuria independent of verapamil
ADVANCE ⁵⁴	2008	Perindopril/indapamide vs placebo	T2D + micro or macrovascular disease or risk factor	11 140	4.3 years	Risk of new or worsening nephropathy; RRR 18%; 95% CI -1-32; time to onset of microalbuminuria RRR 21%; 95% CI 14-27
ROADMAP ⁵⁵	2011	Olmесartan vs placebo	T2D + preserved kidney function	4447	3.2 years	Time to onset of microalbuminuria; HR 0.77; 95% CI 0.63-0.94
VA NEPHRON D ⁵⁶	2013	Losartan + lisinopril vs monotherapy	T2D + macroalbuminuria	1448	2.2 years	Prematurely stopped owing to safety concerns

TABLE 1 (Continued)

Trial	Year	Treatment arms	Patient population	Number of patients	Median follow-up	Renal outcome
CCB						
<i>FACET</i> ⁴⁷	1997	Amlodipine vs fosinopril	Hypertensive T2D	380	3.5 years	Albuminuria change from baseline: Amlodipine: -11, 95% CI -14 to -8
<i>IDNT</i> ⁴⁹	2001	Amlodipine vs Irbesartan vs placebo	T2D + nephropathy	1715	2.6 years	Composite: (dSCr, ESKD, death from any cause); RR 1.04 95% CI 0.86-1.25) vs placebo
<i>BENEDICT-A</i> ⁵²	2004	Verapamil vs trandolapril vs combination vs placebo	Hypertensive T2D	1204	3.6 years	Time to onset of microalbuminuria: Verapamil monotherapy; HR 0.83; 95% CI 0.45-1.51
<i>BENEDICT-B</i> ⁵³	2011	Trandolapril vs trandolapril/verapamil	T2D ± microalbuminuria	281	4.5 years	Verapamil added on trandolapril did not improve renal outcomes compared to trandolapril or placebo

Abbreviations: CCB, calcium channel blocker; CVD, cardiovascular disease; dSCr, doubling of serum creatinine; eGFR estimated glomerular filtration rate; ESKD, end-stage kidney disease; P/I perindopril/indapamide; RAS renin-angiotensin system; SGLT-2 sodium glucose cotransporter-2; T2D type 2 diabetes; UACR, urinary albumin creatinine ratio.

detect such an association, which may relate to definitions and methods of renal function measurement.¹⁰⁻¹² While glomerular hyperfiltration is often referred to as elevated whole-kidney GFR (eg, >2 SD above mean for age and sex), the number of functioning nephrons should also be taken into account, especially in elderly people with T2D.¹³ In this setting, glomerular hyperfiltration and increased intraglomerular pressure at the single-nephron level may occur while whole-kidney GFR is normal or even reduced due to extensive nephron loss. Thus, they are misclassified as being normofilters based on their apparently normal whole-kidney eGFR.^{3,14} Perhaps the strongest evidence for a role of glomerular hypertension in the pathogenesis of DKD is the fact that interventions that modulate renal haemodynamic function by lowering intraglomerular pressure seem most effective in reducing the DKD burden, including the sodium-glucose cotransporter (SGLT)2 inhibitors.

2 | NEPHROPROTECTION BY SGLT2 INHIBITION: LOWERING OF GLOMERULAR PRESSURE?

SGLT2 inhibitors were initially designed to lower plasma glucose concentrations by blocking reabsorption of filtered glucose in the proximal tubule, thereby inducing glycosuria.¹⁵ The glucose-lowering efficacy of SGLT2 inhibitors is directly related to GFR and degree of hyperglycaemia.^{16,17} In addition, SGLT2 inhibitors improve several renal risk factors independent of GFR and degree of hyperglycaemia, including reductions in blood pressure (BP), uric acid, body weight and urinary albumin-to-creatinine ratio (UACR).¹⁸ Despite the beneficial effects of SGLT2 inhibition on these renal risk factors, the results from three completed cardiovascular (CV) safety trials with SGLT2 inhibitors in people with T2D¹⁹⁻²¹: EMPA-REG OUTCOME (empagliflozin), CANVAS Program (canagliflozin) and DECLARE-TIMI 58 (dapagliflozin)

SUMMARY AT A GLANCE

This invited review describes the renal haemodynamic and protective effects of commonly prescribed drugs in people with type 2 diabetes and their interaction with SGLT2 inhibitors.

were nevertheless surprising. In these trials (Table 1), SGLT2 inhibition lowered renal endpoints by 44% in people with established atherosclerotic disease (hazard ratio [HR], 0.56; 95% CI, 0.47 to 0.67; $P < .0001$) and by 46% in people with multiple CV risk factors (HR, 0.54; 95% CI, 0.42-0.71 $P < .0001$).²² In the dedicated DKD trial CREDENCE (canagliflozin), hard renal outcomes (kidney failure, doubling of serum creatinine, or renal or cardiovascular death) were improved with a relative risk reduction of 34% (HR, 0.66; 95% CI, 0.53-0.81; $P < .001$) and corresponding number needed to treat (NNT) of 22 (95% CI, 15-38).²³

The mechanisms by which SGLT2 inhibitors attenuate renal events remain under extensive discussion and have been reviewed in detail elsewhere.²⁴ One of the haemodynamic factors that could impact renal outcomes is a reduction in blood pressure. SGLT2 inhibitors lower blood pressure in hypertensive adults with T2D regardless of baseline renal function.²⁵ Accordingly, the blood pressure-lowering effects are preserved in the setting of impaired renal function in several separate analyses in T2D patients.²⁶ Until now, it is not yet established how blood pressure lowering occurs with SGLT2 inhibition. Yet, several factors may be involved, including natriuresis, osmotic diuretic effects and a contraction in plasma volume.²⁷ Other factors beyond renal haemodynamic actions have also been proposed to underlie the renoprotective effects of SGLT2 inhibitors, including reduction of serum

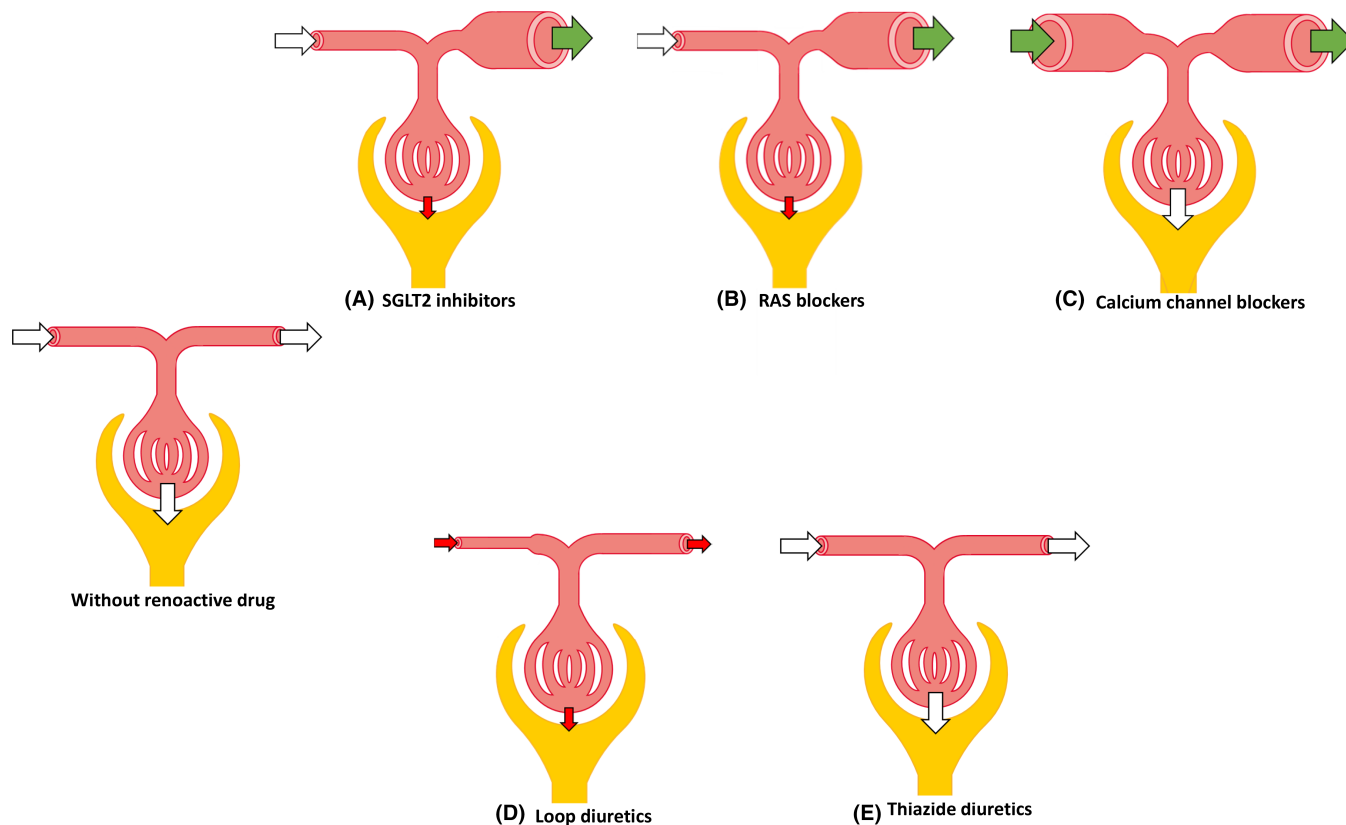


FIGURE 1 Evidence of different renoactive drugs on kidney haemodynamics in people with type 2 diabetes. A, SGLT2 inhibitors, B, RAS blockers, C, calcium channel blockers, D, loop diuretics, E, thiazide diuretics. White arrows indicate no change in glomerular resistance or GFR, green arrows indicate reduction in glomerular resistance, red arrows indicate increase in glomerular resistance or reduction in GFR. GFR glomerular filtration rate; RAS renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2

uric acid, amelioration of renal hypoxia and reductions in glucose levels, however, this is beyond the scope of this review.

Besides blood pressure lowering, a reduction in intraglomerular pressure remains a leading hypothesis for renal protection. This is due to the observation that in clinical practice, SGLT2 inhibitors induce an acute ‘dip’ in GFR in people with T2D, an effect that occurs even after a single dose,²⁸ and is reversible after drug discontinuation.³¹ It has been hypothesized that the drop in GFR is caused by an activation of tubuloglomerular feedback (TGF) response due to higher presence of sodium and chloride at the level of the macula densa. In rodent models of type 1 diabetes (T1D) and in people with T1D with glomerular hyperfiltration (GFR > 135 mL/min/1.73 m²) this led to vasoconstriction of the preglomerular arteriole and GFR lowering.^{29–32} On the other hand, in people with T2D that were older, similar decreases in GFR were induced by post-glomerular vasodilatory effects in two separate studies rather than preglomerular vasoconstriction (Figure 1), indicating genuine renal haemodynamic differences between people with T1D and T2D as well as different effects of SGLT2 inhibition.^{33–35} As such, these studies showed a reduction in renal vascular resistance (RVR) and post-glomerular resistance, while ERPF was not reduced. The results of these studies in adults with T2D were unexpected, as post-glomerular vasodilation has been linked to RAS inhibitors with respect to renal haemodynamic actions, contributing to their renal protective properties (as discussed below).

3 | RENAL HAEMODYNAMIC EFFECTS OF SGLT2 INHIBITION: INTERACTION WITH OTHER DRUGS

A logical question that arises from the previous observations, is how SGLT2 inhibitors might interact with RAS inhibitors regarding renal haemodynamic function, efficacy and safety; questions that could also be broadened to other commonly-prescribed medication.³⁶ In a recent post-hoc analysis of the EMPA-REG OUTCOME study, Mayer et al investigated whether relevant interactions between SGLT2 inhibitor empagliflozin and RAS inhibitors, calcium channel blockers (CCB) and diuretics occurred.³⁶ They reported no significant interactions between these drugs with respect to efficacy and safety, however, the study had several limitations including its post-hoc and exploratory design, small subgroups and potential bias by indication.³⁷

When assessing potential interactions with respect to renal haemodynamic actions of different drugs in people with T2D, it is important to understand the actions of each individual drug class, specifically studied in this population, as baseline characteristics strongly drive response to drug therapy.^{35,38} In previous literature, many conclusions regarding the renal haemodynamic actions of drug classes have been based on data from animal studies or from human studies comprising different populations, including adults with hypertension or T1D.³⁷ In addition, not all studies have assessed renal

haemodynamic function with gold standard methods for GFR and ERPF. Thus, in the present review, we critically review the effects of drugs commonly prescribed to people with T2D, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), CCBs and diuretics, on renal haemodynamic function. Although other actions of SGLT2 inhibitors might be involved in the cardiorenal protection of these drugs, this was beyond the scope of this review. We focused only on clinical studies in adults with T2D in whom renal haemodynamic function was assessed with one of the following gold-standard substances: for GFR: iohexol, inulin, thiosulfate sodium, iothalamate, ^{99m}Tc -diethylenetriaminepentaacetic acid (DTPA), ^{51}Cr -ethylenediaminetetraacetic acid (EDTA), technetium pentetate and for ERPF: para-aminohippuric acid (PAH), iodohippurate, ^{131}I hippuran, ^{123}I orthohippurate or ^{125}I iodohippurate. Based on these data, we speculate on interactions with SGLT2 inhibitors, both concerning efficacy and safety.

4 | RAS INHIBITORS

The renin-angiotensin-aldosterone system (RAAS) regulates blood volume, blood pressure, electrolyte balance, as well as systemic vascular resistance and is mainly activated in times of hypoperfusion as measured by the juxtaglomerular cells and baroreceptors in the carotids and aortic branch.³⁹ Through renin secretion and modulation by ACE, the important effector of the RAAS angiotensin (Ang)-II is activated, leading to vasoconstriction and aldosterone secretion, which stimulates sodium retention.⁴⁰⁻⁴² Furthermore, experimental studies showed that Ang-II plays an important role in the regulation of GFR and renal blood flow (RBF) by constricting renal arterioles.^{43,44} Although both pre- and post-glomerular arterioles are constricted by Ang-II, the efferent arteriole has a greater increase in resistance due to a smaller basal diameter.⁴⁵ The three major classes of drugs that target the RAAS are the ACE inhibitors, the ARB and aldosterone antagonists. ACE inhibitors block the enzyme ACE and therefore reduce the production of Ang-II.⁴⁶ In contrast to the ACE inhibitors, ARB do not reduce Ang II concentrations, but produce a selective, dose-dependent blockade of the AT_1 receptor, independently of the non-ACE pathways of Ang-II generation.⁴² Despite these theoretical differences, the net effect of both ACE inhibitors and ARB is a decrease in total body sodium, total body water and vascular tone, resulting in comparable clinical actions.⁴⁶ As there is no information on interaction between SGLT2 inhibitors and aldosterone antagonists (see the section on potassium-sparing diuretics), we will focus on interaction between SGLT2 inhibitors with ACE inhibitors and ARB, collectively termed RAS inhibitors.

4.1 | Results of RAS inhibitors on renal outcome trials and actions on renal haemodynamic function

Based on their interference with Ang-II production or blockade of the receptor, RAS inhibitors lower blood pressure effectively. In line with this reduction, these agents also reduce CV morbidity and mortality.

In addition, in several trials they were shown to improve renal outcomes as well (Table 1). Since the beneficial renal effects are beyond the impact of blood pressure lowering, RAS inhibitors are suggested to exert beneficial pleiotropic renal effects which have also been linked to a renal haemodynamic phenomenon, in line with the biological effects of Ang-II activation.^{57,58} Given the actions of Ang-II, post-glomerular vasodilation reported in experimental research has been widely thought to contribute to these renoprotective effects. Indeed, data from studies have demonstrated that treatment with RAS inhibitors is associated with an initial fall in eGFR or increase in serum creatinine concentrations in adults with T2D,^{59,60} but whether this reduction in GFR is relevant has been debated ever since. A post-hoc analysis conducted by Clase et al showed an association between an acute RAS-induced GFR decline over the first 2 weeks and higher risk of doubling of creatinine or dialysis, and did not support the long-term stabilization of renal function.⁶¹ Notably, the degree of GFR decline appears to be clinically relevant as well. As such, two meta-analyses reported that the risk of developing kidney failure was higher in patients with a larger estimated GFR decline compared to a smaller or no estimated GFR decline.^{62,63} In contrast, other studies found that in patients using RAS inhibitors a large initial fall in eGFR showed a more stable long-term estimated GFR course compared with patients with a moderate fall or an increase in initial eGFR.^{64,65} Indeed, since this drop has been found to be reversible after discontinuation of the drug, there is no doubt that this phenomenon is of haemodynamic origin due to reduction of intraglomerular pressure rather than treatment-induced damage to functioning nephrons.^{66,67}

The impact of RAS inhibitors on renal haemodynamic function in people with T2D has been investigated in at least 15 studies using gold-standard methods, as shown in Table 2. The majority of the included studies investigated ACE inhibitors, only two studies were using ARB as investigational product. The study population varied between participants who were normotensive with normoalbuminuria and participants with hypertension and macroalbuminuria, and the number of participants as well as the study duration also differed widely among the included trials. Despite this heterogeneity, all studies showed a reduction or no significant change in GFR, beside two studies that reported an increase in GFR, possibly attributed to the opening of additional glomeruli and capillary loops or increased flow.^{68,75} Nearly, all studies showed a reduction in mean arterial pressure (MAP). If GFR would have been reduced by an increase in preglomerular resistance, an increase in RVR would have been expected. However, most studies showed either a reduction or no change in renal vascular resistance (RVR), without decreasing renal RBF. Thus, these results seem to support the proposed mechanism of a post-glomerular vasodilative effect of RAS inhibitors in people with T2D (Figure 1).

4.2 | Combining RAS inhibitors and SGLT2 inhibitors

Two mechanistic trials investigating renal haemodynamic effects of SGLT2 inhibition using gold standard techniques in people with T2D

TABLE 2 Effect of ACE inhibitors and ARB on renal haemodynamic function in people with T2D measured with gold-standard methods

Authors	Year	Treatment arms	Patient population	Intervention	Method (GFR/ERPF)	Effect of RAS blocker			
						MAP	GFR	ERP/RBF	RVR
Price et al ⁶⁸	1999	Irbesartan vs placebo	Hypertensive T2D + macroalbuminuria (n = 12)	Single dose	Inulin/PAH	↓	↔	↑	↔
De'Oliveira et al ⁶⁹	1997	Enalapril vs placebo	Hypertensive T2D (n = 19)	3 days	Inulin/PAH	↓	↔	↑	↔
New et al ⁷⁰	1998	Trandolapril vs placebo	Normotensive T2D (n = 29)	10 days	⁵¹ Cr-EDTA/125-I iodohippurate	0.5 mg: ↔ ↔ 4.0 mg: ↔	↔	↔	↓ ^a ↑ ^a
Stornello et al ⁷¹	1989	Captopril vs nifedipine vs both	Hypertensive T2D + macroalbuminuria (n = 12)	4 weeks cross-over	^{99m} Tc-DTPA/I-131 hippuran	↓	↔	↔	↓
Baba et al ⁷²	1989	Enalapril vs nifedipine	T2D + microalbuminuria (n = 7)	4 weeks cross-over	Thiosulfate sodium/PAH	↓	↔	↔	↔
Ruggenenti et al ⁷³	1999	Perindopril vs nitrendipine	Hypertensive T2D + macroalbuminuria (n = 9)	10 weeks cross-over	Inulin/PAH	↓	↔	↔	↔
Fliser et al. ⁷⁴	2005	Olmesartan vs placebo	Normotensive T2D (n = 35)	12 weeks	Inulin/PAH	↓	↔	↑	↓
Marre et al ⁷⁵	1987	Enalapril vs placebo	Normotensive T2D ± microalbuminuria (n = 20)	6 months	lothalamate/ I-131 hippuran	↓	↑	↑	↓
Valvo et al ⁷⁶	1988	Captopril vs placebo	Hypertensive T2D + microalbuminuria (n = 12)	6 months	lothalamate/ I-131 hippuran	↔	↔	↔	↔
Romero et al ⁷⁷	1992	Captopril vs nifedipine	T2D + macroalbuminuria (n = 20)	6 months	lothalamate/ I-131 hippuran	↓	↓	↔	↓ ^a
Bakris et al ⁷⁸	1992	Lisinopril vs verapamil vs both vs hydrochlorothiazide	T2D + macroalbuminuria (n = 30)	12 months	^{99m} Tc-DTPA /PAH	↓	↓	↑	↓ ^a
CAPEK et al ⁷⁹	1994	Captopril vs placebo	T2D + microalbuminuria (n = 15)	12 months	⁶¹ Cr-EDTA/123-I orthohippurate	↔	↔	↔	↔ ^a
Vora et al ⁸⁰	1996	Captopril vs placebo	T2D + microalbuminuria (n = 8)	12 months	⁵¹ Cr-EDTA/125-I iodohippurate	↓	↔	↔	↓ ^a
Ruggenenti et al. ⁸¹	1994	Enalapril vs nitrendipine	Hypertensive T2D + biopsy proven nephropathy (n=16)	98 days and 1 year	Inulin/PAH	Short term: ↔ ↓ Long term: ↓	↑	↔	NA NA
Slataper et al ⁸²	1993	Lisinopril vs diltiazem vs furosemide + atenolol	Hypertensive T2D (n = 30)	18 months	Technetium pentetate/ Iodohippurate	↓	↔	↔	↓ ^a

Abbreviations: ACE angiotensin-converting enzyme, ARB angiotensin II receptor blocker, T2D type 2 diabetes, GFR glomerular filtration rate, ERPF effective renal plasma flow, RAS renin-angiotensin system, MAP mean arterial pressure, RVR renal vascular resistance, DTPA diethylenetriaminepentaacetic acid, PAH para-amino hippuric acid, EDTA ethylenediaminetetraacetic acid, NA not able to calculate.

^aRVR not reported in manuscript, manually calculated as follows: MAP divided by RBF (not statistically tested).

^bOnly abstract available.

both suggested post-glomerular vasodilation (ie, a reduction in GFR without increasing RVR).^{33,34} As there is enough evidence confirming the proposed mechanism of RAS inhibitors in people with T2D,

combining these two drugs might possibly have an additive effect regarding renal haemodynamic function, as they both would exert their effect on the efferent arteriole. On the other hand, one could

hypothesize that due to overlapping pathways the effects of SGLT2 inhibitors on a RAS inhibitor background are reduced, which would be called sub-additive. However, in both a mechanistic clinical trial and in a post-hoc analysis investigating the effect of SGLT2 inhibitors on cardio-renal risk factors in people with T2D with and without RAS inhibitors, the results were not modulated by the use of RAS inhibitors, suggesting the pre-SGLT2 inhibitor effect of RAS inhibitors to be much less.^{33,83} Similar observations were performed in the large outcome trials and outcomes were not affected by concomitant RAS treatment. However, most patients used RAS inhibitors at baseline (>90%). Consequently, it is difficult to conclude from the outcome trials what the precise effects of SGLT2 inhibition monotherapy are and whether there are relevant interactions when using both drugs. Therefore, trials comparing and/or combining both renoactive drugs (eg, NCT04238702 and NCT03078101) are necessary to put the beneficial effects seen in the outcome trials into perspective. Finally, no additional safety findings were reported in patients treated with SGLT2 inhibitors and RAS inhibitors, such as acute kidney injury (AKI), which seems encouraging from a safety perspective.

5 | CALCIUM CHANNEL BLOCKERS

Calcium channel blockers inhibit the inward movement of extracellular calcium through ion-specific channels that span the cell membrane. Various types of such channels have been identified, however, almost all of them preferentially or exclusively block the L-type voltage-gated calcium channel. The two major classes of L-type-selective CCB are the non-dihydropyridines (eg, verapamil, diltiazem) and the dihydropyridines (eg, amlodipine, nifedipine, lercanidipine). When the influx of calcium is blocked, vascular smooth muscle cells relax, resulting in vasodilation and lowering of blood pressure and heart rate.⁸⁴

5.1 | Results of CCB on renal outcome trials in people with T2D and their actions on renal haemodynamic function

Currently, ACE inhibitors and ARB have been the first choice for treatment of hypertension in people with diabetes or DKD. However, most of these patients require two or more drugs to optimize blood pressure levels, and therefore CCB, are suggested as add-on therapy, mainly because of their strong BP-lowering properties and good tolerability.^{85,86}

In particular non-dihydropyridines CCB (ndCCB) are associated with a reduction in proteinuria by 30%, independent of blood pressure lowering, compared to baseline in hypertensive patients with proteinuric renal disease.⁸⁷ However, the use of CCB to reduce albuminuria in DKD has been discussed, since different results regarding the effect on renal outcomes in people with T2D have been observed (Table 1). The renoprotective effect of RAS inhibitors does not seem to be enhanced by

the addition of verapamil, as shown in the BENEDICT study.⁵² In this primary prevention trial, trandolapril plus verapamil and trandolapril alone decreased the incidence of microalbuminuria to a similar extent. However, the TRAVEND study, where the effect of antihypertensive combinations on metabolic control (HbA1c and blood glucose levels) and albuminuria in people with T2D was investigated, showed that the combination of verapamil plus trandolapril allowed better metabolic control than enalapril plus hydrochlorothiazide (HCTZ).⁸⁸

These uncertain renoprotective effects may be due to the presence of L-type calcium channels at the afferent but not efferent arterioles of the kidney.⁸⁹ L-type CCB cause afferent vasodilation which would theoretically increase GFR and intraglomerular pressure in case of unaffected efferent resistance. This adverse action counteracts their ability to attenuate glomerular hypertension through the systemic reduction in BP and therefore may not always be beneficial in people with CKD.⁹⁰ On the other hand, other CCB, such as mibefradil and efonidipine, block both T- and L-types calcium channels and dilate both afferent and efferent arterioles.⁹¹ In addition, combined L-/N-type CCB, such as cilnidipine, inhibit norepinephrine release from the sympathetic nerve terminal by blockade of N-type calcium channels which innervates both afferent and efferent arterioles, resulting in a decrease in intraglomerular pressure as demonstrated in rat kidney arterioles.^{92,93}

At least 10 studies using gold-standard methods have investigated renal haemodynamic function effects of CCB in people with T2D, as shown in Table 3. The patient populations varied widely among the studies, as well as the used CCB and study duration. In general, the majority of the trials did not report significant changes in GFR and RBF, while all showed significant reductions in both MAP and RVR, suggesting concomitant post-glomerular dilation to maintain stable glomerular pressure (Figure 1). As these trials only used L-type CCB, these findings are in contrast with the hypothesized mechanism of action, that is, selective preglomerular vasodilation, since, in case of unchanged efferent vascular resistance, an increase in GFR and RBF then would have been expected.⁹⁷ Only two studies indeed reported an increase in GFR and RBF and reduction in MAP and RVR.^{81,95}

5.2 | The potential combination of CCB and SGLT2 inhibitors

One could speculate that L-type CCB might counteract the beneficial renal haemodynamic effects caused by SGLT2 inhibitors due to preglomerular vasodilation counteracting the effects of SGLT2 inhibition to reduce GFR, however, CCB's have shown mostly neutral effects on GFR due to concomitant post-glomerular vasodilation. Of course, the small sample sizes and fairly different study designs have to be taken into account when making conclusions in this regard. Moreover, the individual effect of ndCCB, alone or in combination with SGLT2 inhibitors, is likely to be small, since the effect of SGLT2 inhibition on renal haemodynamics was not modulated by CCB and data suggest that the effect of CCB on renal outcomes is modest.^{33,36}

TABLE 3 Effect of CCBs on renal haemodynamic function in people with T2D measured with gold-standard methods

Authors	Year	Treatment arms	Patient population	Intervention	Methods (GFR/ERPF)	Effect of CCB			
						MAP	GFR	RBF	RVR
Baba et al ⁷²	1989	Enalapril vs nifedipine	T2D + microalbuminuria (n = 7)	4 weeks cross-over	Thiosulfate sodium/PAH	↓	↔	↔	↓
Stornello et al ⁷¹	1989	Captopril vs nifedipine vs both	Hypertensive T2D + macroalbuminuria (n = 12)	4 weeks cross-over	DTPA/I-131 hippuran	↓	↔	↔	↓
Baba et al ⁹⁴	1990	Nicardipine vs placebo	Hypertensive T2D ± microalbuminuria or overt nephropathy (n = 18)	4 weeks	Thiosulfate sodium/PAH	Normoalbuminuria: ↓ Microalbuminuria: ↓ Overt nephropathy: ↓	↔ ↔ ↔	↔ ↔ ↑	↓ ↓ ↓
Ruggenti et al. ⁷³	1999	Perindopril vs nitrendipine	Hypertensive T2D + macroalbuminuria (n = 9)	10 weeks cross-over	Inulin/PAH	↓	↔	↔	↔
Baba et al ⁹⁵	1986	Nicardipine vs placebo	Hypertensive T2D + mild-to-moderate or severe DN (n = 12)	6 months	Thiosulfate sodium/PAH	Mild-to-moderate DN: ↓ Severe DN: ↓	↑ ↔	↑ ↔	↓ ↔
Romero et al ⁷⁷	1992	Captopril vs nifedipine	T2D + macroalbuminuria (n = 20)	6 months	lothalamate/I-131 hippuran	↓	↔	↔	↔ ^a
Ruggenti et al ⁸¹	1994	Enalapril vs nitrendipine	Hypertensive T2D + biopsy proven nephropathy	98 days and 12 months	Inulin/PAH	Short term: ↓ Long term: ↓	↔ ↑	↔ ↑	NA NA
Bakris et al ⁷⁸	1992	Lisinopril vs verapamil vs both vs HCTZ	T2D + macroalbuminuria (n = 30)	12 months	DTPA/PAH	↓	↔	↔	↓ ^a
Slataper et al ⁸²	1993	Lisinopril vs diltiazem vs furosemide + atenolol	Hypertensive T2D (n = 30)	18 months	Technetium pentetate/iodohippurate	↓	↔	↔	↓ ^a
Smith et al ⁹⁶	1998	Diltiazem vs nifedipine	Hypertensive T2D + macroalbuminuria (n = 21)	21 months	Inulin/PAH	Both: ↓	↔	↔	↓ ^a

Abbreviations: CCB calcium channel blocker, T2D type 2 diabetes, GFR glomerular filtration rate, ERPF effective renal plasma flow, PAH para-amino hippuric acid, MAP mean arterial pressure, RVR renal vascular resistance, DTPA diethylenetriaminepentaacetic acid, HCTZ hydrochlorothiazide, NA not able to calculate.

^aRVR not reported in manuscript, manually calculated as follows: MAP divided by RBF (not statistically tested).

^bOnly abstract available.

6 | DIURETICS

6.1 | Proposed mechanism of action

Diuretics are a heterogeneous group of drugs, and with the exception of vasopressin receptor antagonists and mannitol, their primary action is to impair sodium reabsorption at different sites along the tubule, thereby increasing urinary excretion of sodium and chloride and inducing increased water excretion.^{98,99} Different types of diuretics are available and this review will focus on loop, thiazide and potassium-sparing diuretics (PSD).

Loop diuretics, such as furosemide, act on the Na-K-2Cl (NKCC2) co-transporter type 2 at the apical surface of the thick ascending limb

cells along the loop of Henle. This transporter reabsorbs up to 25% of filtered salt and its blockade is responsible for most natriuretic effects of loop diuretics.¹⁰⁰ Besides their natriuretic effect, however, it is thought that the blood pressure-lowering effect caused by loop diuretics may be, at least partly, due to a direct vasodilative effect.¹⁰¹

Thiazide and related diuretics inhibit sodium reabsorption by blocking the sodium-chloride co-transporter (NCC) transporter on the apical membrane in the proximal segment of the distal convoluted tubule (DCT),^{62,63} where approximately 5% to 10% of the filtered sodium normally is reabsorbed.¹⁰²

Potassium-sparing diuretics were developed to reduce the risk of cardiac arrhythmias, which can be induced by loop and thiazide diuretics due to increased potassium excretion.⁹⁹ These drugs either

compete with aldosterone for intracellular cytoplasmic receptor sites (eg, spironolactone, eplerenone and finerenone), or directly block epithelial sodium channels (ENaC) in the distal parts of the nephron (eg, amiloride).¹⁰³

6.2 | Results of diuretics on renal outcome trials in people with T2D and their actions on renal haemodynamic function

Diuretics play a major role in the treatment of hypertension and heart failure (HF),¹⁰⁴ two common comorbidities associated with T2D and CKD,^{105,106} and are used either as monotherapy or as part of any combined therapy.¹⁰⁷ Thus far, there is no evidence from large outcome studies or meta-analyses that diuretics are superior to other classes of antihypertensive drugs in reducing CV risk in hypertensive individuals and potential benefits in people with T2D or renal failure remain unclear.¹⁰⁸ Yet, in a post-hoc analysis of the ALLHAT study, data could be extracted from a T2D subgroup, which showed no significant differences in the incidence of total mortality or kidney failure for patients assigned to thiazide-type diuretic chlorthalidone compared to amlodipine or lisinopril.¹⁰⁹ In another study, albuminuria appeared more reduced in patients treated with ACE inhibitor/diuretic (benazepril/HCT) group compared to the ACE inhibitor/CCB (benazepril/amlodipine) group, but this difference was explained by a significantly greater fall in GFR in the benazepril/HCTZ group, resulting in a relatively greater fall in albuminuria.¹¹⁰

Steroidal mineralocorticoid receptor antagonists (MRA), such as spironolactone and eplerenone, are highly efficacious for further reducing albuminuria when added to RAS inhibitors.¹¹¹⁻¹¹³ Blockade of mineralocorticoid receptors has proven clinical efficacy in patients with HF with reduced ejection fraction (HFrEF), hypertension and in CKD with or without T2D.¹¹⁴⁻¹¹⁶ However, steroidal MRAs can cause significant elevation of serum potassium.^{117,118} Therefore, novel, selective non-steroidal MRAs, such as finerenone, are being developed and revealed a lower risk for hyperkalaemia. Finerenone has had promising results with respect to renal endpoints in phase 2 trials. The mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) found a reduction in UACR in patients with HFrEF, while adverse events were mild. The next, phase 2b, ARTS-Diabetic Nephropathy trial showed a dose-dependent reduction in UACR, with the largest reduction (−48%) in the group receiving 20 mg. Currently, two large renal/CV outcome trials are conducted in patients with or without T2D, the FIDELIO and FIGARO trials.^{119,120}

However, whether diuretics per se alter renal haemodynamics in people with T2D is not completely understood as only limited data are available. To our knowledge, only two studies have investigated the long-term effects of diuretic drugs on renal haemodynamic function using gold-standard methods. The first study, conducted in 1993 by Slataper et al,⁸² investigated the effect of loop diuretic furosemide in 30 hypertensive people with T2D, and showed a decrease in GFR, RPF and MAP after 18 months of treatment (Figure 1). As the NKCC2 transporter is located at the luminal membrane of the macula densa

cells, stimulating renin secretion,¹²¹ these results imply a tubuloglomerular feedback (TGF) response of the kidney in these individuals, which also has been reported by others,¹²² but would not have been expected. These effects may be both harmful and beneficial, since elevated plasma renin activity increases angiotensin II, while blocking TGF helps to preserve GFR in individuals with glomerular hyperfiltration.¹²³ In the second study, thiazide-type diuretic, HCTZ, did not alter GFR and RPF, while MAP was decreased, in 30 people with T2D after 12 months of treatment.⁷⁸ These results are in line with the proposed mechanism of action, since the NCC transporter is located distally to the macula densa, which would not impair the TGF response by blockade of this transporter (Figure 1).¹²²

The effect of potassium-sparing diuretics on renal haemodynamic function has not been assessed in people with T2D.

6.3 | The potential combination of diuretics and SGLT2 inhibitors

As stated previously, the underlying mechanisms for the renal benefits of SGLT2 inhibitors remain unclear, but the same can be stated for their beneficial effects on HF outcomes.^{19-21,124} A central hypothesis is that SGLT2 inhibitors induce systemic haemodynamic actions including a diuretic effect, secondary to glycosuria and natriuresis, leading to contraction of plasma and possibly interstitial volume. Therefore, given that both drugs induce natriuresis, interactions could be plausible. Indeed, in the CANVAS program, a marked reduction in the composite CV endpoint was reported with canagliflozin in patients using diuretics at baseline compared to no reduction in patients without a diuretic background therapy.¹²⁵ In contrast, although results of the DECLARE-TIMI 58 trial also suggest a potential interactive effect of diuretics, the observed renal benefits appeared to be the greatest among those who were not on diuretics at baseline.¹²⁶ These results are in contrast with findings of the EPMA-REG OUTCOME trial, in which reductions in HF or renal outcomes were irrespective of diuretic use at baseline.⁴⁶ However, the multiple and post-hoc analyses performed for these trials had limited statistical power to test for interactions, and the risk of missing real differences or observing spurious chance differences is high. Therefore, the clinical significance of these differences remains unclear and these post-hoc subgroup analyses were exploratory at the most.

The effect on volume status of diuretics, alone or compared to SGLT2 inhibitors, in people with T2D remains incompletely understood. A mechanistic study assessed the effects of dapagliflozin, HCTZ and placebo on blood pressure, plasma volume and renal function and concluded that both drugs reduced day-time blood pressure and GFR to the same extent, whereas only dapagliflozin lowered plasma volume by 7%.³⁷ Weber et al investigated the blood pressure-lowering effect of SGLT2 inhibitors in inadequately controlled hypertensive T2D patients and showed that for patients already taking RAS inhibitors and diuretics, the reduction in placebo-adjusted blood pressure with dapagliflozin was smaller compared with those receiving RAS inhibitors and beta-blockers or CCB.¹²⁷ Given the view that

Key messages

- SGLT2 inhibitors and RAAS blockers are the most powerful drugs that reduce the diabetic kidney disease burden
- Both SGLT2 and RAAS blockers both reduce intraglomerular pressure by inducing postglomerular vasodilation; their interaction however is currently unclear.
- Many patients with T2D that use other drugs to optimize blood pressure control including CCBs and thiazide, loop or potassium-sparing diuretics which could also affect renal hemodynamic function
- Clinicians should be aware of potential interactions to minimize risk for hypovolemia and acute kidney injury
- Renoactive drugs do not seem to alter the effect of SGLT2 inhibitors on hard kidney endpoints in large outcome trials

FIGURE 2 Key messages

SGLT2 inhibitors have diuretic-like properties, this finding may have been anticipated, since the additive effect of this drug in patients already receiving thiazide diuretics might be modest. In addition, combining two drugs with diuretic-like properties and a different mechanism (eg, SGLT2 inhibitors and loop diuretics) could increase the risk for volume depletion, although proof for this potential interaction is currently lacking. SGLT2 inhibitors seem to reduce the risk for AKI across trials^{128,129} and no interaction with diuretic use has been observed.⁴⁶ The recently published RECODE-CHF trial investigated the diuretic and natriuretic effect of empagliflozin in combination with loop diuretics in patients with T2D and HF and showed a significant increase in 24-hour urine volume at day 3 and week 6, while the combined effects on renal haemodynamic function remain unknown as measured GFR and effective renal plasma flow have not been measured.^{130,131}

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Inhibitors SGLT2 and RAS are the most effective renoprotective drugs and have most prominent effects on estimated intraglomerular pressure (Figure 2). However, as most patients with T2D need more than

one drug to reach optimal control of renal risk factors, interactions with respect to renal haemodynamic function with different background medication might occur. We have summarized the studies that quantified renal haemodynamic function for the most commonly used drugs in this population. In patients with T2D, SGLT2 inhibitors induce post-glomerular vasodilation, which also seems the mode of action of RAS inhibitors. Whether this same mechanism of action is favourable or results in lower efficacy is unclear at present. CCB do not seem to strongly affect renal outcomes, while at renal haemodynamic level they seem to induce both pre and post-glomerular vasodilation, with no net effect on GFR. Although loop diuretic drugs appear to impact TGF and sodium excretion, their interaction with SGLT2 inhibitors seems limited based on available data from large outcome trials. Despite the fact that both MRA and other glucose-lowering drugs, such as GLP-1 receptor agonists, might affect renal outcomes, mechanistic studies in combination with SGLT2 in T2D are lacking.

Several studies are needed in the future. Mechanistic cross-over design studies with gold-standard quantification of renal haemodynamic function may shed light on interactions that these drugs have. Moreover, with the completion of several large-sized outcome trials, post-hoc analyses of these studies, despite several limitations generally associated with such analyses, could reveal certain

signals. Finally, with the implementation of these drugs in clinical practice, real-world data could be informative. Ultimately, these studies could (a) help to maximize the benefits of these renoactive drugs by choosing the best regimen for a particular patient and (b) help to identify adverse effects such as AKI, volume depletion and other side effects potentially associated with renal haemodynamic drug actions.

CONFLICT OF INTEREST

Petter Bjornstad has acted as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Novo Nordisk and Horizon Pharma. Petter Bjornstad serves on the advisory boards of XORTX and Boehringer Ingelheim. David Z. I. Cherney has received honoraria from Abbvie, AstraZeneca, Bayer, BMS, Boehringer Ingelheim-Lilly, Janssen, Merck, Mitsubishi-Tanabe, Novo-Nordisk, Prometic and Sanofi and has received operational funding for clinical trials from AstraZeneca, Boehringer Ingelheim-Lilly, Janssen, Merck, Novo-Nordisk and Sanofi. Daniël H. van Raalte has acted as a consultant and received honoraria from Boehringer Ingelheim and Lilly, Merck, Novo Nordisk, Sanofi and AstraZeneca and has received research operating funds from Boehringer Ingelheim-Lilly Diabetes Alliance, AstraZeneca and Novo Nordisk; all honoraria are paid to his employer (AUMC, location VUMC). All other authors reports nothing to disclosure.

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How to cite this article: Scholtes RA, van Baar MJB, Kok MD, et al. Renal haemodynamic and protective effects of renoactive drugs in type 2 diabetes: Interaction with SGLT2 inhibitors. *Nephrology*. 2021;26:377-390. <https://doi.org/10.1111/nep.13839>