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REVIEW

Preventing and treating kidney disease in patients with type 2 diabetes

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ABSTRACT

Introduction: Chronic kidney disease (CKD) represents a huge burden in patients with type 2 diabetes (T2DM). This review therefore has the aim of assessing the add-on value of new glucose-lowering agents compared or combined with inhibitors of the renin angiotensin aldosterone system (RAAS) on renal outcomes in T2DM patients.

Areas covered: This article first summarizes the results reported with RAAS inhibitors, mainstay of nephroprotection in T2DM with albuminuria. Second, it describes the positive results with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and, even more impressive, sodium-glucose cotransporter type 2 inhibitors (SGLT2is). Third, besides the potential of combined therapies, it briefly considers some new approaches currently in development.

Expert opinion: RAAS inhibitors exert renoprotective effects beyond their blood pressure lowering effects while SGLT2is, and possibly GLP-1RAs, exert nephroprotection independently of their glucose-lowering activity. These effects were demonstrated not only on surrogate endpoints such as albuminuria and estimated glomerular filtration rate decline, but also on hard endpoints, including progression to end-stage renal disease requiring replacement therapy. The underlying mechanisms are different and potentially complementary on glomerular hemodynamics, arguing for combined therapies. Nevertheless, there is still room for new emerging drugs to tackle CKD in T2DM.

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Chronic kidney disease; GLP-1 receptor agonist; RAS inhibitors; SGLT2 inhibitor; Type 2 diabetes

1. Introduction

Chronic kidney disease (CKD) is a classical complication of diabetes mellitus, which may lead to end-stage renal disease (ESRD) [1]. Its pathophysiology is more complex in type 2 diabetes (T2DM) than in type 1, especially because of the intervention of several other risk factors beyond chronic hyperglycemia: arterial hypertension, abdominal obesity, dyslipidemia, hyperuricemia, which all are associated with insulin resistance, low-grade inflammation and oxidative stress [2,3]. Globally, the burden of diabetes and hypertension considered as the two leading drivers of CKD has increased dramatically worldwide over the past several decades. The number of patients with known diabetes quadrupled between 1980 and 2014 while the number of adults with elevated blood pressure almost doubled between 1975 and 2014. Globally, CKD due to diabetes and CKD due to hypertension contributed to about half and near a quarter of the overall increase in CKD disability-adjusted-life-years, respectively [4]. Hypertension and diabetes are coexisting in the vast majority of patients with T2DM. Making a clear distinction between these two entities (patient primarily hypertensive or diabetic) might be difficult but pragmatically little relevant from a therapeutic point of view. This is illustrated by the fact that a kidney biopsy to prove diabetic nephropathy was not required in all large trials that will be discussed hereafter. The annual incidence of microalbuminuria and albuminuria in patients with T2DM averaged ~ 8%, with an incidence of developing estimated glomerular filtration rate (eGFR) using the Modification of Diet on Renal Disease (MDRD) equation – < 60 ml/min/1.73 m^2 estimated to be ~ 2–4% per year and an annual incidence of ESRD ranging from 0.04% to 1.8% [5]. Over the last two decades, the prevalence of CKD is increasing in patients with T2DM, a paradoxical effect of the better management of cardiovascular risk factors that increases life expectancy in this high-risk population [6]. Thus, both the prevention and early appropriate management of CKD in patients with T2DM currently represents a major challenge [7,8].

Tight glucose control is the first step to prevent microangiopathy, whose early renal biological marker is the development and progression of albuminuria [9]. Evidence also suggests that it can ameliorate eGFR loss and possibly progression to ESRD, yet these benefits appear to be most pronounced when applied to T2DM patients with the early stages of CKD [10]. However, tight glucose control is not easy to reach and maintain in many T2DM patients, requires long-term follow-up to prove its efficacy on hard clinical endpoints and may be insufficient to improve renal outcomes, especially when CKD is already present [11]. Furthermore, CKD may alter the pharmacokinetic parameters of several glucose-lowering agents, an effect that renders their use more difficult or even contraindicated in clinical practice [12,13].

Lowering arterial blood pressure also reduces renal events in patients with T2DM [14]. This effect may be additive to the

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Article Highlights

- Glucose and blood pressure control are essential to prevent CKD in T2DM, an increasing prevalent complication of the disease.
- RAAS blockade, either with ACE inhibitor or ARA II, is the cornerstone of nephroprotection in T2DM, but dual blockade should be avoided for safety reasons.
- Metformin may now be used in patients with CKD (if eGFR > 30 ml/min per 1.73 m^2) and might be associated with a reduced risk of progression of renal impairment.
- New glucose-lowering agents, that is, GLP-1RAs and SGLT2 inhibitors, exert renoprotective effects beyond improvement of glucose control, in combination with RAAS blockers, in T2DM patients at high cardiovascular risk.
- Because SGLT2is reduce hard renal outcomes and not only surrogate endpoints (albuminuria) as GLP-1RAs, they are considered as the best option after metformin in T2DM patients with CKD provided that eGFR is adequate.
- RAAS blockers and SGLT2 inhibitors exert different effects that can protect kidney function, yet the complementary effects on intrarenal hemodynamics appear predominant.
- To reduce the residual risk, new medications are in development targeting low-grade inflammation, oxidative stress, and renal fibrosis, as add-on therapies to existing drugs.

This box summarizes key points contained in the article.

positive effect of intensive glucose control as shown in the ADVANCE trial that tested both strategies [15]. Inhibition of the renin-angiotensin-aldosterone system (RAAS) has proven its ability to prevent and slow down the progression of CKD in diabetic patients, an effect being partially independent of the effect on arterial blood pressure [16]. The benefit is particularly prominent in patients with micro- or macro-albuminuria. According to a network meta-analysis comparing efficacy and safety of blood-pressure lowering agents in adults with diabetes and CKD, RAAS inhibitors were the most effective strategies against ESRD [17].

As add-on therapy, new glucose-lowering agents, especially sodium-glucose cotransporter type 2 inhibitors (SGLT2is) [18–21], showed beneficial renal outcomes in T2DM patients with established cardiovascular disease [22,23]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) also showed positive effects on composite renal outcomes in patients with T2DM [24,25]. These newer glucose-lowering approaches seem to be promising for the prevention and treatment of CKD in patients with T2DM, an effect occurring beyond improvement of glucose control [13,26,27].

Increasing evidence showed that oxidative stress and low-grade inflammation play a major role in diabetic complications; furthermore, renal fibrosis is an emerging entity that contribute to the early development of diabetic kidney disease. These new concepts pave the road to innovative pharmacological approaches currently in development [28,29]. The notion of diabetic nephropathy as a purely vascular disease is outdated and it has become clear that it is a multidimensional, multicellular condition [29].

The aim of the present narrative review is to analyze the effects of the different pharmacological therapies used to prevent or retard the progression of CKD in patients with T2DM. We will successively summarize (i) the effects of inhibitors of the RAAS, the best validated pharmacological approach regarding nephroprotection, (ii) describe the effects of new glucose lowering agents that recently showed promising results on surrogate and clinical renal outcomes, and finally (iii) introduce future therapies currently in development that target innovative mechanisms. As a main objective, the respective add-on value of SGLT2is and GLP-1RAs on renal outcomes will be discussed, both in comparison and in combination with RAAS inhibitors.

2. Inhibitors of the renin-angiotensin-aldosterone system

Blood pressure control is beneficial for both cardiovascular and renal outcomes in T2DM patients [30,31], as it is clearly emphasized in different guidelines in the fields of nephrology [32], diabetes [9], or hypertension [33]. More debated is whether the target levels should be different in patients with and without T2DM [33–36]. It is classically recognized that RAAS inhibition therapies have potential added value compared with other antihypertensive therapies in T2DM patients, especially in patients with (micro)albuminuria [9,32,33]. However, even if RAAS inhibitors have proven some superiority in terms of renal outcomes compared to other antihypertensive agents [17], we must keep in mind that more than one medication will be necessary to adequately control arterial blood pressure in a majority of T2DM patients with hypertension [37,38]. Of note, although beyond the scope of this review paper devoted to renal outcomes, RAAS inhibitors exert potential benefits on other clinically relevant outcomes, notably by reducing the incidence of major cardiovascular events [38–40].

RAAS inhibition can lead to renal protection in an independent way of blood pressure control via different pathways. One of the most important is certainly the effect of RAAS inhibitors on the intraglomerular pressure. Indeed, RAAS inhibitors decreased intraglomerular hypertension by limiting the vasoconstriction of postglomerular arteriole induced by angiotensin II (Figure 1). This effect will lead to a decrease in albuminuria and, at long term, to beneficial effects on kidney function [41]. This so-called 'hemodynamic' effect also explains why starting therapy with RAAS inhibitors frequently goes with an initial slight increase in serum creatinine or decrease in eGFR. This functional decrease in renal filtration is generally limited and reversible. Other mechanisms of action have been suggested to explain renal damage when the RAAS system is activated: increased oxidative stress, endothelial dysfunction, promotion of inflammation, mesangial cell proliferation, and transforming growth factor beta (TGF-β) profibrotic effect [42,43] .

Tables 1 and 2 reviewed some important randomized controlled trials (RCTs) comparing different RAAS inhibitors with placebo or other antihypertensive therapies, respectively. We will limit our analysis to studies with the largest samples (> 250 patients in each arm), focusing on patients with T2DM and, if possible, reporting 'hard' clinical renal endpoints (i.e. doubling of serum creatinine and/or ESRD, usually defined as need for dialysis or renal transplantation).

2.1. Angiotensin converting enzyme inhibitors

The specific role of ACE inhibitors has been first studied in type 1 diabetic patients. It is considered nowadays as the classical therapy for type 1 diabetic nephropathy, already from the early stage of

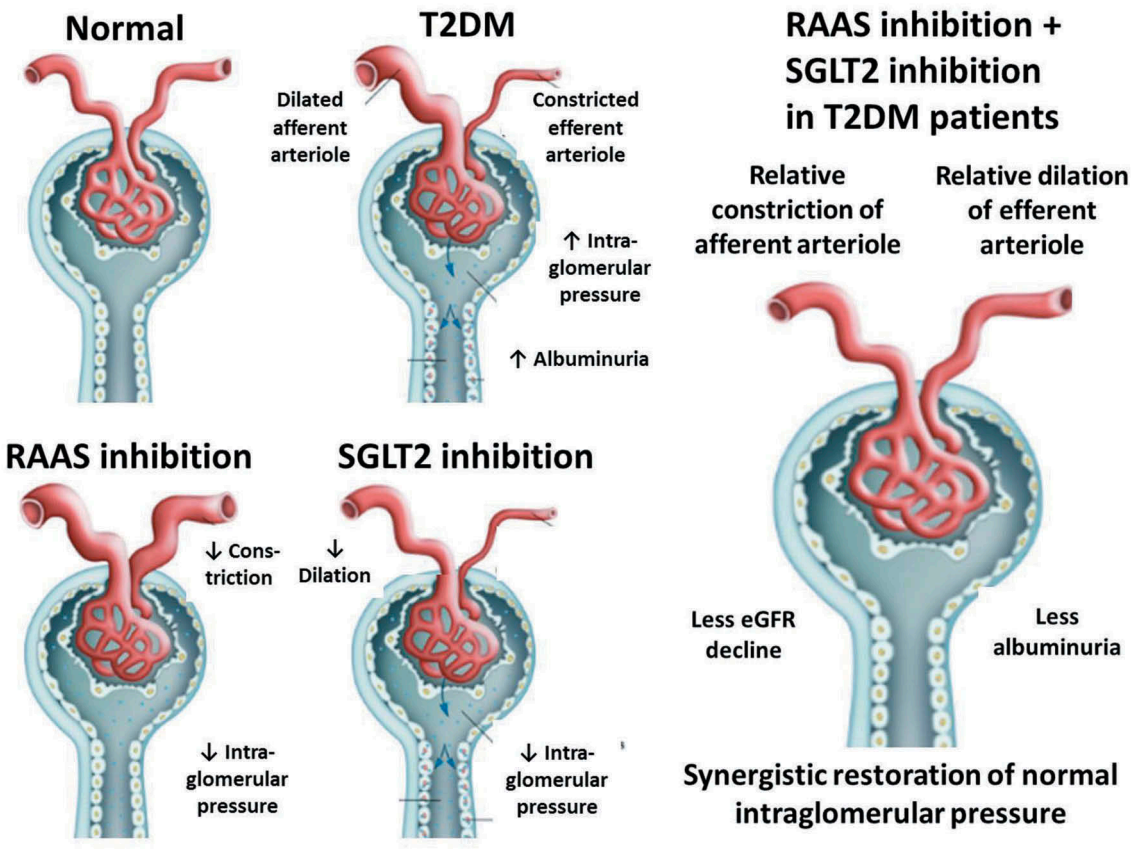

Figure 1. Complementary renoprotective effects of RAAS inhibitors and SGLT2 inhibitors by targeting efferent (through blockade of angiotensin 2 vasoconstriction) and afferent (through restoration of tubuloglomerular feedback) arterioles, respectively.

kidney damage, that is, in patients with normal GFR but presence of microalbuminuria [9]. By analogy, the indication of ACE inhibitors in T2DM patients with albuminuria is now largely adopted, even in absence of hypertension but presence of (micro-)albuminuria [9]. However, most of the studies in patients with T2DM were performed in hypertensive patients. This potential confounding factor makes the definitive proof of a positive blood pressure-independent effect of ACE inhibitors more challenging. This is particularly the case in comparative studies 'versus placebo', as the RAAS inhibitor group has frequently a better control of blood pressure. Most of the studies showed positive impacts on usual surrogate markers such as change of proteinuria (or new onset of albuminuria) and decline in GFR (or increase in serum creatinine). Specific studies with renal 'hard' end-points in T2DM patients are less numerous, and some of them are underpowered, with rather few events because a baseline low risk (normal eGFR with no or only marginal microalbuminuria) and/or with an insufficient follow-up (Table 1). For instance, in the UKPDS study, despite a long follow-up of 9 years, no significant differences could be detected between captopril and atenolol when considering the progression to microalbuminuria, macroproteinuria or ESRD (very few events); indeed, these results were obtained in patients with newly diagnosed T2DM and hypertension, but normal kidney function and low proportion of albuminuria at baseline, and reaching similar blood pressure control with both antihypertensive medications [44]. Two large prospective long-term trials, ALLHAT [45] and ADVANCE [40], have reported data on renal endpoints, including 'hard' outcomes. In ALLHAT, an ACE inhibitor (lisinopril) was not better than a diuretic (chlorthalidone, prespecified head-to head comparison with statistical analysis) or a calcium channel blocker (amlodipine, but no head-to-head prespecified statistical analysis) on the renal composite outcomes (or the single endpoint ESRD) (Table 1). The absence of significant difference in ESRD between lisinopril and either chorthalidone or amlodipine was confirmed after an extended follow-up of about 9 years in the diabetic population of ALLHAT [46]. The impact of ALLHAT is, however, limited by the absence of any data on albuminuria and by the fact that the blood pressure control was different in the therapeutic groups [45,46]. ADVANCE compared an association of perindopril and indapamide versus placebo in patients with normal renal function, and only a minority had micro- or macroalbuminuria (25% and 3.5%, respectively) [40]. The composite renal outcome was significantly better in the perindopril group than in the placebo group, but the results were mainly explained by the positive effect on new onset of microalbuminuria, whereas the impact on doubling serum creatinine or ESRD was not significant in this population with a relatively low ESRD risk (Table 1). As in ALLHAT, the results could be explained, at least in part, by a better blood pressure control in the active group [14,40], but possibly also by the concomitant prescription of indapamide, a thiazide-like diuretic that showed some positive vascular and renal effects [47].

Table 1. Renal outcomes with ACE inhibitors in type 2 diabetic patients in large studies with renal « hard » endpoints. Only trials with >250 patients in each arm are considered. When available, results are expressed as hazard ratio (HR) with 95% confidence interval.

Studies	ACE inhibitor Daily dose vs. placebo	N Active vs. placebo	Median Follow-up years	Mean baseline serum creatinine (mg/dL) or MDRD (ml/min per 1.73 m^2)	Baseline UACR (mg/g) % micro/ macro ACE inhibitor vs. comparator	Change in renal function (SCr or MDRD)	Change in UACR	New onset of persistent macroalbuminuria	Doubling of serum creatinine	Progression to ESRD requiring renal replacement therapy	Composite renal outcome
ACE inhibitors versus placebo											
MICRO-HOPE [39]	Ramipril 10 mg	1808 vs. 1769	4.5	1.07	8.85 vs. 8.85 (32 % micro)	NA	NA	0.76 (0.60–0.97) (p = 0.027)	NA	1.00 (NA)	NA
DIABHYCAR [48]	Ramipril 1.25 mg	2443 vs. 2469	3.9	1.01	74 % micro 26 % macro	SCr +0.9 vs. +0.10 mg/ dL	0.86 (0.72–1.04) (p = 0.07)	NA	0.81 (0.56–1.12)	0.93 (0.41–2.10)	1.03 (a) (0.89–1.2)
PERSUADE [49]	Perindopril 8 mg	721 vs. 781	4.3	1.07	NA	SCr>1.71 mg/ dL 1.6 vs. 1.6% Variation of SCr not different	NA	NA	1 vs. 1%	NA	NA
ADVANCE [40]	Perindopril 4 mg + Indapamide 1.25 mg	5569 vs. 5571	4.3	0.99 MDRD 78	15 vs. 15	MDRD -0.5 vs. −0.6 mL/ min	NA	0.59 (0.54–0.88) (p = 0.0027)	(and at least 2.27 mg/dL) 1.21 (0.81–1.79)	1.18 (0.66–2.11)	0.79 (b) (0.73–0.85) (p < 0.0001)
ACE inhibitors versus active comparator											
UKPDS [44]	Captopril 50–100 mg vs. Atenolol 50–100 mg	400 vs. 358	9.0	NA	16 vs. 20 % micro 2 vs. 3 % macro	No difference in SCr change	Micro 31 vs. 26 % p = 0.31	0.50 (NA) p = 0.09	No difference	NA	0.91 (0.15–5.64) p = 0.90 (c)
ALLHAT [45]	Lisinopril 10–40 mg vs. CTD 12.5–25 mg	3212 vs. 5528	4.9	MDRD 78	NA	No difference in MDRD decrease	NA	NA	NA	Lisinopril vs. CTD 1.17 (0.87–1.57)	Lisinopril vs. CTD 1.04 (0.85–1.26) p = 0.71 (d)

(a) Cardiovascular death, myocardial infract, stroke, heart failure and ESRD (dialysis or transplantation)
(b) Renal events (new macro- and microalbuminuria, doubling SCr reaching at least 2.27 mg/dL, ESRD, death to renal cause)
(c) Renal failure: not precisely defined in the UKPDS publication.
(d) ESRD (death due to renal cause, transplantation, dialysis) or eGFR decline of 50%
ACE: angiotensin converting enzyme. UACR: urinary albumin-creatinine ratio. eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. MDRD: Modification of Diet on Renal Disease. SCr: serum creatinine. NA: not available.
CTD: chlorthalidone. Micro: microalbuminuria. Macro: macroalbuminuria.

In three other studies in T2DM patients with normal serum creatinine levels (MICROHOPE, DIABHYCAR, PERSUADE), no significant differences in the changes of serum creatinine or in renal outcomes were reported when comparing an ACE inhibitor with a placebo [39,48,49]. However, in MICROHOPE (32% of T2DM patients with microalbuminuria at baseline) [39] and in DIABHYCAR (74% of T2DM patients with microalbuminuria and 26 % with macroalbuminuria at baseline) [48], the rate of new onset of persistent macroalbuminuria was significantly lower and the rate of regression from macro to micro or from micro to normal albuminuria was numerically higher in the ACE inhibitor group compared with the placebo group, respectively. No data on albuminuria neither at baseline nor at the end of the trial were available in PERSUADE, an analysis that evaluated a large subgroup of T2DM patients from the cardiovascular EUROPA study [49] (Table 1).

Several meta-analyses (however, most of them mixing patients with type 1 and type 2 diabetes) support the use of ACE inhibitors in diabetic patients with renal diabetic nephropathy, especially in the presence of significant albuminuria [34,50,51]. The specific (independent of any blood pressure effect) added value of ACE inhibitors in the absence of albuminuria remains more debatable [52,53]. Also, data in T2DM patients with low or very low GFR values are scarce [35].

2.2. Angiotensin II receptor antagonists

Evidence of the role of angiotensin II receptor antagonists (ARA II) in T2DM patients is more robust than for ACE inhibitors. Two big trials focusing on renal events (with no equivalent in terms of patient characteristics and sample size for ACE inhibitors) are available with ARA II in T2DM patients: IDNT [37] and RENAAL [38] (Table 2). Both studies included a majority of hypertensive patients with already advanced CKD (elevated mean serum creatinine around 1.65 mg/dL and 1.9 mg/dL and significant (macro) albuminuria around 1.9 g/day and 1.2 g/g in IDNT and RENAAL, respectively) [37,38]. IDNT compared irbesartan versus placebo versus amlodipine [37]. RENAAL compared losartan with placebo [38]. In both studies, the reduction effect on albuminuria was significantly better in the ARA II groups. Still more relevant, the risk of renal composite outcome was significantly lower with ARA II compared with placebo (or even amlodipine). Also, the specific risk of doubling serum creatinine was significantly lower with ARA II in the two studies, whereas the reductions of the risk of reaching ESRD were borderline in IDNT ($p = 0.07$) and significant in RENAAL [37,38] (Table 2). This effect seems independent of blood pressure control. Other studies comparing ARA II and placebo focused on diabetic nephropathy, but in patients with a baseline lower renal risk: normal (or near to normal) renal function, well- controlled hypertension, and normoalbuminuria (or only a slight proportion of microalbuminuria) [51,53]. If some results suggest positive results in terms of albuminuria (notably on the new onset of albuminuria), results are much less evident in terms of 'hard' clinical endpoints in this population with less advanced disease and at much lower risk to progress to ESRD, as shown in the ROADMAP trial comparing olmesartan with placebo [54] (Table 2). In the Japanese study CASE-J evaluating a subgroup of T2DM patients, the ARA II candesartan was associated with a significantly lower rate of a composite renal outcome compared with the calcium channel blocker amlodipine after a follow-up of 3.3 years [55], thus confirming the results of INDT that compared irbesartan with amlodipine (Table 2). Unfortunately, no data on the albuminuria status at baseline and during the study were reported in CASE-J trial [55].

The question of the superiority of ARA II compared to ACE inhibitors has been debated for a long time, but today, most authors agree on a similar effect of the two classes of RAAS inhibitors. In a head-to-head comparative RCT in T2DM patients with albuminuria, a similar effect on albuminuria and GFR decline was observed with telmisartan and enalapril [56]. The large trial ONTARGET, although not specifically dedicated to T2DM patients (9612 diabetics among 25,620 patients included) did not show any superiority in terms of renal endpoints (GFR decline, albuminuria) but also 'hard' endpoints (such as doubling serum creatinine or reaching ESRD) of telmisartan compared with ramipril [57]. Also, pooled analyses, including network meta-analyses, do not support any clear superiority of ARA II over ACE inhibitors in T2DM patients [34,50,52,58,59].

2.3. Dual blockade of RAAS

High-risk diabetic patients, as those included in the RENAAL or IDNT studies, had a lower albuminuria with ARA II and a better renal outcome, yet a rather high 'renal residual risk' may persist [60]. Based on first results showing an additional decrease of albuminuria with dual RAAS blockade [59], studies were carried out in high renal risk patients with therapies combining an ACE inhibitor and an ARA II (Table 3). ORIENT [61] compared renal outcomes with ACE inhibitor plus olmesartan versus ACE inhibitor plus placebo while VA-NEPHRON D [62] compared lisinopril plus losartan versus lisinopril plus placebo. Both studies included T2DM patients with macroalbuminuria and moderately decreased renal function. In both trials, a significantly better control of albuminuria was observed, but with only marginal effects on other renal outcomes (Table 3). Safety was a concern with a higher risk of dialysis and hyperkalemia in the combined therapy group [62] These data, and data from meta-analyses, confirm the absence of clear added value of ACE inhibitor- ARA II combined therapy on renal events [17,50].

A similar conclusion may be drawn for aliskiren a direct renin inhibitor whose effect was investigated as add-on therapy to an ARA II or an ACE inhibitor. Preliminary encouraging results (better control of albuminuria in the aliskiren group compared with placebo) were not confirmed in the largest ALTITUDE study [63]. Even if patients had a slightly better control of albuminuria, the effect was not significant on the renal composite endpoint (and on secondary renal endpoints such as doubling serum creatinine and ESRD) (Table 3). Moreover, again safety was a concern, notably with a significantly higher risk of hyperkalemia [63].

Another way to reinforce the RAAS blockade is to add an aldosterone receptor blocker to either an ACE inhibitor or an ARA II. Several studies have been performed with the classical non-selective aldosterone antagonist spironolactone with some positive results, as summarized in several meta-analyses [64,65]. However, up to now, spironolactone has

Table 2. Renal outcomes with ARA II in type 2 diabetic patients in large studies with renal « hard » endpoints. No data available on new onset of persistent macroalbuminuria in these studies. Only trials with > 250 patients in each arm are considered. When available, results are expressed as hazard ratio (HR) with 95% confidence interval.

Studies	ARA II Daily dose vs. comparator	N Active vs. placebo	Median Follow-up years	Mean baseline serum creatinine (mg/dL) or MDRD (ml/min per 1.73 m^2)	Baseline UACR (mg/g) or UA 24 h (g/24 h) ARA II vs. comparator	Change in renal function (MDRD or CrCL)	Change in UA or UACR	Doubling of serum creatinine	Progression to ESRD requiring renal replacement therapy	Composite renal outcome
ARA II versus placebo										
IDNT [37]	Irbesartan 300 mg	579 vs. 569	2.6	1.68	(median UA) 1.9 g/24h	CrCl -5.5 vs. −6.5 mL/min ($p < 0.05$)	UA: −1.1 vs. −0.3 g/24h (p = NA)	0.67 (0.52–0.87) ($p = 0.003$)	0.77 (0.57–1.03) ($p = 0.07$)	0.80 (a) (0.66–0.97) ($p = 0.02$)
RENAAL [38]	Losartan (50 or 100 mg)	751 vs. 762	3.4	1.9	1237 vs. 1261 mg/g	MDRD -4.4 vs. −5.2 ($p = 0.01$)	UACR: -35% vs. increasing ($p < 0.001$)	0.75 (0.61–0.92) ($p = 0.006$)	0.72 (0.58–0.89) ($p = 0.002$)	0.84 (b) (0.72–0.98) ($p = 0.02$)
ROADMAP [54]	Olmesartan (40 mg)	2232 vs. 2215	3.2	MDRD 85	4 vs. 3 mg/g Geometric mean 6.3 vs. 5.9	MDRD −5 vs. −1 mL/min ($p < 0.001$)	Microalbuminuria 0.77 (0.63–0.94) ($p = 0.01$)	23% vs. 23%	0 vs. 0	NA
ARAII versus active comparator										
IDNT [37]	Irbesartan 300 mg vs. Amlodipine 10 mg	579 vs. 567	2.6	1.67 vs. 1.65	(median UA) 1.9 vs. 1.9 g/24h	CrCl -5.5 vs. −6.8 mL/min (significant)	UA: −1.1 vs. −0.1 g/24h (p = NA)	0.63 (0.48–0.61) ($p < 0.001$)	0.77 (0.57–1.03) (p = 0.07)	0.77 (c) (0.63–0.93) (p = 0.006)
CASE-J [55]	Candesartan 12 mg vs. Amlodipine 10 mg	1011 vs. 1007	3.3	NA	NA	NA	NA	NA	NA	0.31 (d) (0.06–1.57)

(a) Doubling SCr or ESRD (dialysis, transplantation, SCr>6.0 mg/dL) or death
(b) Doubling SCr or ESRD (dialysis or transplantation) or death
(c) Doubling SCr or ESRD (dialysis, transplantation, SCr>6.0 mg/dL) or death
(d) SCr ≥4.0 mg/dL, doubling of SCr with SCr > 2.0 mg/dL and ESRD
ARA II: angiotensin receptor antagonist type 2. UA: urinary albumin. UACR: urinary albumin-creatinine ratio. eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. MDRD: Modification of Diet on Renal Disease. SCr: serum creatinine. CrCl: creatinine clearance. NA: not available.

Table 3. Renal outcomes with dual blockade of RAAS in type 2 diabetic patients in large studies with renal « hard » endpoints. No data available on 'new onset of persistent macroalbuminuria' in these studies. Only trials with > 250 patients in each arm are considered. When available, results are expressed as hazard ratio (HR) with 95% confidence interval.

Studies	RAAS inhibitor Daily dose vs. placebo	N Active vs. placebo	Median Follow-up years	Mean baseline SCr (mg/dL) or MDRD (ml/min per 1.73 m^2)	Baseline UACR (mg/g) RAAS inhibitor vs. Placebo	Change in renal function (1/SCr or eGFR)	Change in UACR from baseline	Doubling of serum creatinine	Progression to ESRD requiring renal replacement therapy	Composite renal outcome
ACE + ARA II										
ORIENT [61]	All treated by ACE Olmesartan 10–40 mg vs. Placebo	282 vs. 284	3.4	1.63	1700 vs. 1690	1/SCr -0.933 vs. −1.164 L/ mmol /year	−24.9 vs. −3.1% ($p < 0.001$)	0.94 (0.73–1.23)	1.08 (0.78–1.49)	0.97 (a) (0.75–1.24)
VA NEPHRON D [62]	All treated with losartan Lisinopril 10–40 mg vs. placebo	724 vs. 724	2.2	MDRD 54	862 vs. 842	−2.9 vs. −2.7 mL/ min/1.73 m^2/year	Decline in UACR higher with combination $p < 0.001$	NA	0.66 (0.41–1.07)	0.88 (b) (0.70–1.12)
Aliskiren + ACE ou ARA II										
ALTITUDE [63]	All treated by ACE or ARA II Aliskiren 300 mg vs. placebo	4274 vs. 4287	2.7	MDRD 57	206 vs. 208	NA	0.86 (0.83–0.89)	0.97 (0.80–1.17)	ESRD (+ renal death) 1.08 (0.84–1.4)	1.03 (c) (0.87–1.23)

(a) Dialysis, transplantation, SCr>5 mg/dL, all cause death or doubling SCr
(b) ESRD, or death or decreased of eGFR of 30 ml/min if baseline eGFR is above 60 or decline of 50% if baseline eGFR < 60
(c) ESRD, death due to renal, doubling SCr (reaching at least 0.9 mg/dL in women and 1.2 mg/dL in men)
ACE: angiotensin converting enzyme. ARA II: angiotensin receptor antagonist type 2. RAAS: renin-angiotensin-aldosterone system. UACR: urinary albumin-creatinine ratio. eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. MDRD: Modification of Diet on Renal Disease. SCr: serum creatinine. CrCl: creatinine clearance. NA: not available.

never crossed the border of limited sample size studies with surrogate markers as endpoints (principally effect on albuminuria). Reduction in albuminuria were also reported with two other mineralocorticoid receptor antagonists eplerenone [66] and finerenone [67]. Some concerns were reported with spironolactone in terms of risk of hyperkalemia, an adverse event that may occur more frequently in real life than in RCTs [68]. Thus, this association to protect renal function is not recommended in clinical practice yet. Larger prospective trials are underway, mainly with finerenone, a more selective nonsteroidal mineralocorticoid receptor antagonist that might induce less hyperkalemia [67,69].

2.4. Still for debate

Beyond their potential benefit on blood pressure control and cardiovascular endpoints, ARA II are the drugs with the better evidence of renal protection in T2DM patients with albuminuria [37,38,70]. Because the evidence of a strong renal protection in type 1 diabetic patients with ACE inhibition [9], and the absence of clear superiority of ARA II compared to ACE inhibitors [9,56], both pharmacological classes are now equally considered as 'standard of care' of diabetic nephropathy with albuminuria, and this is clearly stated in several guidelines [9,32,33,35]. Having said that, some points and 'gray zones' need to be briefly discussed. As already mentioned, the blood pressure control is of main importance in T2DM patients and this goal requires a combination of several different antihypertensive agents in a majority of patients with CKD and albuminuria [9]. The additional benefit of RAAS inhibitors, beyond blood pressure control, is mainly proven in T2DM patients with micro- and, still more, macro-albuminuria and is more debatable in absence of (micro)albuminuria [9,32]. RAAS inhibitors reduce proteinuria, a risk marker for renal disease progression and their antiproteinuric effect correlates with their additional renal benefits [71]. Data emerged from clinical trials demonstrating that use of 'supratherapeutic doses' of RAAS inhibitors (doses greater than those approved for lowering blood pressure), compared with standard doses, has favorable efficacy in reducing proteinuria in T2DM patients with CKD. Supratherapeutic dosing may be a valuable approach for optimizing RAAS blockade and providing renoprotection [72].

The benefit/risk ratio of this RAAS blocker therapy has been questioned in patients older than 70 years (such aged patients being excluded from large RCTs discussed above and presented in Table 1–3), especially in people with relatively preserved GFR and low albuminuria [73]. Renal safety (risk of hyperkalemia and acute renal failure) remains a concern, especially beyond the reassuring context of RCTs [68]. Indeed, in real life, RAAS blockade is considered as the main of cause of hospitalizations for hyperkalemia, and it is estimated that around 10% of patients will develop hyperkalemia within the first year after starting RAAS blockade therapy [74]. CKD patients have a higher risk of hyperkalemia, and this risk is dependent on the renal function (the lower the eGFR, the higher the risk), being particularly high in patients with GFR below 30 mL/min/1.73 m^2. Diabetes in itself is also a risk of hyperkalemia, as diabetic patients have hyporeninemic hypoaldosteronism and insulin defect may impair the shift of potassium from plasma

into cells. Other important risk factors for hyperkalemia are advanced age, heart failure, volume depletion, and concomitantly use of other drugs interfering with renal excretion of potassium (for example, trimethoprim or nonsteroidal anti-inflammatory drugs). The risk will be particularly relevant in patients combining risks, typically the elderly treated by RAAS inhibitor and anti-inflammatory agents and suffering from acute diarrhea. The risk of hyperkalemia is also dependent on the dose of ACE inhibitor or ARA II [74,75]. The risk profile of acute renal failure mirrors the risk profile of hyperkalemia and both conditions are frequently concomitant. In patients with abnormally high potassium level, it seems unreasonable to start therapies blocking RAAS. In RENAAL, including T2DM patients with CKD, the mean potassium concentration at baseline was 4.6 mmol/L and losartan was associated with a mean increase of up to 0.3 mmol/l [76] However, more than considering a potassium concentration threshold to start or not RAAS blocking therapy, it seems very important to monitor potassium in high risk patients and applying preventive actions [74,75], including the use of potassium binders [77].

Also for safety reasons, the dual RAAS blockade, especially the combination of ARA II and ACE inhibitors, is not recommended. Their use might be discussed in very specific patients with uncontrolled massive albuminuria, under the supervision of a nephrologist [42]. Lastly, because the hemodynamic effect of RAAS inhibitors, therapy interruption can significantly increase GFR level, a mirror image of the decline in eGFR generally observed at the initiation of a RAAS inhibitor. Thus, stopping ACE inhibitors or ARA II may be discussed in very specific patients with advanced renal failure (GFR below 20–30 mL/min/1.73m^2) with the aim of delaying dialysis [78].

3. Glucose-lowering medications

Most antihyperglycemic medications can be used safely in patients with mild to moderate CKD. However, several glucose-lowering agents are either not advised or require dose adjustments in more advanced CKD [12,79]. Of note, regulations guiding the use of metformin, the first-line treatment for the pharmacological management of T2DM, in patients with stable, moderate renal dysfunction have become more lenient in recent years and metformin may be used at half dose in patients with eGFR between 30 and 45 ml/min/1.73 m^2. In the American recommendations, no precise dosages are recommended in cases of renal impairment, but metformin should not be initiated if eGFR is below 45 ml/min/1.73 m^2. In Europe, the maximum daily metformin recommended dose is 2000 mg/day in CKD stage 3a (eGFR = 45–59 ml/min/1.73 m^2) and 1000 mg/day in CKD stage 3b (GFR = 30–44 ml/min/1.73 m^2). There is agreement upon the fact that metformin must be stopped if eGFR consistently falls below 30 ml/min/1.73 m^2 [80]. Also the concurrent withdrawal (albeit temporarily) of metformin is recommended when conditions leading to intermittent hypovolemic state are present, circumstances that also should lead to the transient interruption of RAAS inhibitors [81].

Intensive glucose control with classical glucose-lowering agents including metformin and insulin reduces the risk of albuminuria, but evidence is lacking that it reduces the risk of relevant clinical renal outcomes, such as doubling of the serum creatinine level, ESRD, or death from renal disease during the years of follow-up of the trials [82,83]. Of increasing interest, some new antidiabetic agents have demonstrated renoprotective effects, which occurred beyond improvement of glucose control [26,84] (Table 4).

3.1. SGLT2 inhibitors

SGLT2is exert their glucose-lowering effects by promoting glucosuria, an effect resulting also in body weight and fat mass reduction. Aside from these effects, they increase natriuresis and osmotic diuresis, thus reducing arterial blood pressure and plasma overload [85]. SGLT2 inhibitors certainly represent the most promising pharmacological class among glucose-lowering agents not only for cardiovascular but also renal protection in T2DM patients. Numerous excellent and extensive reviews were devoted to this topic in recent years, which summarized the preclinical and clinical data and provided several hypotheses to explain the nephroprotective effects of these new antidiabetic agents [18,19,21,86–90]. Effects of SGLT2is on the kidney are likely explained by multiple pathways, beyond the systemic effects via reductions in blood glucose, body weight and blood pressure. SGLT2is are associated with a reduction in glomerular hyperfiltration, an effect that is mediated through increased natriuresis and restored tubuloglomerular feedback, and independent of glycemic control (Figure 1). In addition, they may improve renal oxygenation and cellular energy metabolism [21] and also reduce intrarenal inflammation [91], thereby slowing the progression of kidney function decline.

Because of their specific mechanism of action targeting the kidney, SGLT2is lose part of their glucose-lowering activity when eGFR falls below 45–60 ml/min/1.73 m^2. Therefore, the use of SGLT2is is currently not recommended below this threshold [92,93], yet further studies may mitigate this restriction in the future. Indeed, blood pressure lowering effect of SGLT2is seems to be maintained [94,95] and a reduction in major cardiovascular events and mortality was reported in subgroups analyses of T2DM patients with eGFR below 60 ml/min/1.73 m^2 in cardiovascular outcome trials [96,97]. Even if SGLT2is consistently reduce systolic blood pressure [98], this specific effect seems to play a minor role in the improvement of renal outcomes in T2DM patients with well-controlled blood pressure at baseline [99].

In patients with T2DM at high cardiovascular risk recruited in EMPA-REG OUTCOME, empagliflozin was associated with slower progression of CKD, reflected by reduction in albuminuria and less decline in eGFR, and lower rates of clinically relevant renal events, including progression to ESRD, than was placebo when added to standard care (Table 4) [22]. A detailed post-hoc analysis supported short-term and long-term benefits of empagliflozin on UACR, irrespective of patients' albuminuria status at baseline [100]. Of note, the reductions in major cardiovascular events and mortality were also consistent across categories of eGFR and UACR at baseline [96].

Table 4. Main renal outcomes reported with GLP-1 receptor agonists and SGLT2 inhibitors in patients with type 2 diabetes and high cardiovascular risk. Results are expressed as hazard ratio (HR) with 95% confidence interval.

Studies	Active drug vs. placebo	N Active vs. placebo	Median Follow-up years	Baseline mean eGFR (MDRD) ml/min/ 1.73 m^2	Annual GFR decline (slope difference) ml/min/1.73 m^2	Baseline UACR Micro/ macro	Change in UACR from baseline %	New onset of persistent macro	Doubling of serum creatinine	Progression to ESRD requiring renal replacement therapy	Composite renal outcome
GLP-1 receptor agonists											
LEADER [24]	Liragutide 1.8 mg vs. placebo	4668 vs. 4672	3.84	80.4	NA (a)	Micro: 26.3% Macro: 10.5%	−17% (−12 to −21) $p < 0.001$	0.74 (0.60–0.91) $p = 0.004$	0.89 (0.67–1.19) $p = 0.43$	0.87 (0.61–1.24) $p = 0.44$	0.78 (c) (0.67–0.92) $p = 0.003$
SUSTAIN-6 [116]	Semaglutide 0.5 or 1.0 mg vs. placebo	1648 vs. 1649	2	NA	NA	NA	NA	0.54 (0.37–0.77) $p = 0.001$	1.28 (0.64–2.58) $p = 0.48$	0.91 (0.40–2.07) $p = 0.83$	0.64 (d) (0.46–0.88) $p = 0.005$
HARMONY-OUTCOMES [119]	Albiglutide 30-50 mg vs. placebo	4717 vs. 4715	1.6	79.1	−1.11 (−1.84 to −0.39) at 8 months -0.43 (−1.26 to 0.41) at 16 months	NA	NA	NA	NA	NA	0.87 (e) (0.75–1.02)
SGLT2 inhibitors											
EMPA-REG OUTCOME [22,100]	Empagliflozin 10 or 25 mg vs. Placebo	4687 vs. 2333	3.1	74.2	1.48 (NA) $p < 0.001$	Micro: 29% Macro: 11%	Range from − 15% to − 49% (b)	0.62 (0.54–0.72) $p < 0.001$	0.56 (0.39–0.79) $p < 0.001$	0.45 (0.21–0.97) $p = 0.04$	0.61 (f) (0.53–0.70) $p < 0.001$
CANVAS [23,112]	Canagliflozin 100–300 mg vs. placebo	5795 vs. 4347	2.4	76.5	1.2 (1.0–1.4) NA	Micro or macro: 27%	−18% (−16 to −20) NA	0.73 (0.67–0.79)	0.50 (0.30–0.84) NA	0.77 (0.30–1.97) NS	0.60 (g) (0.47–0.77) $p < 0.001$
DECLARE-TIMI 58 [102,103]	Dapagliflozin 10 mg vs. placebo	8582 vs. 8578	4.2	85.4	NA	Micro: 23.4% Macro: 6.8%	NA	NA	NA	NA	0.53 (h) (0.43–0.66)

(a) The decline was slightly lower in the liraglutide group than in the placebo group (estimated trial-ratio at 36 months, 1.02; 95%CI, 1.00 to 1.03; $p = 0.01$), corresponding to a 2% less decrease wit liraglutide: – 7.44 versus −7.82 ml/min/1.73 m^2).

(b) Normoalbuminuria at baseline: – 15% (95% CI −22 to −7), $p = 0.0004$; Microalbuminuria at baseline: – 42% (95% CI −49 to – 34), $p < 0.0001$. Macroalbuminuria at baseline: −49% (95% CI −60 to – 36), $p < 0.0001$

(c) New-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, ESRD, or death due to renal disease In LEADER: persistent doubling of the serum creatinine level, or need for continuous replacement therapy (end-stage renal disease): HR:0.85 (95%CI 0.66–1.10), $p = 0.20$

(d) Persistent macroalbuminuria, or persistent doubling of serum creatinine level and creatinine clearance per MDRD < 45 ml/min/1.73 m^2, or the need for continuous renal replacement therapy.

(e) Renal impairment but not specified in the publication (safety measurement instead of efficacy measurement)

(f) Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease. In EMPA-REG; *Post hoc* renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease): HR 0.54 (95%CI 0.40–0.75), $p < 0.001$)

(g) Sustained 40% reduction in the eGFR, the need for renal-replacement therapy, or death from renal causes. In CANVAS: the composite outcome of sustained doubling of serum creatinine, ESRD, and death from renal causes occurred less frequently in the canagliflozin group compared with the placebo (HR 0.53, 95% CI 0.33–0.84).

(h) Sustained decrease of 40% or more in eGFR to less than 60 ml/min/1.73 m^2, new ESRD, or death from renal causes

GLP-1: glucagon-like peptide −1. SGLT2: sodium-glucose cotransporter 2. UACR: urinary albumin-creatinine ratio. eGFR: estimated glomerular filtration rate. ESRD: end-stage renal disease. MDRD: Modification of Diet on Renal Disease. NA: not available. NS: not significant

In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, prespecified composite endpoint of sustained and adjudicated doubling in serum creatinine, ESRD, or death from renal causes occurred less frequently in the canagliflozin group compared with the placebo group, with consistent findings across prespecified patient subgroups [23]. Annual eGFR decline was slower and mean UACR was lower in participants treated with canagliflozin than in those treated with placebo. After a rather short median follow-up of 2.4 years, only a numerical trend for less progression to ESRD requiring renal replacement therapy was noticed (Table 4) [23]. Renal outcomes (HR, 0.59; 95% CI, 0.44–0.79 versus HR, 0.63; 95% CI, 0.39–1.02; interaction p value = 0.73) were similarly reduced in the secondary and primary cardiovascular prevention cohorts of CANVAS, respectively [101]. Furthermore, relative effects on most cardiovascular and renal outcomes were similar across eGFR subgroups [97].

In the DECLARE ('Dapagliflozin Effect on CardiovascuLAR Events') TIMI 58 cardiovascular outcome trial [102], a prespecified renal event (including cardiovascular death) occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR 0.76; 95% CI, 0.67–0.87) [103]. When the analysis excluded cardiovascular death (which was not affected by the treatment), the difference in the prespecified renal composite endpoint (40% decrease in eGFR, ESRD, or renal death) was even more important: HR 0.53 (0.43–0.66). No significant interaction (p = 0.87) was detected when the analysis was performed according to baseline eGFR levels, with less events in the dapagliglozin groups versus the placebo groups: < 60 ml/min/1.73 m^2 (n = 606 vs. n = 659) HR 0.60 (0.35–1.02); eGFR 60 to < 90 ml/min/1.73 m^2 (n = 3838 vs. 3894): HR 0.54 (0.40–0.73); eGFR ≥ 90 ml/min/1.73 m^2 (n = 4137 vs. n = 4025): HR 0.50 (0.34–0.73). Acute kidney injury occurred less frequently in the dapagliflozin group than in the placebo group (1.5% vs. 2.0%; HR 0.69 (0.55–0.87), p = 0.002) [103]. Of note, in DECLARE-TIMI 58, less patients with eGFR < 60 ml/min/1.73 m^2 (7.4%, in fact a predefined exclusion criterion, but not always respected by the investigators) were recruited than in EMPA-REG OUTCOME (26 %) and CANVAS (20%), which allowed recruitment of patients provided that eGFR was > 30 ml/min/1.73 m^2).

It is noteworthy that EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 were cardiovascular outcome RCTs, with renal outcomes as secondary rather than primary endpoints, even if prespecified. According to a recent meta-analysis, the results regarding renal protection using the composite endpoint of renal worsening, ESRD, and renal death were remarkably consistent in the three trials and comparable in patients in secondary cardiovascular prevention (HR 0.56; 0.47–0.67) and primary cardiovascular prevention (HR 0.54; 0.42–0.71) [104]. The magnitude of benefit of SGLT2is varied with baseline renal function, with lesser reductions in progression of renal disease (p for interaction = 0.0258) but greater reductions in hospitalizations for heart failure (p for interaction = 0.0073) in patients with more severe kidney disease at baseline. These data should be confirmed in dedicated renal outcome trials such as three ongoing large prospective RCTs, CREDENCE ("Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation [105] EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin: Clinical Trials.gov Identifier: NCT03594110)and Dapa-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease: ClinicalTrials.gov Identifier: NCT03036150).

Even if SGLT2is offer nephroprotection (together with cardioprotection), they may also be associated with adverse effects, including an increased risk of acute kidney injury [106], so that an individual benefit-risk balance should be taken into consideration [107,108]. Several mechanisms have been proposed to explain a risk of acute kidney injury with SGLT2is: effective volume depletion (dehydration, diuretic therapy), excessive decline in transglomerular pressure (concomitant RAAS blockade), induction of renal medullary hypoxic injury (for instance, triggered by nonsteroidal anti-inflammatory drugs) [108]. Combining these three conditions, which may act synergistically, would dramatically increase the risk of acute renal failure. A higher proportion of reports with acute renal failure were collected among reports with SGLT2is in the FDA adverse event report system (FAERS) database [109]. As a consequence, the Food and Drug Administration (FDA) now requires that acute kidney injury be listed as a potential side effect of the SGLT2is along with cautious prescription of these glucose-lowering agents with other medications, such as RAAS antagonists, diuretics, and nonsteroidal anti-inflammatory drugs. It is imperative to ascertain whether the reported acute renal failure represents true structural kidney injury or only a functional decline in glomerular filtration rate [110]. Of note, the recent data of the DECLARE-TIMI 58 trial are reassuring to this respect, with less cases of renal impairment in the dapagliflozin group than in the placebo group, despite 81.3% of patients were treated with RAAS inhibitors at baseline [103].

Another dreaded adverse event that has been associated with SGLT2 use is lower-limb amputation. In a recent extensive systematic review, there are strong overall associations of SGLT2 inhibition with protection against serious decline in kidney function (RR 0.59, 95% CI 0.49–0.71), besides major cardiovascular events, heart failure and all-cause death. However, SGLT2 inhibitors were associated with amputations (RR 1.44, 95% CI 1.13–1.83), aside of well-known adverse events such as genital infections and volume depletion effects [111]. According to this review, this association with amputation appears to differ between individual SGLT2 inhibitors, with a higher risk for canagliflozin [111], a difference mainly driven by the results of CANVAS [112]. This increased risk of lower limb amputation was also observed in some observational studies and pharmacovigilance reports, yet whether it is a class effect or not remains an open question [113]. Of note, patients with ESRD who receive dialysis are at high risk of lower extremity amputation, which is associated with a high mortality rate, and among those people with ESRD, patients with diabetes had amputation rates more than five times as high as patients without diabetes [114].

3.2. GLP-1 receptor agonists

GLP-1RAs act on traditional risk factors for progressive kidney disease including improved glucose control, blood pressure

lowering, insulin-sparing effect and body weight reduction. Furthermore, GLP-1RAs can also have direct effects in the kidney (review in [25] and [115]). However, the mechanisms that may underlie any direct actions in the kidney remain to be established and might be multiple: effects on the intrarenal RAAS, ischemia/hypoxia, apoptosis, and neural signaling. Furthermore, GLP-1RAs have also been shown to reduce inflammation, macrophage infiltration, oxidative stress, and the accumulation of type 4 collagen in the kidney [25,115]. The GLP-1 receptor is expressed in glomeruli and arterioles, yet kidney protective actions independent of the GLP-1 receptor have also been proposed. GLP-1 induces natriuresis by reducing Na/H exchange transporter isoform 3-dependent sodium reabsorption in the proximal tubule [25].

In cardiovascular outcome trial LEADER, the prespecified secondary renal outcome was a composite of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease [24]. After a median follow-up of 3.84 years in T2DM patients at high risk of cardiovascular disease, this renal outcome occurred in fewer participants in the liraglutide group than in the placebo group (HR 0.78; 95% CI, 0.67–0.92; $p = 0.003$) (Table 4). This result was driven primarily by the new onset of persistent macroalbuminuria, whereas no significant differences were noticed for persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease (Table 4). The rates of renal adverse events were similar in the liraglutide group and the placebo group (15.1 events and 16.5 events per 1000 patient-years), including the rate of acute kidney injury (7.1 and 6.2 events per 1000 patient-years, respectively) [24].

In SUSTAIN-6, after a median follow-up of 2 years, new or worsening nephropathy occurred less frequently in T2DM patients treated with semaglutide (HR = 0.64; 95% CI 0.46–0.88; $p < 0.01$). However, as in LEADER, this composite outcome was largely driven by a reduction in new-onset macroalbuminuria, whereas doubling of serum creatinine concentration to an eGFR ≤ 45 ml/min per 1.73 m^2, ESRD, and death of renal cause were unaffected (Table 4) [116]. In EXSCEL, a reduction of new-onset macroalbuminuria (2.2% vs. 2.8%; $P = 0.03$) was also reported in patients treated with once weekly exenatide compared with placebo, without significant changes neither in microalbuminuria (7.2 vs. 7.5%) nor in ESRD requiring replacement therapy (0.7 vs. 0.9%) after a median follow-up of 3.2 years [117]. ELIXA recruited T2DM patients who had had a recent acute coronary event and a eGFR > 30 ml/min/1.73 m^2 (mean value 76) [118]. Baseline characteristics showed that 74.3% of patients had normoalbuminuria, 19.2% microalbuminuria and 6.5% macroalbuminuria. A modest reduction in the increase in albuminuria was observed after 24-month treatment with lixisenatide compared with placebo (+ 24% vs. + 34 %, $p = 0.004$, but $p = 0.07$ after adjustment for HbA1c) [118]. In HARMONY-OUTCOMES, T2DM patients with established cardiovascular disease treated with albiglutide showed significantly less cardiovascular complications than those treated with placebo [119]. Around 19% of patients had diabetic nephropathy at baseline, yet mean eGFR averaged 79 ml/min/1.73 m^2 and no data on albuminuria were reported. A slight reduction in eGFR was noticed in the albiglutide group compared with the placebo group, significant at 8 months but not anymore at 16 months (Table 4). Renal events were not analyzed as an efficacy but a safety outcome. Renal impairment (not precisely defined) trended to occur less frequently in patients treated with albiglutide than in patients having received placebo (6 vs. 7%) (Table 4).

Integrated data from 9 phase 2 and 3 trials in T2DM patients ($N = 6005$) showed that dulaglutide did not affect eGFR, but slightly decreased UACR, without increasing kidney adverse events, when compared to placebo or active comparators [120]. In the 52-week AWARD-7 trial in patients with T2DM and moderate-to-severe CKD, once-weekly dulaglutide produced glycemic control similar to that achieved with insulin glargine, no greater reduction in UACR, but significantly reduced decline in eGFR ($p = 0.005$ for dulgalutide 1.5 mg and $p = 0.009$ for dulaglutide 0.75 mg vs. insulin) [121]. Overall these short-term data suggest that dulaglutide has the potential to exert renal protection in patients with T2DM, an effect that should be confirm in long-term studies with clinical hard endpoints [122].

Divergent results were reported in recent meta-analyses that investigated the effects of GLP-1RAs on microvascular and renal complications [123–125]. Thus, even if most studies report beneficial effects of GLP-1RAs on the incidence of albuminuria, more evidence is needed to convincingly support positive effects on renal function and progression to ESRD in patients with T2DM.

4. Other pharmacological agents in development

Considering the complex pathophysiology of CKD in T2DM and the residual renal risk despite RAAS inhibition, even when some new glucose-lowering agents with proven renoprotective properties are added, there is still room for innovative strategies. Whereas classical approaches targeted intrarenal hemodynamic abnormalities, new approaches focus on the potential to reduce fibrosis, low-grade inflammation, oxidative stress, advanced glycation end products (AGE), all processes involved in renal failure in T2DM [22]. Table 5 summarizes new therapies tested in humans at different stages of development and in-depth reviews on this topic may be found elsewhere [8,126–130]. In phase 2 trials, most agents showed their ability to reduce albuminuria and may also exert some protection on eGFR decline, but these effects were not yet confirmed in phase 3 trials for many of them. Of note, some promising drugs tested in large RCTs gave negative results or were associated with adverse events [131]. Globally, confirming safety remains a priority before use in clinical practice. Some concerns exist, for example, with endothelin receptor antagonist (fluid overload and heart failure, especially with avosentan whose development has been stopped, whereas the efficacy and safety of another compound atrasentan is currently investigated in the ongoing SONAR trial) [132], or bardoxolone (more cardiovascular events and worse albuminuria) [131]. Overall, for all these pharmacological interventions, the nephroprotective efficacy was mainly speculative and remains largely unproven.

Table 5. Innovative therapies to prevent or retard the progression of chronic kidney disease in T2DM. Of note, promising preliminary results were not always confirmed because of poor efficacy or safety reasons. See reviews in [8,126–130].

Anti-fibrotic effects	
PKC (protein kinase C) inhibitors	Ruboxistaurin
Glycosaminoglycans	Sulodexide
Anti-TGF (transforming growth factor)	FG-3019, pirfenidone, LY2382770, LY3016859
Metalloprotease inhibitors	XL 784, doxycycline, minocycline
Serotonin receptor antagonists	Sarpogrelate
Anti-inflammatory effects	
Phosphodiesterase inhibitors	Pentoxifylline, CPT-499, PF-00489791
Janus kinase inhibitors	Baricitinib
Endothelin receptor antagonists	Avosentan, atrasentan, dagutril
Chemokine inhibitors	CCX140-13, PF-04634817, BMS-813160
	Bindarit, Emapticap pegol
Anti-oxidant effects	
Activation of Nrf2 pathway	Bardoxolone
Inhibitors of NADPH oxidase 1 and 4	GKT-137831
α-Lipoic acid (+ losartan)	INV-144
Reduction of oxidative stress, reduction of Ox-LDL	Probucol
Pleiotropic effects, activation of Nrf2 pathway	Silymarin
Pleiotropic effects of polyphenol	Resveratrol
AGEs inhibitors	
	Pyridoxamine, pimagedine, TTP448
Vitamin D activators	
Multiple effects	Cholecalciferol, paricalcitol, calcitriol, and α-calcidol

AGEs: advanced glycation end products

5. Conclusions

Diabetic kidney disease becomes increasingly prevalent among patients with T2DM and is associated with increased mortality, decreased quality of life and high healthcare cost. Thus preventing early CKD in T2DM patients and limiting the progression toward ESRD are major challenges in clinical practice. Besides healthy lifestyle and the avoidance of nephrotoxic agents, it is essential to maintain adequate control of blood glucose and blood pressure as both chronic hyperglycemia and hypertension exert deleterious effects on kidney structure and function. RAAS inhibitors were the first drugs that have proven their efficacy to prevent surrogate and hard clinical renal outcomes, independently of their antihypertensive effects. Their ability to control albuminuria/proteinuria beyond the reduction of blood pressure appears of major importance. In all guidelines, they are recommended in T2DM patients with any stage of CKD, from very early stage to more advanced disease, that is 3 to 4 stages CKD, especially if (micro)albuminuria is present. Overall, ACE inhibitors and ARA II are considered to exert equal renoprotective effects.

New glucose-lowering agents, GLP-1RAs and especially SGLT2is, have recently shown nephroprotective properties on composite renal outcomes combining surrogate endpoints (albuminuria, eGFR decline) and hard clinical events (progression to ESRD requiring renal replacement therapies). These effects were observed when added to standard care, including RAAS blockers, in T2DM patients with established or at high risk of cardiovascular disease. The nephroprotection by SGLT2is occurs independently of glucose control and this observation opens new perspectives for the treatment on nondiabetic CKD currently in investigation. Whether SGLT2is also exert nephroprotection in T2DM patients with more advanced stages of the disease (stages 3b–4 CKD) remains to be carefully investigated in dedicated studies with renal outcomes as primary endpoints, as well as the complex and pleiotropic underlying mechanisms contributing to renoprotection.

Finally, despite the favorable effects of these pharmacological approaches, even if combined, the renal residual risk remains high in many T2DM patients. Therefore, new therapies are in development targeting fibrosis, low-grade inflammation, oxidative stress or AGE deposition, all processes involved in progressive renal impairment in T2DM. However, despite some promising results, all these new drugs first have to prove both their efficacy and safety in large RCTs before any future use in clinical practice.

6. Expert opinion

In parallel with the T2DM pandemic, CKD related to diabetes has become the leading cause of ESRD in many countries worldwide, and is associated with high cardiovascular morbidity and mortality. Based on landmark clinical trials, diabetes-related CKD is preventable by controlling conventional factors, mainly hyperglycemia and hypertension, with multifactorial therapies combining lifestyle and drug interventions. Many antidiabetic medications (metformin, glitazones, DPP-4 inhibitors) have shown promising results in animal models of CKD and offered the possibility to investigate potential molecular mechanisms that may explain renoprotection. However, although useful, these animal models are not perfect [133], so that preclinical data should be confirmed in well-designed clinical studies. For all these antidiabetic agents, only effects on biomarkers and soft surrogate endpoints such as reduction of albuminuria and more rarely reduction in eGFR have been reported [83].

A biomarker is an objectively measured characteristic that is indicative of some underlying phenomenon or process (i.e. albuminuria), while a surrogate is a biomarker that 'takes the place' of a clinically meaningful outcome, usually earlier in the disease process (i.e. reduction in eGFR) [134]. Even, if changes in albuminuria and eGFR were associated with a greater risk of experiencing clinical outcomes [135], clinicians are waiting for clear-cut data on more relevant hard endpoints, such as avoiding the progression to ESRD or renal death. Some well-known agents (RAAS inhibitors) and, more recently, new antidiabetic medications (SGLT2is) have shown renoprotective effects, not only on surrogate endpoints but also on hard clinical outcomes, independently of their blood pressure-lowering activity and glucose-lowering activity, respectively. However, even if combined therapy is used, the remaining risk of CKD progression in T2DM patients is still high.

Direct comparison of agents within a pharmacologic class or between drug classes is hazardous, as renal outcomes are inconsistently defined across trials. As a consequence, the impact of many specific drugs on renal outcome measures in patients with T2DM remains unclear. The evaluation of hard clinical outcomes such as progression to ESRD or death of renal cause requires a long follow-up in large cohorts. As it is hard to carry out and finance such studies, most recent publications use composite renal outcomes, a mix of surrogate and hard endpoints, which, however, may differ across RCTs (Table 1–4). Of note, these composite endpoints can reveal significant results driven by a single surrogate marker, for instance reduction in albuminuria, but not clinical events of true relevance to T2DM patients, for instance need for renal replacement therapy. Renal outcome studies including a well-defined, standardized core set of patient-relevant outcomes are needed to achieve evidence-based guidance and improve clinical care for T2DM patients at risk of CKD [136,137]. A doubling of serum creatinine level is generally used in most studies either as individual endpoint or as part of a composite outcome. However, it is a rather late event in CKD natural history, corresponding to a change in eGFR of more than 50%. There is great interest in considering alternative endpoints for clinical trials to shorten their duration, reduce sample size, and extend their conduct to patients with earlier stages of CKD. A 30% declines in eGFR over 2 years occurred more commonly than a doubling of serum creatinine concentration and was strongly and consistently associated with the risk of ESRD and mortality [138]. A scientific workshop sponsored by the National Kidney Foundation and the US FDA concluded that a confirmed decline in eGFR of 30% over 2–3 years may be a valuable alternative surrogate end point for CKD progression in most circumstances [139]. Another challenge is to improve clinical trial enrolment criterion to identify T2DM patients at higher risk of ESRD [140]. This improvement will be crucial to reduce the sample size and ameliorate the statistical power by increasing the number of key events in RCTs. It will also be of major importance in clinical practice to more effectively select T2DM patients who should require intensive combining therapy for a better renal protection.

RAAS inhibitors and SGLT2 inhibitors are the two pharmacologic classes that have best proven to improve both surrogate and hard clinical endpoints in patients with T2DM. RAAS inhibitors were initially developed as antihypertensive agents, yet they renoprotective effects appear to be at least partially independent of their blood pressure lowering effects. These agents also reduce proteinuria, a risk marker for renal disease progression [70] and accumulating evidence indicates that their antiproteinuric effect correlates with their additional renal benefits [71]. High dosing of ACE inhibitors or ARA II may be a valuable approach for providing greater reduction in proteinuria and ultimately renoprotection [72]. Similarly, SGLT2 inhibitors were developed as antihyperglycemic agents, yet their nephroprotection is essentially independent of their glucose-lowering effects. Both pharmacological classes modify intrarenal hemodynamic properties by complementary mechanisms contributing to reduce intraglomerular pressure [141,142] (Figure 1). RAAS inhibitors, by inhibiting vasoconstrictive effects of angiotensin 2, dilate postglomerular artery whereas SGLT2 inhibitors, by restoring tubuloglomerular feedback, constrict preglomerular artery. Intriguingly, experimental studies in rats suggested that dapagliflozin-associated beneficial effects on diabetic nephropathy might result from suppression of renal RAAS component expression, contributing to reduction in oxidative stress and interstitial fibrosis [143]. In hypertensive patients with T2DM on stable RAAS blocker therapy, dapagliflozin significantly reduced albuminuria, a reduction that remained present after adjusting for changes in HbA1c, systolic blood pressure, body weight and eGFR [144]. However, T2DM patients who did not respond to RAAS inhibition by a reduction in albuminuria also did not respond to dapagliflozin, indicating that individual therapy resistance to RAAS inhibition cannot be overcome with the addition of SGLT2 inhibitors. These data suggest that the individual drug resistance may be an intrinsic individual characteristic unrelated to the type of pharmacologic intervention, unless the mode of action of the SGLT2 inhibitor on albuminuria is through the RAAS [145]. Of note, in both EMPA-REG OUTCOME and CANVAS, almost three-quarters of T2DM patients were treated with RAAS inhibitors at baseline and throughout the trials. Subgroup analyses showed no significant interaction between users and non-users of RAAS blockers regarding primary cardiovascular composite endpoints and cardiovascular death both in EMPA-REG OUTCOME [146] and in CANVAS [112]. No such subanalysis is reported in DECLARE-TIMI 58 [103] neither for renal outcomes yet. Both RAAS inhibitors and SGLT2 inhibitors are renoprotective, but may also exert deleterious effects leading to acute kidney insufficiency in certain circumstances, such as dehydration and association with nonsteroidal anti-inflammatory agents [106,110,147]. As a consequence, caution and appropriate supervision should be recommended when using these agents in more frailty patients, for instance elderly patients. Whereas RAAS blockers may induce hyperkalemia, as previous discussed, SGLT2 inhibitors are generally not associated with ionic disturbances.

The effects of empagliflozin [96] and canagliflozin [97] on cardiovascular and renal outcomes were not modified by baseline level of kidney function in T2DM patients with a history or high risk of cardiovascular disease down to eGFR levels of 30 mL/min/1.73 m^2. Thus, reassessing current limitations on the use of SGLT2 inhibitors in patients with CKD at high risk of cardiovascular disease may allow additional individuals to benefit from

this therapy. Furthermore, the glucose-independent hemodynamic intrarenal mechanisms of SGLT2 inhibitors provide the possibility to extend the use of these medications to non-diabetic kidney disease. This should be confirmed in ongoing dedicated trials. If results were positive, they will have the potential to change clinical practice and outlook of high-risk patients with diabetic and nondiabetic CKD.

Because of the beneficial effects of SGLT2 inhibitors not only on surrogate endpoints but also on hard renal outcomes (in contrast to what has been shown with GLP-1RAs) [148], the recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) considers that SGLT2 inhibitors with evidence of reducing CKD in cardiovascular outcome trials should be considered as the best pharmacological option to be added to metformin in T2DM patients with CKD, provided that eGFR is adequate. If SGLT2 inhibitors are not tolerated or contraindicated or if eGFR is less than adequate, the addition of a GLP-1RA with proven cardiovascular benefit may be considered [149].

The economic burden of progressive CKD among T2DM patients is high [150]. Whether new pharmacological approaches currently in development will succeed to reduce the residual risk of CKD in T2DM patients remains an open question. The future challenge will be to find combined pharmacological therapies offering the best renal (and cardiovascular) protection, with a good safety profile and at a reasonable cost.

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