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Published in:
Diabetologia

DOI:
10.1007/s00125-023-06015-1

Diabetologia (2024) 67:3–18
https://doi.org/10.1007/s00125-023-06015-1

REVIEW

Chronic kidney disease in type 1 diabetes: translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes

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Received: 26 April 2023 / Accepted: 21 July 2023 / Published online: 6 October 2023

Abstract

Current management of chronic kidney disease (CKD) in type 1 diabetes centres on glycaemic control, renin–angiotensin system inhibition and optimisation of risk factors including blood pressure, lipids and body weight. While these therapeutic approaches have significantly improved outcomes among people with type 1 diabetes and CKD, this population remains at substantial elevated risk for adverse kidney and cardiovascular events, with limited improvements over the last few decades. The significant burden of CKD and CVD in type 1 diabetes populations highlights the need to identify novel therapies with the potential for heart and kidney protection. Over the last decade, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists have emerged as potent kidney-protective and/or cardioprotective agents in type 2 diabetes. The consistent, substantial kidney and cardiovascular benefits of these agents has led to their incorporation into professional guidelines as foundational care for type 2 diabetes. Furthermore, introduction of these agents into clinical practice has been accompanied by a shift in the focus of diabetes care from a 'glucose-centric' to a 'cardiorenal risk-centric' approach. In this review, we evaluate the potential translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes with the lens of preventing the development and progression of CKD.

Keywords Cardiorenal · Chronic kidney disease · Glucagon-like peptide 1 receptor agonist · Mechanisms · Review · Sodium–glucose cotransporter-2 inhibitor · Therapeutics · Type 1 diabetes

Abbreviations

ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
CRP	C-reactive protein
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease

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ERA	Endothelin receptor antagonist
ESKD	End-stage kidney disease
GIP	Glucose-dependent insulinotropic polypeptide
GLP1	Glucagon-like peptide 1
GLP1-RA	Glucagon-like peptide 1 receptor agonist
HF	Heart failure
hsCRP	High-sensitivity C-reactive protein
MACE	Major adverse cardiovascular events
MRA	Mineralocorticoid receptor antagonist
NO	Nitric oxide
RAS	Renin–angiotensin system
sGC	Soluble guanylate cyclase
SGLT2i	Sodium–glucose cotransporter-2 inhibitor(s)
UACR	Urine albumin to creatinine ratio

Burden of chronic kidney disease in type 1 diabetes: an unmet clinical need

Similar to type 2 diabetes, hyperglycaemia in type 1 diabetes increases the risk of end-organ damage, including chronic kidney disease (CKD). CKD can be classified and prognosticated using eGFR and albuminuria (quantified using the urine albumin to creatinine ratio [UACR]) [1]. The relative risks of complications, including progression of CKD to end-stage kidney disease (ESKD), CVD and mortality, are increased with both reduced eGFR and elevated UACR levels [1]. The prevalence of CKD in type 1 diabetes increases with diabetes duration, with approximately 33% and 25% of adults developing albuminuria and eGFR <60 ml/min per 1.73 m^2, respectively, after >40 years of diabetes; overall, the lifetime risk of ESKD is 10–30% [2, 3]. Notably, there was a decrease in the cumulative incidence of severe albuminuria in individuals diagnosed with type 1 diabetes in the 1980s compared with those diagnosed in the 1970s in Finland, although no further improvement was apparent in the 1990–1999 diagnosis cohort [4]. This study also showed that, from the onset of recurrent albuminuria screening in 1980 until 2020, the cumulative incidence of moderate albuminuria had shown no signs of decrease. The decrease between the 1970s and the 1980s coincided with the emergence of renin–angiotensin system (RAS) blockers, but the conspicuous lack of further improvements after the 1980s highlights the need for additional kidney-protective medications [4]. In a similar analysis of the Swedish National Diabetes Register, a decreasing trend in standardised incidence rates of diabetic nephropathy in people with type 1 diabetes was observed from 2001 to 2019, with no changes in the rates of ESKD over the same period [5]. Additionally, CVD remains a leading cause of morbidity and mortality in type 1 diabetes. Compared with matched controls, individuals diagnosed with type 1 diabetes between 0 and 10 years of age have a nearly 30 times increased risk of coronary heart disease, with greater than seven times the risk of cardiovascular death [6].

While the prevalence of CVD is similar in individuals with type 1 diabetes and those with type 2 diabetes, the risk of CKD may be greater in those with type 1 diabetes. Following age stratification, the risk of CKD was 1.4- to 3.0-fold higher in individuals with type 1 diabetes at all ages than in those with type 2 diabetes [7]. Additionally, in Scandinavian cohort studies, event rates of heart failure (HF), stroke, incident CKD and 'cardiorenal'-related death were higher in type 1 diabetes than in type 2 diabetes [7]. Consistent with these results, age-, sex- and socioeconomic status-adjusted data from national Scottish registries demonstrated that incident HF hospitalisations were higher among those with type 1 diabetes than those with type 2 diabetes [8]. Importantly, underuse of therapies directed at heart and kidney protection was noted in individuals with type 1 diabetes compared with those with type 2 diabetes in the Scandinavian cohort [7]. Fewer people with type 1 diabetes than type 2 diabetes were on CVD medication (53.9% vs 82.1%), ACE inhibitors (22.5% vs 32.0%) and angiotensin receptor blockers (ARB) (16.7% vs 31.3%).

The significant burden of CKD and CVD in type 1 diabetes highlights the need to identify novel therapies with the potential for heart and kidney protection. Although significant therapeutic advances have been made for people living with type 2 diabetes, similar benefits have yet to be achieved in those with type 1 diabetes. In this review, we evaluate the potential translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes with the lens of preventing the development and progression of CKD.

Mechanistic underpinnings of CKD in diabetes

The development and progression of CKD in diabetes is driven by metabolic and haemodynamic factors, which contribute to endothelial dysfunction and activation of inflammatory and pro-fibrotic pathways [9, 10]. These processes interact with one another in a pathological feed-forward cycle, ultimately yielding functional and structural kidney abnormalities characteristic of diabetic kidney disease (DKD) (Fig. 1).

Persistent hyperglycaemia induces deleterious changes in kidney cellular metabolism and function through a variety of mechanisms. Hyperglycaemia differentially affects energy metabolism across kidney cell types, for example impeding glycolysis in glomerular epithelial cells (where glucose is the preferred energy substrate) while enhancing glycolysis in proximal tubular epithelial cells (which typically rely on fatty acid oxidation) [11]. Changes in glucose metabolism culminate in endothelial dysfunction and the activation of

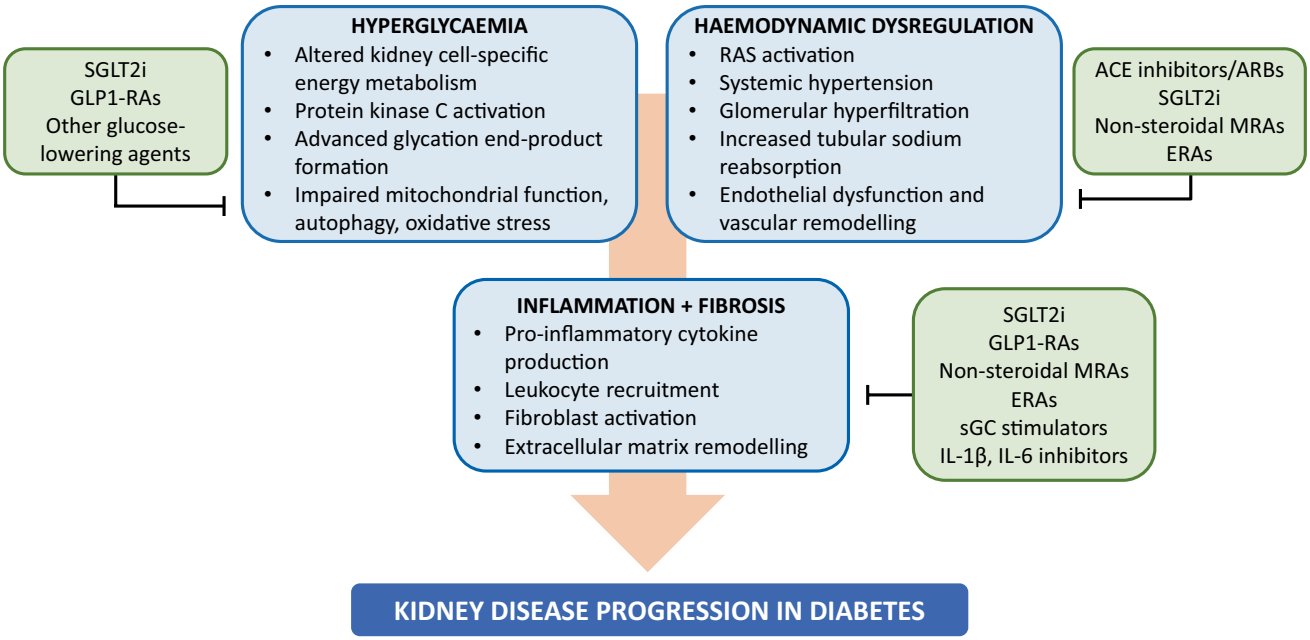

Fig. 1 Mechanisms underlying kidney disease progression in diabetes. Processes contributing to kidney disease progression in diabetes are summarised in the blue boxes. Pharmacological agents targeting these processes are shown in the green boxes. ERA, endothelin receptor antagonist; sGC, soluble guanylate cyclase. This figure is available as a downloadable slide

downstream inflammatory and pro-fibrotic pathways involving immune cell recruitment and TGF-β1 production. These changes are also accompanied by mitochondrial dysfunction, impaired autophagy and oxidative stress. Additionally, non-enzymatic binding of glucose to circulating proteins results in generation of AGEs. AGEs cause injury by binding to AGE-specific receptors and alteration of cellular structures and protein metabolism, augmenting inflammation and oxidative stress [12].

Haemodynamic factors, RAS overactivation and hypertension are central to CKD development and progression in diabetes. Diabetes-associated excess kidney tissue RAS activation increases angiotensin II-mediated glomerular efferent arteriolar vasoconstriction and glomerular hyperfiltration, tubular sodium reabsorption, and signalling through intracellular pathways, resulting in inflammation and oxidative stress [13]. Additionally, angiotensin II contributes to endothelial dysfunction by inducing expression of vascular endothelial growth factor and increasing reactive oxygen species, which reduce the bioavailability of vasodilators (such as nitrous oxide) responsible for maintaining normal glomerular vascular tone [14]. Hyperglycaemia also disrupts tubuloglomerular feedback, causing afferent arteriolar vasodilation and exacerbating glomerular hyperfiltration. Excess aldosterone, in addition to increasing tubular sodium reabsorption, activates inflammatory and pro-fibrotic pathways and promotes vascular remodelling [15]. Elevated systemic blood pressure, exacerbated by RAS activation and transmitted to the glomerular capillary system in the context of impaired autoregulation, further worsens glomerular endothelial injury and dysfunction.

Together, the combined outcomes of these metabolic and haemodynamic factors and their downstream inflammatory and pro-fibrotic effects result in glomerular and tubular injury, amounting to clinical and histopathological disease. This manifests as progressively worsening albuminuria and eGFR decline, with glomerular mesangial expansion, podocyte effacement, segmental glomerulosclerosis and tubular injury, which progress to diffuse glomerular and tubulointerstitial fibrosis [10].

Current pharmacological treatment landscape

Current management of CKD in type 1 diabetes centres on glycaemic control, RAS inhibition and optimisation of risk factors including blood pressure, lipids and body weight [1, 16]. Insulin-based glycaemic control is the pharmacological cornerstone in type 1 diabetes and delays the onset and progression of kidney disease. The benefits of intensive insulin therapy for kidney and other microvascular complications, cardiovascular outcomes and mortality in adults with type 1 diabetes were comprehensively demonstrated in the DCCT/

EDIC study [17]. In DCCT, participants were randomised to either intensive or conventional insulin therapy (achieving a median HbA_{1c} level of 7% vs 9% [53 vs 75 mmol/mol], respectively) and followed for a mean of 6.5 years. In the observational follow-up study EDIC, all participants were encouraged to attempt intensive glycaemic control and were followed for >15 years. Intensive therapy resulted in a reduced risk of albuminuria and eGFR decline, extending beyond the randomisation period, indicating the importance of early glycaemic control in preventing long-term adverse kidney outcomes [18].

RAS inhibition using an ACE inhibitor or an ARB is recommended for adults with type 1 diabetes and albuminuria, with numerous placebo-controlled trials demonstrating a reduced risk of albuminuria progression and eGFR decline independent of blood pressure-lowering effects [19, 20]. Overall, in adults with type 1 diabetes and CKD, RAS inhibition reduces the risks of progression of microalbuminuria to macroalbuminuria by approximately 50% and of serum creatinine doubling by 20–30% [21]. However, RAS inhibition has not yet been found to prevent kidney disease among those with type 1 diabetes, normal blood pressure and without albuminuria, and also does not prevent the progression of histological changes associated with DKD at the early stage of disease [22].

Hypertension is highly prevalent in individuals with CKD and contributes to disease progression. Blood pressure management is important for reducing the risk of kidney disease and CVD in type 1 diabetes, with 2023 ADA guidelines recommending a target goal of <130/80 mmHg [16]. Hyperlipidaemia treatment and weight loss are additionally part of foundational type 1 diabetes care.

While glycaemic control, RAS inhibition and risk factor management have significantly improved outcomes among people with type 1 diabetes and CKD, this population remains at substantial elevated risk for adverse kidney and cardiovascular events. In the aforementioned RAS inhibition trials, 20–40% of participants randomised to ACE inhibitors or ARBs still experienced the primary kidney endpoint [19, 20]. More recently, in the PERL trial of adults with type 1 diabetes and CKD, iohexol-based GFR declined by ~3 ml/min per 1.73 m^2 per year, despite 90% of participants using RAS inhibitors [23]. Treatment strategies for type 1 diabetes and CKD have remained largely unchanged over the last 30 years, with RAS inhibitors introduced in 1993. There is therefore a critical need for the development and implementation of novel therapies that not only address residual kidney and cardiovascular risk in this population but also target metabolic, haemodynamic, inflammatory and profibrotic processes that contribute to kidney disease onset and progression. Concurrently, more sensitive screening methods and biomarkers for DKD are warranted, considering the limitations of albuminuria and eGFR in detecting early disease.

Pharmacological advancements in type 2 diabetes and CKD and translation to type 1 diabetes and CKD

Over the last decade, sodium–glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP1-RAs) and non-steroidal mineralocorticoid receptor antagonists (MRAs) have emerged as potent kidney- and/or cardioprotective agents in type 2 diabetes. The consistent substantial kidney and cardiovascular benefits of these agents has led to their incorporation into professional guidelines as foundational care for the management of CKD in type 2 diabetes [1, 24]. Furthermore, introduction of these agents into clinical practice has been accompanied by a shift in the focus of diabetes care from a 'glucose-centric' to a 'cardiorenal risk-centric' approach. However, SGLT2i, GLP1-RAs and non-steroidal MRAs have yet to be integrated into standard type 1 diabetes practice because of their limited availability or absence of clinical trial data in this population. In the following sections we discuss the potential for translation of SGLT2i, GLPA1-RAs and MRAs to people living with type 1 diabetes and CKD (Table 1, Fig. 1).

Sodium–glucose cotransporter-2 inhibitors SGLT2i block kidney proximal tubular sodium–glucose cotransport and were initially used as glucose-lowering agents. SGLT2i have consistently demonstrated kidney and cardiovascular benefits in people with type 2 diabetes across numerous large randomised placebo-controlled clinical trials evaluating primary kidney and cardiovascular clinical outcomes [25]. The dedicated kidney outcomes trials include the CREDENCE trial, conducted in adults with type 2 diabetes and CKD, and the DAPA-CKD and EMPA-KIDNEY trials, conducted in adults with CKD and including people with and without type 2 diabetes [26–28]. In each of these studies, SGLT2i were associated with a ~30–40% reduction in the risk of eGFR decline, progression to ESKD or death due to kidney or CVD.

The mechanisms by which SGLT2i exert their kidney-protective effects are multifactorial, related to their metabolic, haemodynamic and anti-inflammatory effects [29]. In addition to improving glycaemic control and inducing weight loss, SGLT2i may ameliorate hyperglycaemia-related kidney cell-specific changes in energy metabolism, thereby modulating mitochondrial function and autophagy [29]. SGLT2i also have prominent haemodynamic effects, normalising tubuloglomerular feedback and reducing glomerular hyperfiltration by increasing distal tubular sodium delivery.

Table 1 Summary of select clinical studies of SGLT2i, GLP1-RAs and MRAs in individuals with type 1 diabetes

Study	Participant cohort	Treatment	Findings
SGLT2i			
inTandem1 and 2 (pooled) [33]	Adults (>18 years) with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.0–11.0%	Sotagliflozin 200 mg/day (n=524) or 400 mg/day (n=525) or placebo (n=526) for 52 weeks	Mean (95% CI) HbA_{1c} reduction at 24 weeks: • Sotagliflozin 200 mg: −0.36% (−0.44, −0.29) (−3.9 mmol/mol [−4.8, −3.2]) • Sotagliflozin 400 mg: −0.38% (−0.45, −0.31) (−4.2 mmol/mol [−4.9, −3.4]) • All p<0.001 vs placebo • Sustained effects through week 52 Mean (95% CI) difference in fat mass between treatments and placebo at 52 weeks: • Sotagliflozin 200 mg: −1.70 kg (−2.70, −0.69), p=0.001 • Sotagliflozin 400 mg: −2.12 kg (−3.11, −1.14), p<0.001
inTandem3 [34]	Adults with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.0–11.0% eGFR ≥45 ml/min per 1.73 m^2	Sotagliflozin 400 mg/day (n=699) or placebo (n=703) for 24 weeks	Mean HbA_{1c} reduction at 24 weeks: • Sotagliflozin 400 mg: −0.79% (−8.6 mmol/mol) • Placebo: −0.33% (−3.6 mmol/mol) • p<0.001 Mean weight reduction at 24 weeks: • Sotagliflozin 400 mg vs placebo: difference −2.98 kg, p<0.001 Insulin reductions from baseline with sotagliflozin 400 mg (placebo corrected) at 24 weeks: • Mean daily total: −5.3 units (−9.7%) • Bolus: −2.8 units (−12.3%) • Basal: −2.6 units (−9.9%) • All p<0.001 Mean SBP pressure reduction at 24 weeks: • Sotagliflozin 400 mg vs placebo: difference −3.5 mmHg, p=0.002

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
EASE-2 and -3 (pooled) [35]	Adults with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.5–10.0% eGFR ≥30 ml/min per 1.73 m^2 Fasting C-peptide <0.23 nmol/l	EASE-2: empagliflozin 10 mg/day (n=243) or 25 mg/day (n=244) or placebo (n=243) for 52 weeks EASE-3: empagliflozin 2.5 mg/day (n=241), 10 mg/day (n=248) or 25 mg/day (n=245) or placebo (n=241) for 26 weeks	Mean (95% CI) placebo-subtracted HbA_{1c} changes at 26 weeks: • Empagliflozin 2.5 mg: −0.28% (−0.42, −0.15) (−3.1 mmol/mol [−4.6, −1.6]) • Empagliflozin 10 mg: −0.54% (−0.65, −0.42) (−5.9 mmol/mol [−7.1, −4.6]) • Empagliflozin 25 mg: −0.53% (−0.65, −0.42) (−5.8 mmol/mol [−7.1, −4.6]) • All p<0.0001. Mean weight change at 26 weeks: • Empagliflozin 2.5 mg: −1.8 kg • Empagliflozin 10 mg: −3.0 kg • Empagliflozin 25 mg: −3.4 kg • All p<0.0001 Mean total daily insulin dose change at 26 weeks: • Empagliflozin 2.5 mg: −6.4% • Empagliflozin 10 mg: −13.3% • Empagliflozin 25 mg: −12.7% • All p<0.0001 Mean SBP change at 26 weeks: • Empagliflozin 2.5 mg: −2.1 mmHg • Empagliflozin 10 mg: −3.9 mmHg • Empagliflozin 25 mg: −3.7 mmHg • All p<0.05
DEPICT-1 and -2 (pooled) [36]	Adults (18–75 years) with type 1 diabetes, taking insulin for ≥12 months HbA_{1c} 7.5–10.5% C-peptide <0.23 nmol/l	Dapagliflozin 5 mg/day (n=548) or 10 mg/day (n=566) or placebo (n=532) for 52 weeks	Mean (95% CI) HbA_{1c} difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −0.26% (−0.37, −0.16) (−2.8 mmol/mol [−4.0, −1.7]) • Dapagliflozin 10 mg: −0.30% (−0.41, −0.20) (−3.3 mmol/mol [−4.5, −2.2]) Mean body weight difference at 52 weeks: • Dapagliflozin 5 mg: −2.57 kg • Dapagliflozin 10 mg: −3.34 kg • Placebo: 0.44 kg Mean insulin dose difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −9.57% (−12.01, −7.07) • Dapagliflozin 10 mg: −11.75% (−14.13, −9.30) Mean SBP difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −3.72 mmHg (−7.76, −0.31) • Dapagliflozin 10 mg: −4.24 mmHg (−8.43, −0.05)

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
GLP1-RAs			
ADJUNCT ONE [53]	Adults (18–75 years) with type 1 diabetes (clinically diagnosed >12 months before visit) Taking insulin for ≥6 months HbA_{1c} 7.0–10.0% BMI ≥20 kg/m^2	Liraglutide 0.6 mg/day (n=350), 1.2 mg/day (n=346) or 1.8 mg/day (n=346) or placebo (n=347) for 26 weeks	Placebo-subtracted HbA_{1c} changes at 52 weeks (ETD [95% CI]): • Liraglutide 0.6 mg: −0.1% (−0.21, 0.03) (−1.1 mmol/mol [−2.3, −0.3]), p=0.13 • Liraglutide 1.2 mg: −0.15% (−0.27, −0.03) (−1.6 mmol/mol [−3.0, −0.3]), p=0.02 • Liraglutide 1.8 mg: −0.2% (−0.32, −0.07) (−2.2 mmol/mol [−3.5, −0.8]), p=0.002 Placebo-subtracted change in body weight (ETD [95% CI]): • Liraglutide 0.6 mg: −2.2 kg (−2.9, −1.5) • Liraglutide 1.2 mg: −3.6 kg (−4.3, −2.8) • Liraglutide 1.8 mg: −4.9 kg (−5.7, −4.2) • All p<0.0001 Ratio of rate of symptomatic hypoglycaemic events with liraglutide vs placebo (ERR [95% CI]): • Liraglutide 0.6 mg: 1.17 (0.97, 1.43), p=0.11 • Liraglutide 1.2 mg: 1.27 (1.03, 1.55), p=0.02 • Liraglutide 1.8 mg: 1.31 (1.07, 1.59), p=0.008 Ratio of total insulin dose with liraglutide vs placebo at 52 weeks (ETR [95% CI]): • Liraglutide 0.6 mg: 1.00 (0.96, 1.04), p=0.96 • Liraglutide 1.2 mg: 0.95 (0.91, 0.99), p=0.015 • Liraglutide 1.8 mg: 0.92 (0.88, 0.96), p<0.0001
ADJUNCT TWO [54]	Adults (>18 years) with type 1 diabetes Taking insulin for ≥6 months and a stable insulin dose for at least 3 months HbA_{1c} 7.0–10.0% BMI ≥20 kg/m^2	Liraglutide 0.6 mg/day (n=350), 1.2 mg/day (n=346) or 1.8 mg/day (n=346) or placebo (n=347) for 26 weeks	Placebo-subtracted HbA_{1c} changes at 52 weeks (ETD [95% CI]): • Liraglutide 0.6 mg: −0.24% (−0.39, −0.10) (−2.6 mmol/mol [−4.3, −1.1]), p=0.001 • Liraglutide 1.2 mg: −0.23% (−0.38, −0.08) (−2.5 mmol/mol [−4.2, −0.9]), p=0.002 • Liraglutide 1.8 mg: −0.35% (−0.50, −0.20) (−3.8 mmol/mol [−5.5, −2.2]), p<0.0001 Change in body weight from baseline to week 26: • Liraglutide 0.6 mg: −2.5 kg • Liraglutide 1.2 mg: −4.0 kg • Liraglutide 1.8 mg: −5.1 kg • Placebo: −0.2 kg • All p<0.0001 Ratio of rate of symptomatic hypoglycaemic events with liraglutide vs placebo (ERR [95% CI]): • Liraglutide 0.6 mg: NS • Liraglutide 1.2 mg: 1.31 (1.03, 1.68), p=0.03 • Liraglutide 1.8 mg: NS Ratio of total insulin dose with liraglutide vs placebo at 26 weeks (ETR [95% CI]): • Liraglutide 0.6 mg: 0.95 (0.92, 0.99), p=0.0075 • Liraglutide 1.2 mg: 0.93 (0.90, 0.96), p<0.0001 • Liraglutide 1.8 mg: 0.90 (0.86, 0.93), p<0.0001

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
MRAs			
Schjoedt et al [63]	Adults (>18 years) with type 1 diabetes Albuminuria (>300 mg/24 h) eGFR >30 ml/min per 1.73 m^2 Taking ACEi or ARB Diabetic retinopathy Absence of clinical/laboratory evidence consistent with non-DKD Plasma potassium <4.5 mmol/l	Crossover trial with *n*=22 participants assigned to spironolactone 25 mg/day and placebo in random order for 2 months each	Geometric mean of albuminuria (95% CI): • Spironolactone 25 mg: 584 mg/24 h (441, 829) • Placebo: 831 mg/24 h (624, 1106) • % mean difference: −30% (−41, −17), $p<0.001$ Geometric mean of fractional albumin clearance (95% CI): • Spironolactone 25 mg: 129×10^{-6} θ_{Alb} (78, 210) • Placebo: 197×10^{-6} θ_{Alb} (122, 317) • % mean difference: −35% (−46, −20), $p<0.001$ Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −8 mmHg (−17, 1) • DBP: −3 mmHg (−7, 0.2) • p=NS Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −3 ml/min per 1.73 m^2 (−7, 0.1), p=NS
Schjoedt et al [64]	Adults (>18 years) with type 1 or type 2 diabetes Nephrotic range albuminuria (>2500 mg/24 h ×3 collections) eGFR >30 ml/min per 1.73 m^2 Taking ACEi or ARB Diabetic retinopathy Absence of clinical/laboratory evidence consistent with non-DKD Plasma potassium <4.5 mmol/l	Crossover trial with *n*=20 participants assigned to spironolactone 25 mg/day and placebo in random order for 2 months each	Geometric mean of albuminuria (95% CI): • Spironolactone 25 mg: 2510 mg/24 h (1831, 3441) • Placebo: 3718 mg/24 h (2910, 4749) • % mean difference: −32% (−42, −21), $p<0.001$ Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −6 mmHg (−10, −2) • DBP: −4 mmHg (−6, −2) • $p<0.01$ for all Mean (95% CI) difference in daytime blood pressure with spironolactone vs placebo: • SBP: −7 mmHg (−12, −3) • DBP: −5 mmHg (−7, −3) • $p<0.01$ for all Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −3 ml/min per 1.73 m^2 (−6, 1), p=NS

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
Schjoedt et al [65]	Adults (>18 and <70 years) with type 1 diabetes Hypertension (>135/90 but <170/100 mmHg) Normoalbuminuria and normal kidney function (plasma creatinine <88 μmol/l in women, <100 μmol/l in men) Plasma potassium <4.8 mmol/l No recent cardiovascular events	Crossover trial with *n*=17 participants assigned to spironolactone 25 mg/day and placebo in random order for 1 month each	Change in measured GFR induced by i.v. clonidine injection (indication of impaired autoregulation [95% CI]): • Spironolactone 25 mg: −15 ml/min per 1.73 m^2 (−19, −11) • Placebo: −11 ml/min per 1.73 m^2 (−17, −5) • Mean difference: −4 ml/min per 1.73 m^2 (−10, −3), *p*=NS Change in mean arterial pressure induced by i.v. clonidine injection (95% CI): • Spironolactone 25 mg: −19 mmHg (−21, −17) • Placebo: −17 mmHg (−21, −13) • Mean difference: −2 mmHg (−6, −2), *p*=NS Correlation between clonidine-induced GFR changes (indication of impaired autoregulation) and diabetes duration among placebo group: • *R*=0.67, *p*<0.01
Nielsen et al [62]	Adults (>18 and <80 years) with type 1 diabetes Microalbuminuria (30–300 mg/24 h in at least two of three urine samples) Taking ACEi or ARB HbA_{1c} <10% Plasma potassium <4.6 mmol/l Without severe hypertension (<160/100 mmHg)	Crossover trial with *n*=21 participants assigned to spironolactone 25 mg/day and placebo in random order for 60 days each	Geometric mean of urinary albumin excretion rate (95% CI): • Spironolactone 25mg: 35 mg/24 h (16, 72) • Placebo: 90 mg/24 h (61, 121) • % mean difference: −60% (−80, −21), *p*=0.011 Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −3 mmHg (−8, 3) • DBP: 0 mmHg (−3, 3) • *p*=NS for all Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −5 ml/min per 1.73 m^2 (−8, −2), *p*=0.003 % difference in tubular injury biomarkers with spironolactone vs placebo (95% CI): • Urinary NGAL/Cr: 22% (−153, 76) • Urinary LFABP/Cr: −26% (−46, 241) • Urinary KIM1/Cr: −61% (−43, 358) • *p*=NS for all

Adapted with permission from Liu et al [46]

ACEi, ACE inhibitor; Cr, creatinine; DBP, diastolic blood pressure; ERR, estimated rate ratio; ETD, estimated treatment difference; ETR, estimated treatment ratio; KIM1, kidney injury molecule-1; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; SBP, systolic blood pressure

In inducing natriuresis, SGLT2i improve blood pressure. Furthermore, SGLT2i have been demonstrated to reduce kidney tissue hypoxia and inflammation in experimental models and in humans [30, 31]. The very similar benefits seen in people with CKD with or without diabetes suggests that the effect on hyperglycaemia is of minor importance for the kidney benefit [32].

In type 1 diabetes, SGLT2i have principally been investigated as glucose-lowering therapies used in conjunction with insulin (Table 1). The EASE, DEPICT and inTandem (studying the SGLT1 and 2 inhibitor sotagliflozin) trial programmes each consisted of a series of randomised placebo-controlled trials assessing the effects of SGLT2i on HbA_{1c} levels in adults with type 1 diabetes over 24–52 weeks' follow-up [33–36]. SGLT2i use was consistently associated with improvements in HbA_{1c}, as well as with reductions in total daily insulin dose, weight and blood pressure. Moreover, SGLT2i did not increase hypoglycaemia risk; rather, these agents reduced participant-reported symptomatic hypoglycaemic events, particularly nocturnal episodes [35].

While no RCTs have examined the effects of SGLT2i on primary kidney outcomes in type 1 diabetes, post hoc analyses of the EASE, DEPICT and inTandem trial programmes have yielded findings suggesting similar physiological effects in people with type 1 diabetes as in those with type 2 diabetes or with non-diabetic CKD. In pooled analyses from each of these three type 1 diabetes trial programmes, among people with a UACR >3 mg/mmol at baseline, SGLT2i resulted in a reduction in UACR of as much as 30% over 52 weeks' follow-up [37–39]. Additionally, these studies noted an acute 'dip' in eGFR with SGLT2i, suggesting a therapeutic reduction in glomerular hypertension. Furthermore, increases in haematocrit and uric acid-lowering effects were observed, which is relevant because these biochemical alterations are closely linked statistically as 'mediators' of clinical benefits of SGLT2i in kidney and cardiovascular outcome trials [40, 41]. These concordant effects on mediators of cardiorenal benefits support the hypothesis that physiological mechanisms of cardiorenal protection may also be pertinent in individuals with type 1 diabetes treated with SGLT2i. In line with this hypothesis, an observational study of 200 adults with type 1 diabetes demonstrated improvements in albuminuria and in eGFR with SGLT2i use over 12 months among adults with a baseline eGFR <90 ml/min per 1.73 m^2 [42]. In another post hoc analysis of the inTandem trials using predictive modelling, sotagliflozin was reported to reduce the estimated risk of CVD and ESKD [43].

Despite apparent kidney and cardiovascular benefits, associations between SGLT2i and increased risk of diabetic ketoacidosis (DKA) have limited the implementation of this drug class in type 1 diabetes. A meta-analysis of 18 RCTs including >7000 participants identified a 2.8-fold greater risk of DKA with SGLT2i use compared with placebo in adults with type 1 diabetes [44]. Notably, DKA risk increased with higher SGLT2i doses and was modified by various factors including BMI and insulin resistance. Specifically, SGLT2 inhibition tends to be associated with euglycaemic DKA, which is more difficult to detect in the absence of regular ketone monitoring. More widespread use of SGLT2i in type 1 diabetes will necessitate implementation of strategies to assess and mitigate DKA risk, including preventative measures, patient education and continuous ketone monitoring, as well as a better understanding of the potential benefits for clinical cardiorenal outcomes, especially in high-risk populations such as people with CKD (Table 2) [46, 47].

Glucagon-like peptide 1 receptor agonists GLP1-RAs promote glucose-dependent insulin secretion and decrease glucagon secretion, providing glycaemic benefits. With respect to non-glycaemic outcomes, GLP1-RAs promote weight loss and have been investigated in randomised placebo-controlled trials focusing on cardiovascular outcomes in adults with type 2 diabetes and high cardiovascular risk. In these trials, GLP1-RAs have consistently demonstrated benefits for both primary cardiovascular and secondary kidney outcomes. Specifically, a meta-analysis of the ELIXA, LEADER, SUSTAIN-6, EXSCEL, REWIND and AMPLITUDE-O trials in type 2 diabetes estimated a 21% reduction in the risk of new-onset macroalbuminuria, eGFR decline, progression to ESKD or death attributable to kidney causes with GLP1-RAs compared with placebo [48]. Kidney benefits may be even greater among those with CKD at baseline [49]. The ongoing FLOW trial (NCT03819153) will be the first large multinational randomised placebo-controlled trial to primarily investigate the effects of a GLP1-RA, once-weekly subcutaneous semaglutide, on major kidney outcomes in adults with type 2 diabetes and CKD [50].

The kidney-protective effects of GLP1-RAs are believed to result from reductions in inflammation and oxidative stress, in part through direct binding to glucagon-like peptide 1 (GLP1) receptors present on kidney glomerular and tubular cells [51]. A study conducted using a rat model of type 1 diabetes demonstrated reduced inflammatory cell infiltration and decreased glomerular expression of inflammatory markers, including TGF-β1 and intercellular adhesion molecule-1, with administration of exendin-4 [51]. Notably, reduced inflammation was accompanied by decreased glomerular hypertrophy, mesangial expansion and type IV collagen deposition. In another study using a rat model of diabetes, GLP1-RAs reduced markers of oxidative stress in the kidney and ameliorated AGE-induced injury [52]. Furthermore, GLP1-RAs are effective at inducing body weight loss and improving insulin sensitivity, which may have kidney and cardiovascular benefits in type 1 diabetes.

Table 2 Strategies to mitigate risk of DKA with SGLT2i use in people with type 1 diabetes

Intervention	Details
Appropriate patient selection	Select patients with no history of reoccurring DKA, normal blood ketone levels (<0.6 mmol/l), low DKA risk factors, good adherence to treatment plans and good lifestyle/behavioural factors [45]. Current label indications in Europe and Japan call for selection of patients with a BMI ≥27 kg/m^2 and a total daily insulin dose of at least 0.5 U kg^{-1} day^{-1}
Enhanced patient education	All patients should be well informed about treatment protocols, DKA risk factors and sick day management Patients should work together with healthcare providers to optimise insulin doses and create a consistent and healthy diet to minimise risk of DKA
Lower dose of SGLT2i	Lower doses of SGLT2i may still be effective while also decreasing risk of DKA [35] Initiate SGLT2 inhibitors at lower doses and titrate up in those with a good response
Limited insulin dose reductions	Reduce basal and prandial insulin after initiation of SGLT2 inhibition by 10–20% in patients with good glycaemic control to mitigate risk of hypoglycaemia Lower or no reductions in insulin may be required for patients with less intensive glycaemic control Too high a reduction in insulin may lead to DKA
Close follow-up	Adjust insulin doses accordingly with close follow-up by healthcare provider based on blood glucose and ketone monitoring
Glucose monitoring	Frequent manual glucose monitoring or continuous glucose monitoring should be carried out to enable quick readjustment of insulin dose if required
Ketone monitoring	Self-testing of β-hydroxybutyrate levels with a blood ketone meter should be carried out routinely, as euglycaemic DKA cannot be detected by glucose monitoring alone. Unlike ketone monitoring in type 1 diabetes populations without SGLT2i use, among SGLT2i users, ketone levels should be tested in the event of symptoms of DKA regardless of the level of blood glucose Urine ketone testing can be used if necessary but this only measures acetoacetate and not β-hydroxybutyrate and will be an estimation of average concentrations since the last void In future clinical practice, continuous ketone monitoring will play a role in the surveillance of ketogenesis and DKA

Adapted with permission from Liu et al [46]

In type 1 diabetes, studies of GLP1-RAs as an adjunctive therapy to insulin have focused on glycaemic control and body weight reduction (Table 1). The ADJUNCT ONE and ADJUNCT TWO trials together randomised >2000 adults with type 1 diabetes to once-daily subcutaneous injections of liraglutide compared with placebo in addition to insulin for 26 and 52 weeks, respectively [53, 54]. Overall, the ADJUNCT programme demonstrated dose-dependent improvements in HbA_{1c}, a decrease in the daily insulin dose and a reduction in body weight with liraglutide compared with placebo. A meta-analysis of five randomised placebo-controlled trials of liraglutide in type 1 diabetes validated these findings and additionally demonstrated no association of liraglutide with severe hypoglycaemia or DKA [55]. Among the GLP1-RA agents, once-weekly semaglutide may be especially promising in type 1 diabetes, as this agent has demonstrated superiority over other GLP1-RAs in terms of glycaemic control and weight loss in type 2 diabetes, as well as good tolerability [56]. The effects of semaglutide on kidney oxygenation, albuminuria and eGFR will be assessed in people with type 1 diabetes as part of the REMODEL-T1D mechanistic trial (NCT05822609).

With the results of the FLOW trial anticipated next year, as well as high rates of obesity and CVD in type 1 diabetes, there remains an unmet need for additional mechanistic and CVD/kidney outcome studies of GLP1-RAs in the population with type 1 diabetes and CKD [50]. Interest in this area similarly applies to dual GLP1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists such as tirzepatide, which have profound effects on glycaemic control and body weight (e.g. 11 kg body weight reduction in the SURPASS-4 trial), preserve the eGFR slope and reduce the UACR [57, 58]. Concurrently, triple GIP, GLP1 and glucagon receptor agonists such as retatrutide are around the corner, which have impressive effects on glycaemic control, obesity and fatty liver disease [59, 60].

Mineralocorticoid receptor antagonists MRAs act by preventing aldosterone binding to mineralocorticoid receptors. The steroidal MRAs spironolactone (first generation) and eplerenone (second generation) were the first to enter clinical practice and act as potassium-sparing diuretics with potent antihypertensive effects. Reductions in morbidity and mortality with steroidal MRA use among individuals with HF with reduced ejection fraction have led to these agents being included as cornerstones of medical therapy for HF [61].

Kidney effects of steroidal MRAs have primarily been investigated in type 2 diabetes and CKD, although several small crossover studies have been performed in adults with type 1 diabetes and CKD, where use of spironolactone resulted in a 30–60% reduction in albuminuria compared

with placebo (Table 1) [62–65]. In a meta-analysis of 16 RCTs of adults with diabetes and CKD (four of which included people with type 1 diabetes), spironolactone added to standard therapy was associated with a reduction in 24 h urinary albumin/protein excretion [66]. However, assessment of long-term, hard clinical kidney endpoints has been limited by the three- to fivefold higher risk of hyperkalaemia with spironolactone use [66]. For this reason, steroidal MRA use is discouraged in severe CKD.

Over the last few years, novel non-steroidal MRAs such as finerenone have been developed that demonstrate greater mineralocorticoid receptor selectivity and other pharmacokinetic differences compared with steroidal MRAs [67]. In safety and tolerability studies conducted in adults with CKD, finerenone was associated with lowering of albuminuria compared with placebo, and a reduced risk of hyperkalaemia compared with spironolactone [68]. Subsequently, in the large randomised placebo-controlled FIDELIO-DKD trial including adults with type 2 diabetes and CKD, finerenone reduced the risk of the primary kidney outcome (a composite of kidney failure, sustained eGFR decline ≥40% or kidney death) by ~20% [69]. While hyperkalaemia occurred more frequently with finerenone than with placebo, this was often mild or moderate and resulted in few drug discontinuations (2.3% vs 0.9%, respectively), despite study participants also being on maximum-tolerated RAS inhibitor therapy. Additionally, finerenone demonstrated significant cardiovascular benefits in adults with type 2 diabetes and CKD, evaluated in the FIGARO-DKD trial [70]. Notably, kidney and cardiovascular benefits of finerenone were apparent even in combination with SGLT2i and GLP1-RA use in secondary analyses of the FIDELIO-DKD and FIGARO-DKD trials [71, 72]. The ongoing CONFIDENCE trial (NCT05254002) is an international randomised controlled double-blind trial that will directly assess the effects of finerenone plus empagliflozin on albuminuria and characterise the efficacy and safety of this drug combination in the setting of type 2 diabetes.

Finerenone's kidney-protective effects likely stem from suppression of inflammatory and pro-fibrotic pathways [73]. Compared with steroidal MRAs, non-steroidal MRAs exert stronger anti-inflammatory and anti-fibrotic effects, probably related to their distinct effects on tissue-specific gene activation [67]. In animal models finerenone reduced the expression of genes encoding monocyte chemoattractant protein-1, matrix metalloproteinase-2 and plasminogen activator inhibitor-1 (related to tissue remodelling and fibrosis) in the kidney, and additionally demonstrated beneficial immunomodulatory effects [73]. While non-steroidal MRAs have not yet been investigated in type 1 diabetes, based on their observed benefits in type 2 diabetes and their mechanism of action, similar kidney-protective effects are anticipated, emphasising the need for dedicated studies with finerenone in people with type 1 diabetes and CKD, including their use in combination with other 'repurposed' therapies such as SGLT2i and GLP1-RAs.

Potential future treatments for CKD in type 1 diabetes

Beyond the classes of medication discussed above, additional pharmacological treatments are being investigated for use in DKD that may be suitable for use in type 1 diabetes.

Endothelin receptor antagonists (ERAs) have been studied in diabetes and CKD for over a decade, with early studies ending prematurely because of complications associated with fluid retention. Newer ERAs have since been designed that preferentially target endothelin A receptors, associated with inflammation and podocytopathy, over endothelin B receptors, associated with vasodilation and natriuresis [74]. The largest trial of ERAs, SONAR, including 2648 participants with type 2 diabetes and proteinuric CKD, demonstrated that atrasentan on top of RAS inhibition significantly lowered the risk of a doubling of serum creatinine or ESKD compared with placebo by 35% [75]. Since then, more potent endothelin A-specific ERAs have been under development for use in CKD. The combination of these agents with SGLT2 inhibition is particularly interesting considering the natriuresis and protection against HF outcomes associated with SGLT2i [76]. Specifically, a study of zibotentan, a highly selective endothelin A ERA, in combination with dapagliflozin in participants with type 2 diabetes (NCT05570305) is currently underway, with similar phase 2 trials in type 1 diabetes being proposed.

Another potential novel therapeutic option for the treatment of CKD in diabetes is the use of soluble guanylate cyclase (sGC) activators. sGC is an enzyme that catalyses the formation of cGMP after nitric oxide (NO) binding [77]. Reduced NO bioavailability and associated impairments in NO–sGC–cGMP signalling have been associated with CKD onset and progression in diabetes. Preclinical models have suggested that stimulation of sGC in diabetes can increase cGMP formation, with resultant improvements in kidney inflammation/fibrosis, glomerular permeability and kidney blood flow [78]. In a Phase II study of 156 individuals with type 2 diabetes and UACR >22.6 and <565 mg/mmol, the sGC stimulator praliciguat demonstrated a non-statistically significant placebo-adjusted decrease in UACR of 15%, accompanied by reductions in blood pressure [79]. Other sGC stimulators and activators are currently in development for the treatment of CKD (NCT04507061, NCT04750577), with at least one study including participants with type 1 diabetes.

Targeting inflammatory pathways, specifically the NLR family pyrin domain containing 3 (NLRP3)/IL-1β/IL6/C-reactive protein (CRP) pathway, has emerged as another strategy for improving cardiorenal outcomes in high-risk

populations. This was emphasised in the CANTOS trial, in which a monoclonal antibody targeting IL-1β in individuals with established atherosclerotic CVD and evidence of systemic inflammation reduced the risk of major adverse cardiovascular events (MACE) by 15–17%, an effect that was likely to be mediated by reductions in serum CRP concentrations [80, 81]. A similar effect size was also observed in a substudy of participants with eGFR <60 ml/min per 1.73 m^2 [82]. The Phase II RESCUE trial subsequently evaluated targeting the more downstream IL-6 with ziltivekimab in participants with CKD and elevated high-sensitivity CRP (hsCRP) [83]. Compared with placebo, ziltivekimab reduced hsCRP concentrations by up to 92%, prompting the formal cardiovascular outcome trial, ZEUS (NCT05021835). ZEUS will enrol 6200 participants with stage 3 or 4 CKD and elevated hsCRP levels, with a primary MACE outcome and secondary kidney endpoints including kidney disease progression, UACR reductions and eGFR slope. ZEUS will also include participants with type 1 diabetes. Additional trials are also underway in participants with type 1 diabetes targeting diverse pathways including oxidative stress, using nicotinamide adenine dinucleotide phosphate oxidase (Nox)-1/4 inhibitors, and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, using bardoxolone (NCT03366337, NCT03550443) [84, 85].

Considering the mechanistic overlap in the development and progression of CKD in type 1 and type 2 diabetes, there exists a strong rationale for simultaneously developing novel CKD therapies for use in both type 1 diabetes and type 2 diabetes and studying the repurposing of existing type 2 diabetes CKD therapies for the treatment of CKD in people with type 1 diabetes.

Conclusion

With the completion of several cardiovascular and kidney outcome trials involving an increasing number of therapeutic agents, tremendous progress has been made in the management of individuals with type 2 diabetes and CKD. Regrettably, people with type 1 diabetes have not been able to benefit from this expanded armamentarium of therapeutic agents and remain at unacceptably high risk of kidney and cardiovascular complications. The translation of these and other novel therapies under development into the clinical care of individuals with type 1 diabetes with established complications requires a concerted demonstration of efficacy and safety in dedicated and properly designed cardiorenal outcome trials.

Supplementary Information The online version contains a slide of the figure for download available at https://doi.org/10.1007/s00125-023-06015-1.

Funding VSS is supported by a Department of Medicine Eliot Phillipson Clinician-Scientist Training Program, a Banting and Best Diabetes Centre Postdoctoral Fellowship at the University of Toronto and a Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Research Award. CPL is supported by an American Kidney Fund's Clinical Scientist in Nephrology Award. DZIC is supported by a Department of Medicine, University of Toronto Merit Award and receives support from the CIHR, Diabetes Canada and the Heart & Stroke/Richard Lewar Centre of Excellence in Cardiovascular Research. DZIC is also the recipient of a 5 year CIHR–Kidney Foundation of Canada Team Grant Award. PR is supported by a Novo Nordisk Foundation grant (NNF22OC0077730; 'Multifactorial intervention to reduce cardiorenal disease in type 1 diabetes – a prospective, randomised, open, multicenter study – the Steno 1 study'). JSS is supported by the Diabetes Research Institute Foundation.

Authors' relationships and activities VSS has received conference travel support from Merck. DZIC has received honoraria from Boehringer Ingelheim–Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi Tanabe, AbbVie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL Behring, Otsuka, Novartis, Youngene, Lexicon, Inversago and Novo Nordisk and has received operational funding for clinical trials from Boehringer Ingelheim–Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL Behring and Novo Nordisk. PR has received the following: consultancy and/or speaking fees (to his institution) from AbbVie, Abbott, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Novo Nordisk and Sanofi-Aventis, and research grants from AstraZeneca, Bayer and Novo Nordisk. REP has received consulting fees from Bayer, Corcept Therapeutics, Dexcom, Hanmi Pharmaceutical, Merck, Novo Nordisk, Pfizer, Sanofi, Scohia Pharma and Sun Pharmaceutical Industries, and grants/research support from Hanmi Pharmaceutical, Janssen, Metavention, Novo Nordisk, Poxel and Sanofi. All funds are paid directly to REP's employer, AdventHealth, a non-profit organisation that supports education and research. JSS has been an advisor to 4Immune, Adocia, Altheia, Arecor, AstraZeneca, Avotres, Bayer, COUR, Cue Biopharma, Dance Biopharm/Aerami, Diasome, Enthera, Imcyse, Immunomolecular Therapeutics, Kriya, Novo Nordisk, Oramed, Orgenesis, Precigen/ActoBiotics, Provention Bio, Sanofi, Signos, Vertex and Viacyte. He is a member of the Board of Directors of Dexcom and Applied Therapeutics. He is Chair of the Strategic Advisory Board of the EU INNODIA consortium. P-HG has received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, Sanofi and Sciarc. He is an advisory board member for AbbVie, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Nestlé, Novartis, Novo Nordisk and Sanofi. CPL declares that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement VSS, CPL, P-HG, HJLH, REP, PR, JSS and DZIC conceived and designed the manuscript; VSS, CPL and DZIC drafted the paper; VSS, CPL, P-HG, HJLH, REP, PR, JSS and DZIC performed critical revision. All authors approved the final version to be published.

References

1. Rossing P, Caramori ML, Chan JCH et al (2022) KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int 102:S1–S127. https://doi.org/10.1016/j.kint.2022.06.008
2. Bakris GL, Molitch M (2018) Are all patients with type 1 diabetes destined for dialysis if they live long enough? Probably not. Diabetes Care 41:389–390. https://doi.org/10.2337/dci17-0047

3. Dena M, Svensson AM, Olofsson KE et al (2021) Renal complications and duration of diabetes: an international comparison in persons with type 1 diabetes. Diabetes Ther 12(12):3093–3105. https://doi.org/10.1007/s13300-021-01169-w
4. Jansson Sigfrids F, Groop PH, Harjutsalo V (2022) Incidence rate patterns, cumulative incidence, and time trends for moderate and severe albuminuria in individuals diagnosed with type 1 diabetes aged 0–14 years: a population-based retrospective cohort study. Lancet Diabetes Endocrinol 10:489–498. https://doi.org/10.1016/S2213-8587(22)00099-7
5. Halminen J, Sattaer N, Rawshani A et al (2022) Range of risk factor levels, risk control, and temporal trends for nephropathy and end-stage kidney disease in patients with type 1 and type 2 diabetes. Diabetes Care 45:2326–2335. https://doi.org/10.2337/dc22-0926
6. Graves L, Donaghue K (2019) Management of diabetes complications in youth. Ther Adv Endocrinol Metab 10:2042018819863226. https://doi.org/10.1177/2042018819863226
7. Kristofi R, Bodegard J, Norhammar A et al (2021) Cardiovascular and renal disease burden in type 1 compared with type 2 diabetes: a two-country nationwide observational study. Diabetes Care 44:1211–1218. https://doi.org/10.2337/dc20-2839
8. McAllister DA, Read SH, Kerssens J et al (2018) Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 138:2774–2786. https://doi.org/10.1161/CIRCULATIONAHA.118.034986
9. Mohandes S, Doke T, Hu H, Mukhi D, Dhillon P, Susztak K (2023) Molecular pathways that drive diabetic kidney disease. J Clin Invest 133:e165654. https://doi.org/10.1172/JCI165654
10. Mora-Fernández C, Dominguez-Pimentel V, Muros de Fuentes M, Gorriz JL, Martinez-Castelao A, Navarro-Gonzalez JF (2014) Diabetic kidney disease: from physiology to therapeutics. J Physiol 592:3997–4009. https://doi.org/10.1113/jphysiol.2014.272328
11. Forbes JM, Thorburn DR (2018) Mitochondrial dysfunction in diabetic kidney disease. Nat Rev Nephrol 14:291–312. https://doi.org/10.1038/nrneph.2018.9
12. Tan ALY, Forbes JM, Cooper ME (2007) AGE, RAGE, and ROS in diabetic nephropathy. Semin Nephrol 27:130–143. https://doi.org/10.1016/j.semnephrol.2007.01.006
13. Giacchetti G, Sechi LA, Rilli S, Carey RM (2005) The renin-angiotensin-aldosterone system, glucose metabolism and diabetes. Trends Endocrinol Metab 16:120–126. https://doi.org/10.1016/j.tem.2005.02.003
14. Leehey DJ, Singh AK, Alavi N, Singh R (2000) Role of angiotensin II in diabetic nephropathy. Kidney Int Suppl 58(Suppl 77):S93-98. https://doi.org/10.1046/j.1523-1755.2000.07715.x
15. Lytvyn Y, Godoy LC, Scholtes RA, van Raalte DH, Cherney DZ (2019) Mineralocorticoid antagonism and diabetic kidney disease. Curr Diab Rep 19:4. https://doi.org/10.1007/s11892-019-1123-8
16. ElSayed NA, Aleppo G, Aroda VR et al (2023) 10. Cardiovascular disease and risk management: standards of care in diabetes-2023. Diabetes Care 46:S158–S190. https://doi.org/10.2337/dc23-S010
17. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group (2002) Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 287:99–111. https://doi.org/10.1001/jama.287.19.2563
18. de Boer IH, DCCT/EDIC Research Group (2014) Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Diabetes Care 37:24–30. https://doi.org/10.2337/dc13-2113
19. Lewis E, Hunsicker L, Bain R, Rohde R (1993) The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Eng J Med 329(20):1456–1462. https://doi.org/10.1056/NEJM199311113292004
20. EUCLID Study Group (1997) Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 349:1787–1792. https://doi.org/10.1016/S0140-6736(96)10244-0
21. Strippoli GFM, Bonifati C, Craig M, Navaneethan SD, Craig JC (2006) Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev 4:CD006257. https://doi.org/10.1002/14651858.CD006257
22. Mauer M, Zinman B, Gardiner R et al (2009) Renal and retinal effects of enalapril and losartan in type 1 diabetes (RASS). N Engl J Med 361:40–51. https://doi.org/10.1056/NEJMoa0808400
23. Doria A, Galecki AT, Spino C et al (2020) Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med 382:2493–2503. https://doi.org/10.1056/NEJMoa1916624
24. ElSayed NA, Aleppo G, Aroda VR et al (2023) 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. Diabetes Care 46:S140–S157. https://doi.org/10.2337/dc23-S009
25. Botana M, Escalada J, Merchante Á, Reyes R, Rozas P (2022) Prevention of cardiorenal complications with sodium–glucose cotransporter type 2 inhibitors: a narrative review. Diabetes Ther 13:5–17. https://doi.org/10.1007/s13300-022-01277-1
26. Perkovic V, Jardine MJ, Neal B et al (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 380:2295–2306. https://doi.org/10.1056/NEJMoa1811744
27. Heerspink HJL, Stefansson BV, Correa-Rotter R et al (2020) Dapagliflozin in patients with chronic kidney disease. N Engl J Med 383:1436–1446. https://doi.org/10.1056/NEJMoa2024816
28. EMPA-KIDNEY Collaborative Group (2023) Empagliflozin in patients with chronic kidney disease. N Engl J Med 388:117–127. https://doi.org/10.1056/NEJMoa2204233
29. Liu H, Sridhar VS, Boulet J et al (2022) Cardiorenal protection with SGLT2 inhibitors in patients with diabetes mellitus: from biomarkers to clinical outcomes in heart failure and diabetic kidney disease. Metabolism 126:154918. https://doi.org/10.1016/j.metabol.2021.154918
30. Laursen JC, Sondergaard-Heinrich N, Lopes de Melo JM et al (2021) Acute effects of dapagliflozin on renal oxygenation and perfusion in type 1 diabetes with albuminuria: a randomised, double-blind, placebo-controlled crossover trial. eClinicalMedicine 37:100895. https://doi.org/10.1016/j.eclinm.2021.100895
31. Schaub JA, AlAkwaa FM, McCown PJ et al (2023) SGLT2 inhibitors mitigate kidney tubular metabolic and mTORC1 perturbations in youth onset type 2 diabetes. J Clin Invest 133(5):e164486. https://doi.org/10.1172/JCI164486
32. Baigent C, Emberson JR, Haynes R et al (2022) Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet 400:1788–1801. https://doi.org/10.1016/S0140-6736(22)02074-8
33. Rodbard HW, Giaccari A, Lajara R et al (2020) Sotagliflozin added to optimized insulin therapy leads to HbA1c reduction without weight gain in adults with type 1 diabetes: a pooled analysis of inTandem1 and inTandem2. Diabetes Obes Metab 22:2089–2096. https://doi.org/10.1111/dom.14127
34. Garg SK, Henry RR, Banks P et al (2017) Effects of Sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 377:2337–2348. https://doi.org/10.1056/NEJMoa1708337
35. Rosenstock J, Marquard J, Laffel LM et al (2018) Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 41:2560–2569. https://doi.org/10.2337/dc18-1749
36. Phillip M, Mathieu C, Lind M et al (2021) Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: pooled 52-week outcomes from the DEPICT-1 and -2 studies. Diabetes Obes Metab 23:549–560. https://doi.org/10.1111/dom.14248

37. van Raalte DH, Bjornstad P, Persson F et al (2019) The impact of sotagliflozin on renal function, albuminuria, blood pressure, and hematocrit in adults with type 1 diabetes. Diabetes Care 42:1921–1929. https://doi.org/10.2337/dc19-0937
38. Cherney DZI, Bjornstad P, Perkins BA et al (2021) Kidney effects of empagliflozin in people with type 1 diabetes. Clin J Am Soc Nephrol 16:1715–1719. https://doi.org/10.2215/CJN.07700621
39. Groop PH, Dandona P, Phillip M et al (2020) Effect of dapagliflozin as an adjunct to insulin over 52 weeks in individuals with type 1 diabetes: post-hoc renal analysis of the DEPICT randomised controlled trials. Lancet Diabetes Endocrinol 8:845–854. https://doi.org/10.1016/S2213-8587(20)30280-1
40. Li J, Woodward M, Perkovic V et al (2020) Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. JACC Heart Fail 8:57–66. https://doi.org/10.1016/j.jchf.2019.08.004
41. Li J, Neal B, Perkovic V et al (2020) Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. Kidney Int 98:769–777. https://doi.org/10.1016/j.kint.2020.04.051
42. Palanca A, van Nes F, Pardo F, Ampudia Blasco FJ, Mathieu C (2022) Real-world evidence of efficacy and safety of SGLT2 inhibitors as adjunctive therapy in adults with type 1 diabetes: a European two-center experience. Diabetes Care 45:650–658. https://doi.org/10.2337/dc21-1584
43. Stougaard EB, Rossing P, Vistisen D et al (2023) Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, reduces the risk of cardiovascular and kidney disease as assessed by Steno T1 Risk Engine in adults with type 1 diabetes. Diabetes Obes Metab 25(7):1874–1882. https://doi.org/10.1111/dom.15047
44. Musso G, Sircana A, Saba F, Cassader M, Gambino R (2020) Assessing the risk of ketoacidosis due to sodium-glucose cotransporter (SGLT)-2 inhibitors in patients with type 1 diabetes: a meta-analysis and meta-regression. PLOS Med 17:e1003461. https://doi.org/10.1371/journal.pmed.1003461
45. Danne T, Garg S, Peters AL et al (2019) International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. Diabetes Care 42:1147–1154. https://doi.org/10.2337/dc18-2316
46. Liu H, Sridhar VS, Perkins BA, Rosenstock J, Cherney DZI (2022) SGLT2 inhibition in type 1 diabetes with diabetic kidney disease: potential cardiorenal benefits can outweigh preventable risk of diabetic ketoacidosis. Curr Diab Rep 22:317–332. https://doi.org/10.1007/s11892-022-01471-2
47. Thomas M, Harjutsalo V, Feodoroff M et al (2020) The long-term incidence of hospitalization for ketoacidosis in adults with established T1D-a prospective cohort study. J Clin Endocrinol Metab 105:231–241. https://doi.org/10.1210/clinem/dgz003
48. Sattar N, Lee MMY, Kristensen SL et al (2021) Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 9:653–662. https://doi.org/10.1016/S2213-8587(21)00203-5
49. Shaman AM, Bain SC, Bakris G et al (2022) Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: pooled analysis of SUSTAIN 6 and LEADER. Circulation 145:575–585. https://doi.org/10.1161/CIRCULATIONAHA.121.055459
50. Rossing P, Baeres FMM, Bakris G et al (2023) The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant. https://doi.org/10.1093/ndt/gfad009
51. Kodera R, Shikata K, Kataoka HU et al (2011) Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. Diabetologia 54:965–978. https://doi.org/10.1007/s00125-010-2028-x
52. Ojima A, Ishibashi Y, Matsui T et al (2013) Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of streptozotocin-induced diabetic rats by blocking advanced glycation end product-induced protein arginine methyltranferase-1 expression. Am J Pathol 182:132–141. https://doi.org/10.1016/j.ajpath.2012.09.016
53. Mathieu C, Zinman B, Hemmingsson JU et al (2016) Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the adjunct one treat-to-target randomized trial. Diabetes Care 39:1702–1710. https://doi.org/10.2337/dc16-0691
54. Ahren B, Hirsch IB, Pieber TR et al (2016) Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the adjunct two randomized trial. Diabetes Care 39:1693–1701. https://doi.org/10.2337/dc16-0690
55. Dimitrios P, Doumas M, Vasilios K et al (2020) Liraglutide as adjunct to insulin treatment in patients with type 1 diabetes: a systematic review and meta-analysis. Curr Diabetes Rev 16:313–326. https://doi.org/10.2174/1573399815666190614141918
56. Mann JFE, Hansen T, Idorn T et al (2020) Effects of once-weekly subcutaneous semaglutide on kidney function and safety in patients with type 2 diabetes: a post-hoc analysis of the SUSTAIN 1–7 randomised controlled trials. Lancet Diabetes Endocrinol 8:880–893. https://doi.org/10.1016/S2213-8587(20)30313-2
57. Jastreboff AM, Aronne LJ, Ahmad NN et al (2022) Tirzepatide once weekly for the treatment of obesity. N Engl J Med 387:205–216. https://doi.org/10.1056/NEJMoa2206038
58. Heerspink HJL, Sattar N, Pavo I et al (2022) Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol 10:774–785. https://doi.org/10.1016/S2213-8587(22)00243-1
59. Jastreboff AM, Kaplan LM, Frias JP et al (2023) Triple-hormone-receptor agonist retatrutide for obesity — a phase 2 trial. N Engl J Med 389:514–526. https://doi.org/10.1056/NEJMoa2301972
60. Rosenstock J, Frias J, Jastreboff AM et al (2023) Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. Lancet 402:529–544. https://doi.org/10.1016/S0140-6736(23)01053-X
61. Heidenreich PA, Bozkurt B, Aguilar D et al (2022) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 145(18):e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
62. Nielsen SE, Persson F, Frandsen E et al (2012) Spironolactone diminishes urinary albumin excretion in patients with type 1 diabetes and microalbuminuria: a randomized placebo-controlled crossover study. Diabet Med 29:184–190. https://doi.org/10.1111/j.1464-5491.2012.03585.x
63. Schjoedt KJ, Rossing K, Juhl TR et al (2005) Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int 68:2829–2836. https://doi.org/10.1111/j.1523-1755.2005.00756.x
64. Schjoedt KJ, Rossing K, Juhl TR et al (2006) Beneficial impact of spironolactone on nephrotic range albuminuria in diabetic nephropathy. Kidney Int 70:536–542. https://doi.org/10.1038/sj.ki.5001580
65. Schjoedt KJ, Christensen PK, Jorsal A et al (2009) Autoregulation of glomerular filtration rate during spironolactone treatment in hypertensive patients with type 1 diabetes: a randomized crossover trial. Nephrol Dial Transplant 24:3343–3349. https://doi.org/10.1093/ndt/gfp311
66. Hou J, Xiong W, Cao L, Wen X, Li A (2015) Spironolactone add-on for preventing or slowing the progression of diabetic

nephropathy: a meta-analysis. Clin Ther 37:2086-2103.e10. https://doi.org/10.1016/j.clinthera.2015.05.508
67. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B (2017) Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Handb Exp Pharmacol 243:271–305. https://doi.org/10.1007/164_2016_76
68. Bakris GL, Agarwal R, Chan JC et al (2015) Effect of finerenone on albuminuria in patients with diabetic nephropathy a randomized clinical trial. JAMA 314:884–894. https://doi.org/10.1001/jama.2015.10081
69. Bakris GL, Agarwal R, Anker SD et al (2020) Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 383:2219–2229. https://doi.org/10.1056/NEJMoa2025845
70. Pitt B, Filippatos G, Agarwal R et al (2021) Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med 385:2252–2263. https://doi.org/10.1056/NEJMoa2110956
71. Rossing P, Filippatos G, Agarwal R et al (2022) Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. Kidney Int Rep 7:36–45. https://doi.org/10.1016/j.ekir.2021.10.008
72. Rossing P, Agarwal R, Anker SD et al (2023) Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by glucagon-like peptide-1 receptor agonist use. Diabetes Obes Metab 25:407–416. https://doi.org/10.1111/dom.14883
73. Agarwal R, Kolkhof P, Bakris G et al (2021) Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J 42:152–161. https://doi.org/10.1093/eurheartj/ehaa736
74. Raina R, Chauvin A, Chakraborty R et al (2020) The role of endothelin and endothelin antagonists in chronic kidney disease. Kidney Dis 6:22–34. https://doi.org/10.1159/000504623
75. Heerspink HJL, Parving HH, Andress DL et al (2019) Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet 393:1937–1947. https://doi.org/10.1016/S0140-6736(19)30772-X
76. Chung EYM, Badve SV, Heerspink HJL, Wong MG (2023) Endothelin receptor antagonists in kidney protection for diabetic kidney disease and beyond? Nephrology 28:97–108. https://doi.org/10.1111/nep.14130
77. Buys ES, Zimmer DP, Chickering J et al (2018) Discovery and development of next generation sGC stimulators with diverse multidimensional pharmacology and broad therapeutic potential. Nitric Oxide Biol Chem 78:72–80. https://doi.org/10.1016/j.niox.2018.05.009
78. Hohenstein B, Daniel C, Wagner A, Stasch JP, Hugo C (2005) Stimulation of soluble guanylyl cyclase inhibits mesangial cell proliferation and matrix accumulation in experimental glomerulonephritis. Am J Physiol Ren Physiol 288:685–693. https://doi.org/10.1152/ajprenal.00280.2004
79. Hanrahan JP, de Boer IH, Bakris GL et al (2021) Effects of the soluble guanylate cyclase stimulator praliciguat in diabetic kidney disease: a randomized placebo-controlled clinical trial. Clin J Am Soc Nephrol 16:59–69. https://doi.org/10.2215/CJN.08410520
80. Ridker PM, Everett BM, Thuren T et al (2017) Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131. https://doi.org/10.1056/NEJMoa1707914
81. Ridker PM, MacFadyen JG, Everett BM et al (2018) Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 391:319–328. https://doi.org/10.1016/S0140-6736(17)32814-3
82. Ridker PM, Macfadyen JG, Glynn RJ et al (2018) Inhibition of interleukin-1β by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. J Am Coll Cardiol 71:2405–2414. https://doi.org/10.1016/j.jacc.2018.03.490
83. Ridker PM, Devalaraja M, Baeres FMM et al (2021) IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 397:2060–2069. https://doi.org/10.1016/S0140-6736(21)00520-1
84. Reutens AT, Jandeleit-Dahm K, Thomas M et al (2020) A physician-initiated double-blind, randomised, placebo-controlled, phase 2 study evaluating the efficacy and safety of inhibition of NADPH oxidase with the first-in-class Nox-1/4 inhibitor, GKT137831, in adults with type 1 diabetes and persistently elevated urinary albumin excretion: protocol and statistical considerations. Contemp Clin Trials 90:105892. https://doi.org/10.1016/j.cct.2019.105892
85. Nangaku M, Takama H, Ichikawa T et al (2023) Randomized, double-blind, placebo-controlled phase 3 study of bardoxolone methyl in patients with diabetic kidney disease: design and baseline characteristics of the AYAME study. Nephrol Dial Transplant 38:1204–1216. https://doi.org/10.1093/ndt/gfac242