SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA

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ABSTRACT

Chronic kidney disease (CKD) in patients with diabetes mellitus (DM) is a major problem of public health. Currently, many of these patients experience progression of cardiovascular and renal disease, even when receiving optimal treatment. In previous years, several new drug classes for the treatment of type 2 DM have emerged, including inhibitors of renal sodium–glucose co-transporter-2 (SGLT-2) and glucagon-like peptide-1 (GLP-1) receptor agonists. Apart from reducing glycaemia, these classes were reported to have other beneficial effects for the cardiovascular and renal systems, such as weight loss and blood pressure reduction. Most importantly, in contrast to all previous studies with anti-diabetic agents, a series of recent randomized, placebo-controlled outcome trials showed that SGLT-2 inhibitors and GLP-1 receptor agonists are able to reduce cardiovascular events and all-cause mortality, as well as progression of renal disease, in patients with type 2 DM. This document presents in detail the available evidence on the cardioprotective and nephroprotective effects of SGLT-2 inhibitors and GLP-1 analogues, analyses the potential mechanisms involved in these actions and discusses their place in the treatment of patients with CKD and DM.

Keywords: albuminuria, diabetic kidney disease, GLP-1 receptor agonists, proteinuria, SGLT-2 inhibitors

INTRODUCTION: THE UNMET NEEDS OF NEPHROPROTECTION AND CARDIOPROTECTION IN DIABETIC KIDNEY DISEASE

According to the World Health Organization, in 2014, an estimated 8.5% of adults worldwide had diabetes mellitus (DM),
with the total number projected to double by 2030 [1]. Diabetes is a potent cardiovascular risk factor, as patients with DM have a 2-fold higher risk of death compared with people without DM and equal to patients with a previous myocardial infarction (MI) [2, 3]. The co-existence of type 2 DM and hypertension has been long established with >90% of patients with type 2 DM being hypertensive [4]. The presence of hypertension increases cardiovascular risk by almost four times in patients with DM, whereas the presence of DM almost triples the risk of cardiovascular disease at any level of systolic blood pressure (SBP) [5, 6]. Chronic kidney disease (CKD) is another major risk factor for cardiovascular morbidity and mortality [7]. Diabetes is a leading cause of CKD, accounting for 30–50% of incident end-stage renal disease (ESRD) in the western world [8]. Microalbuminuria (A2 albuminuria category) is one of the earliest detectable manifestations of CKD in DM, with a prevalence of 25% after 10 years and an annual rate of progression to macroalbuminuria (A3 albuminuria category) around 3% [9]. However, current knowledge indicates that several patients with DM will progress to ESRD without advancing to micro- or macroalbuminuria, suggesting that ischaemic vascular disease or non-glomerular injury is involved in these cases [10, 11].

Evidence from clinical trials with primary renal outcomes in the previous decades supported that the use of single blockade of the renin–angiotensin system (RAS) was able to delay the progression of kidney disease in patients with proteinuric diabetic kidney disease (DKD) [12, 13]. Guidelines recommend the use of an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) for patients with DKD and micro- or macroalbuminuria [10, 14–16]. However, many patients with DKD will experience renal and cardiovascular disease progression, despite RAS blockade for various reasons, including uncontrolled blood pressure (BP), use of suboptimal doses of ACEi/ARB due to intolerance and angiotensin-II or aldosterone escape [17]. These observations led to examination of alternative pathways to delay DKD, such as combined use of ACEi and ARB, or addition of an endothelin antagonist, bardoxolone and others, all with disappointing results so far.

Adequate glycaemic control represents another unmet need. Half of patients with DM in western countries fail to achieve optimal glycaemic control (HbA1c <7%) [18]. In type 2 DM, the prevalence of obesity or overweight status is estimated at ~80%, while some established anti-diabetic therapies cause weight gain [19]. Progressive β-cell failure is another major problem with oral anti-diabetic agents, with one out of four patients eventually requiring insulin therapy. Over the previous years, novel oral or injectable drug classes for type 2 DM have emerged, including glucagon-like peptide-1 (GLP-1) analogues (also called GLP-1 receptor agonists), dipeptidyl peptidase-4 (DPP-4) inhibitors and inhibitors of renal sodium–glucose co-transporter-2 (SGLT-2); these drugs offer effective glycaemic control and can ameliorate abnormalities such as weight gain and progressive β-cell failure [20]. Following uncertainty over the cardiovascular safety of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, about 10 years ago [21], the Food and Drug Administration (FDA) in the USA required all new anti-diabetic agents to have proven non-inferiority compared with standard treatment in major cardiovascular outcomes before licensing [22]. After the first trials with DDP-4 inhibitors showing non-inferiority, studies with SGLT-2 inhibitors [23, 24] and GLP-1 analogues [25–27] showed superiority. That is, these agents reduced the incidence of cardiovascular events and, in some cases, improved mortality in patients with DM compared with standard practice. Secondary analyses of some of these trials suggested that these agents were also able to slow the progression of CKD. This document presents current evidence on the cardioprotective and nephroprotective effects of SGLT-2 inhibitors and GLP-1 analogues, analyses potential mechanisms involved in these beneficial actions and discusses their place in the treatment of patients with DKD.

**CARDIOPROTECTIVE PROPERTIES OF SGLT-2 INHIBITORS**

Two randomized controlled trials (RCTs) reported significant reductions in cardiovascular events and mortality following treatment with SGLT-2 inhibitors compared with placebo (Table 1). These are the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus patients (EMPA-REG OUTCOME) [23] and The CANagliflozin cardioVascular Assessment Study (CANVAS) [24]. The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) showed reduction in one of the two co-primary endpoints [30].

The EMPA-REG OUTCOME trial randomized 7028 patients with established cardiovascular disease to placebo, empagliflozin 10 mg or empagliflozin 25 mg for 3.1 years. The primary endpoint was the 3-point major adverse cardiovascular event (MACE) including cardiovascular mortality, non-fatal MI and non-fatal stroke [23]. Patients randomized to empagliflozin had a modest reduction in the primary endpoint [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.74–0.99; P = 0.04 for superiority; absolute risk reduction = 1.6%]. This was driven predominantly by a substantial reduction in cardiovascular death (HR 0.62, 95% CI 0.49–0.77), whereas non-fatal MI and stroke were not significantly different. Interestingly, the benefit from empagliflozin in EMPA-REG OUTCOME was similar in the two doses tested. In recognition of the statistically robust effect on cardiovascular mortality, the FDA recently granted an indication to empagliflozin for reducing the risk of cardiovascular death [31]. In addition, patients treated with empagliflozin in the EMPA-REG OUTCOME trial had a 35% reduction in heart failure hospitalization compared with placebo (HR 0.65, 95% CI 0.50–0.85), with a rapid separation in the survival curves suggesting acute benefit of the drug [32] and, most importantly, a 32% risk reduction in all-cause mortality (HR 0.68, 95% CI 0.57–0.82). No difference was observed in the rate of fatal/non-fatal stroke (HR 1.18, 95% CI 0.89–1.56). In subgroup analyses, empagliflozin demonstrated a consistent benefit on cardiovascular mortality across all subgroups studied [31].

In *post hoc* analyses of EMPA-REG OUTCOME, participants with a self-reported history of coronary artery bypass surgery treated with empagliflozin had profound reductions in cardiovascular and all-cause mortality, hospitalization for heart
<table>
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<th>Study</th>
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<tr>
<td>EMPA-REG OUTCOME</td>
<td>Double-blind</td>
<td>Type 2 DM with</td>
<td>7028</td>
<td>1:1:1 ratio: empagliflozin 10 mg, empagliflozin 25 mg, placebo</td>
<td>Median of 3.1 years</td>
<td>3-point MACE (cardiovascular mortality, non-fatal MI and non-fatal stroke)</td>
<td>Primary outcome: HR 0.86, 95% CI 0.74–0.99; cardiovascular death: HR 0.62, 95% CI 0.49–0.77; all-cause mortality: HR 0.68, 95% CI 0.57–0.82; HF hospitalization: HR 0.65, 95% CI 0.50–0.85; stroke: HR 1.18, 95% CI 0.89–1.56</td>
<td>Mean Age: 63.1 years</td>
<td>Progression to macroalbuminuria, doubling of Scr, initiation of RRT or death from renal disease</td>
<td>Renal composite: HR 0.61, 95% CI 0.53–0.70; Doubling of Scr and eGFR of ≤45 mL/min/1.73 m²: HR 0.56, 95% CI 0.39–0.79; Initiation of RRT: HR 0.45, 95% CI 0.21–0.97; Progression to macroalbuminuria: HR 0.62, 95% CI 0.54–0.72</td>
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<td>CANVAS</td>
<td>Double-blind</td>
<td>Type 2 DM with</td>
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<td>CANVAS: 1:1:1 ratio, canagliflozin 300 mg, canagliflozin 100 mg or placebo CANVAS-R: 1:1 ratio, canagliflozin 100 mg (optional increase to 300 mg) or placebo</td>
<td>Mean of 188.2 weeks</td>
<td>Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke</td>
<td>Primary outcome: HR 0.86, 95% CI 0.75–0.97; all-cause mortality: HR 0.87, 95% CI 0.74–1.01; HF hospitalization: HR 0.67, 95% CI 0.52–0.87; stroke: HR 0.87, 95% CI 0.67–1.09</td>
<td>Mean Age: 63.3 years</td>
<td>40% reduction in eGFR, need for RRT or death from renal causes</td>
<td>Renal composite HR 0.60, 95% CI 0.47–0.77; Doubling of Scr: HR 0.50, 95% CI 0.30–0.84; ESRD: HR 0.77, 95% CI 0.30–1.97</td>
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<tr>
<td>DECLARE-TIMI 58</td>
<td>Double-blind</td>
<td>Type 2 DM with</td>
<td>17 160</td>
<td>1:1 ratio dapagliflozin 10 mg or placebo</td>
<td>Median of 4.2 years</td>
<td>Safety outcome: composite of cardiovascular death, MI or ischaemic stroke (MACE). Efficacy outcomes: MACE and a composite of cardiovascular death or hospitalization for heart failure</td>
<td>MACE: HR 0.93, 95% CI 0.84–1.03; cardiovascular death or HF hospitalization HR 0.83, 95% CI 0.73–0.95; cardiovascular death: HR 0.98, 95% CI 0.82–1.17; all-cause mortality: HR 0.98, 95% CI 0.82–1.17; HF hospitalization: HR 0.73, 95% CI 0.61–0.88; ischaemic stroke: HR 1.01, 95% CI 0.84–1.21</td>
<td>Mean Age: 64 years</td>
<td>&gt;40% decrease in eGFR to &lt;60 mL/min/1.73 m², ESRD or death from renal causes</td>
<td>Renal composite: HR 0.76, 95% CI 0.67–0.87; Ad hoc: &gt;40% decrease in eGFR to &lt;60 mL/min/1.73 m², ESRD or death from renal causes: HR 0.53, 95% CI 0.43–0.66</td>
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RCT, randomized controlled trial; DM, diabetes mellitus; MACE, major adverse cardiovascular event; HR, hazard ratio; CI, confidence interval; HF, heart failure; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; Scr, serum creatinine; RRT, renal replacement therapy; ESRD, end-stage renal disease.
failure and incident or worsening nephropathy [33]. Cardiovascular death, heart failure hospitalization and incident or worsening nephropathy rate reductions induced by empagliflozin were not different between women and men [34]. In addition, in patients with prevalent kidney disease at baseline defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and/or urine albumin-to-creatinine-ratio (UACR) >300 mg/g, empagliflozin reduced cardiovascular death by 29% compared with placebo (HR 0.71, 95% CI 0.52–0.98), all-cause mortality by 24% (HR 0.76, 95% CI 0.59–0.99), hospitalization for heart failure by 39% (HR 0.61, 95% CI 0.42–0.87) and all-cause hospitalization by 19% (HR 0.81, 95% CI 0.72–0.92) [35].

The CANVAS programme comprised two sister trials, CANVAS and CANVAS-renal (CANVAS-R), where 10 142 participants with type 2 DM and high cardiovascular risk were followed for a mean of 188.2 weeks [36]. In CANVAS, patients were randomly assigned in the ratio of 1:1 to receive canagliflozin 300 mg, canagliflozin 100 mg or placebo and in CANVAS-R, they were randomized in the ratio of 1:1 to canagliflozin starting at 100 mg with an optional increase to 300 mg daily or placebo. The primary outcome in both trials was a composite of cardiovascular death, non-fatal MI or non-fatal stroke. Canagliflozin was associated with a significant reduction in the risk of primary outcome (HR 0.86, 95% CI 0.75–0.97; P = 0.02 for superiority), hospitalization for heart failure (HR 0.67, 95% CI 0.52–0.87) and a marginal, yet not statistically significant, reduction in all-cause mortality (HR 0.87, 95% CI 0.74–1.01). The risk of stroke was not different between groups (HR 0.87, 95% CI 0.67–1.09) [36].

A secondary analysis of CANVAS described outcomes in participants with and without CKD, defined as eGFR <60 and ≥60 mL/min/1.73 m², and according to baseline kidney function categories (eGFR <45, 45 to <60, 60 to <90 and ≥90 mL/min/1.73 m²). The reduction in the primary outcome for the overall trial population was similar across the eGFR subgroups and for participants with and without CKD (P heterogeneity = 0.33 and 0.08, respectively). Similarly, the effect on cardiovascular death was not modified by baseline kidney function (P heterogeneity >0.50) [37]. In another CANVAS analysis, canagliflozin reduced hospitalization for heart failure across a broad range of different patient subgroups. Benefits may be greater in those with a history of heart failure at baseline [38].

DECLARE-TIMI 58 evaluating the cardiovascular outcomes of dapagliflozin versus placebo in 17 160 participants with type 2 DM over a period of 4.2 years was recently reported [30]. Participants either had established cardiovascular disease or were at risk for cardiovascular disease (n = 10 186, men >55 years or women >60 years of age or who had one or more additional cardiovascular risk factors). The primary safety outcome was a composite of cardiovascular death, MI or ischaemic stroke (MACE). The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure [39]. In the primary safety analysis, dapagliflozin met the pre-specified non-inferiority criterion (upper boundary of the 95% CI <1.3; P < 0.001). In the efficacy analyses, dapagliflozin was not superior to placebo in reducing the rate of MACE (8.8 versus 9.4%, respectively; HR 0.93, 95% CI 0.84–1.03; P = 0.17), but showed lower rate of cardiovascular death or hospitalization for heart failure (4.9% versus 5.8%; HR 0.83, 95% CI 0.73–0.95). The latter is attributed rather to decrease of hospitalization for heart failure (HR 0.73, 95% CI 0.61–0.88), as cardiovascular death events were similar in the two groups (HR 0.98, 95% CI 0.82–1.17). Furthermore, dapagliflozin was associated with a reduction in MI of borderline significance (HR 0.89, 95% CI 0.77–1.01), but did not affect ischaemic stroke (HR 1.01, 95% CI 0.84–1.21) or all-cause mortality (HR 0.98, 95% CI 0.82–1.17).

DECLARE-TIMI 58 excluded patients with creatinine clearance <60 mL/min, whereas proportions of patients with baseline micro- or macroalbuminuria are not reported [30]. In subgroup analyses, the rates of MACE did not differ according to eGFR groups; however, the rates of the composite ‘cardiovascular death or hospitalization for heart failure’ were more favourable for dapagliflozin compared with placebo in patients with eGFR 60–90 mL/min/1.73 m² (HR 0.79, 95% CI 0.66–0.95) and in the few patients (n = 189) with eGFR <60 mL/min/1.73 m² (HR 0.78, 95% CI 0.55–1.09), but not in patients with eGFR >90 mL/min/1.73 m² (HR 0.96, 95% CI 0.77–1.19). Among differences in study design that could participate in the less robust effect of DECLARE-TIMI 58 on outcomes when compared with other SGLT-2 inhibitor trials, the authors of the study list first the fact that patients with creatinine clearance <60 mL/min were excluded (in contrast to EMPA-REG OUTCOME and CANVAS trials, excluding patients at 30 mL/min/1.73 m²); this is in line with the aforementioned subgroup analysis and coincides with the possibility of greater natriuretic effects and benefits of these drugs in patients with lower eGFR, discussed in a later section.

In a meta-analysis including data from the three aforementioned trials (adding up to 34 322 patients, 60% of whom established atherosclerotic cardiovascular disease), SGLT-2 inhibitors were shown to reduce the composite of MI, stroke and cardiovascular death by 11% (HR 0.89, 95% CI 0.83–0.96), but the benefit was evident only in patients with baseline cardiovascular disease (HR 0.86, 95% CI 0.80–0.93) and not in those without (HR 1.00, 95% CI 0.87–1.16) [40]. However, these agents reduced the risk of heart failure hospitalization by about 30% both in patients with or without cardiovascular disease. In addition to the above, CVD-REAL is a real-world observational study of 309 056 patients with DM, 87% of whom had no history of cardiovascular disease [41]. It included new users’ dispensed prescriptions of SGLT-2 inhibitors or other oral or injectable glucose-lowering drugs, including fixed dose combinations. In this cohort, 76% of the US patients studied used canagliflozin and 92% of the European patients used dapagliflozin, with empagliflozin accounting for <7% of total exposure time; reductions of 39% in heart failure and 51% in all-cause mortality were reported with SGLT-2 inhibitors.

**POTENTIAL MECHANISMS FOR THE CARDIOPROTECTIVE ACTIONS OF SGLT-2 INHIBITORS**

Several hypotheses have tried to explain the positive impact of SGLT-2 inhibitors on all-cause and cardiovascular mortality, respectively: HR 0.85, 95% CI 0.74–0.98; P = 0.004; HR 0.83, 95% CI 0.73–0.93; P = 0.001; HR 0.81, 95% CI 0.70–0.93; P = 0.002. The latter is attributed rather to decrease of hospitalization for heart failure (HR 0.73, 95% CI 0.61–0.88), as cardiovascular death events were similar in the two groups (HR 0.98, 95% CI 0.82–1.17). Furthermore, dapagliflozin was associated with a reduction in MI of borderline significance (HR 0.89, 95% CI 0.77–1.01), but did not affect ischaemic stroke (HR 1.01, 95% CI 0.84–1.21) or all-cause mortality (HR 0.98, 95% CI 0.82–1.17).
observed within weeks, without an impact on atherogenesis-related outcomes such as MI and stroke. However, none has been conclusively proved and several mechanisms of action may be acting in combination [42–44]. A single pathway would seem unlikely since RCTs testing other anti-diabetic classes failed to result in similar cardiovascular outcomes. For example, improvement in glycaemic control is unlikely to be involved as recent RCTs with DPP-4 inhibitors failed to impact mortality or heart failure. Lowering uric acid has also been proposed, but recent trials of urate-lowering therapy observed higher mortality in patients achieving lower serum urate [45, 46].

BP lowering of 3–5/1–3 mmHg is consistently reported with SGLT-2 inhibitors, attributed mainly to their diuretic action [20]. In patients with type 2 DM, BP reduction is known to confer the largest cardiovascular benefits among all risk-factor treatments. In the United Kingdom Prospective Diabetes Study 38 (UKPDS-38) a BP drop of 10/5 mmHg was associated with a 32% reduction in diabetes-related (including cardiovascular) death [47]. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study, BP difference of 5/2 mmHg (135/75 versus 140/77 mmHg) favouring the active group was associated with reductions of 14% in all-cause mortality (P = 0.025) and 18% in cardiovascular mortality (P = 0.02) [48]. Both EMPA-REG OUTCOME and CANVAS included individuals very well-treated in terms of risk factors (patients in the pooled empagliflozin group in EMPA-REG OUTCOME had a mean BP of 135.3/76.6 mmHg at baseline moving to 131.3/75.1 mmHg at study end, while in CANVAS and DECLARE-TIMI 58, mean BP decreased from about 136.4/77.6 to 132.5/76.2 and from 135.1/77.6 to 132.3/75.8 mmHg, respectively) [4, 49]. The impact of BP reduction in these trials was questioned owing to the insignificant effect on the incidence of MI and stroke [49]. However, data from the major outcome RCTs in hypertension treatment suggest that the endpoint mostly reduced with active treatment was congestive heart failure and not stroke [50], in a timeline relevant to SGLT-2 inhibitor trials. Overall, BP reduction with SGLT-2 inhibitors should have conferred at least part of the observed benefit in these studies.

A diuretic effect is also suggested to play a role in observed benefits. In EMPA-REG OUTCOME, a 38% reduction in the number of patients needing loop diuretics was noted in the empagliflozin groups, confirming the diuretic action [51]. Current guidelines for patients with heart failure indicate diuretics to reduce the signs/symptoms of congestion as their effects on mortality have not been studied in large RCTs [52]. The Anti-hypertensive and Lipid-Lowering Treatment to Reduce the Incidence of Nephropathy in Patients with Type 2 Diabetes (ALLHAT) enrolled 33,357 patients with hypertension and showed that chlorothalidone, lisinopril and amiodipine did not differ with regards to the primary outcome or all-cause mortality. However, chlorothalidone was associated with reduced rates of heart failure compared with either of the other two drugs, an effect also present in patients with DM [53]. Side effects of thiazide and loop diuretics, mainly hypokalaemia, were previously suggested to prevent the appearance of the full cardiovascular benefit of these drugs [54, 55]. In EMPA-REG OUTCOME, there were no differences in sodium, potassium, calcium, magnesium and phosphate between groups [23]. Furthermore, data from a recent study in 42 healthy subjects randomized to dapagliflozin or bumetanide coupled with a mathematical model illustrating that electrolyte-free water clearance results in greater reduction in interstitial volume than blood volume, showed that osmotic diuresis with dapagliflozin produces a 2-fold greater reduction in interstitial compared with blood volume, while the relevant reduction with bumetanide was 0.8-fold [56]. The authors suggested that this SGLT-2 inhibitor action could be particularly beneficial for heart failure, characterized by whole-body fluid accumulation, yet in many patients by arterial underfilling, which may be aggravated by conventional diuretics. Thus, this physiologically different, milder and continuous diuretic action of SGLT-2 inhibitors may also confer to their clinical benefits. Reduction in fat body mass due to calorie loss [23, 36] could be another protective mechanism of SGLT-2 inhibitors since obesity is a known cardiovascular risk factor [57].

At a pathophysiological level, current hypotheses on SGLT-2 inhibitor-derived benefits are related to three target organs: the kidney, the pancreas and the heart (Figure 1). The cardiovascular system may be affected by several actions of the SGLT-2 inhibitors on the kidney, including reduction in glomerular hyperfiltration, modulation of RAS and erythropoietin increase. SGLT-2 inhibitors prevent glucose entry into proximal tubular cells, protecting them from glucotoxicity and oxidative stress—factors associated with release of inflammatory mediators and decrease in anti-ageing factor Klotho [58–60]. They are the only anti-diabetic drugs to increase glucose excretion rather than glucose entry into cells, leading to glucosuria (loss of calories) and osmotic diuresis. SGLT-2 inhibitors also decrease glomerular hyperfiltration by decreasing proximal tubular sodium reabsorption, and modifying tubuloglomerular feedback [61], as described in detail in the following section. The decreased intraglomerular pressure and hyperfiltration are nephroprotective in the long term, but are not expected to explain the short-term improvement in cardiovascular outcomes. However, diabetic patients with glomerular hyperfiltration also have an increased renal blood flow (RBF), which may be 60% higher than that in normofiltering subjects [61]. Since RBF represents 25% of cardiac output, decreasing RBF is expected to favourably impact on cardiac workload, effective immediately. This could be one of the explanations for the lack of sympathetic nervous system activation, evidenced by a stable heart rate [23, 61]. SGLT-2 inhibitors decreased RBF by 30% in hyperfiltrating type 1 DM [61]. This may translate into an 8% decrease in cardiac output. With regards to sympathetic activation, it is known that diuretic effects are usually associated with reflex-mediated increases in sympathetic tone, whereas caloric loss is associated with decreases; a recent uncontrolled study in 22 patients with type 2 DM showed that empagliflozin treatment did not affect muscle sympathetic nerve activity or heart rate, despite numerical increases in urine volume, reduction in BP and significant weight loss [62].

The impact on the RAS has been discussed, with some suggesting that SGLT-2 inhibitors may suppress renin production, through increase of sodium and chloride delivery to the macula...
In individuals with genetic defects in SGLT-2 and in diabetes not on RAS blockade, SGLT-2 inhibition resulted in RAS activation as evidenced by serum renin, angiotensin II and aldosterone levels, although renin increase with SGLT-2 inhibitors is much smaller than that with classical diuretics [61, 63]. In this regard, most patients in RCTs were under RAS blockade, and this may have limited the consequences of any RAS activation. Increased haemoglobin and haematocrit values can also be ascribed to kidney effects and may improve tissue oxygenation and cardiac preload. They represent a combination of haemoconcentration due to decreased plasma volume and increased red blood cell mass (and oxygen transport capacity) [63]. In mediation analysis, these were key determinants of beneficial cardiovascular outcomes [64]. Increased erythropoietin levels have been documented with SGLT-2 inhibitors [63]. The decreased RBF may be one of the factors behind this observation. Indeed, SGLT-2 inhibitors may contribute to attenuate the RAS blockade-linked increase in RBF and decreased erythropoietin production [65].

SGLT-2 inhibition in pancreatic alpha-cells triggers glucagon secretion [66]. Although the impact on heart function of glucagon itself has been debated, glucagon likely contributes to increase in hepatic ketogenesis and circulating ketone levels (and of the risk of euglycaemic ketoadiposis) [67]. Increased circulating ketone levels are thought to be an efficient source of adenosine triphosphate (ATP) for the heart (thrifty substrate hypothesis) [68]. The heart is the organ with the highest energy expenditure and 70% originates from fatty acid oxidation [69]. Hearts oxidize ketone bodies as energy source if available at the expense of fatty acid and glucose oxidation, which are less energetically efficient, yielding less ATP synthesis per molecule of oxygen invested [69]. Against this hypothesis, it has been argued that the mechanisms of ketone accumulation have not been completely clarified and that in heart failure, the myocardium is already switched to ketone bodies use [70].

In addition to the above, direct effects of SGLT-2 inhibitors on cardiomyocytes have been proposed [43]. Cardiomyocytes lack SGLT-2, but off-target inhibition of the sodium–hydrogen exchanger-1 (NHE1) may occur, lowering cytosolic Na⁺ (sodium hypothesis) and shifting intracellular calcium from the cytosol to the mitochondria [71–73]. However, while NHE1 targeting improved heart failure in mice, RCTs of NHE1 inhibitors in humans were inconclusive.

**Nephroprotective Properties of SGLT-2 Inhibitors**

Further to data on SGLT-2 inhibitors effects on cardiovascular outcomes, several lines of evidence directly support a nephroprotective role of these agents (Table 1). In an analysis of renal outcomes of the EMPA-REG OUTCOME [28], patients treated with empagliflozin had a reduction in the pre-specified composite outcome of progression to macroalbuminuria, doubling of serum creatinine (SCr), initiation of renal replacement therapy or death from renal disease (HR 0.61, 95% CI 0.53–0.70). Patients on empagliflozin had also reduced incidence of a *post hoc* renal composite of doubling of SCr, initiation of renal replacement therapy or death from renal disease (HR 0.54, 95% CI 0.40–0.75). Significant differences of the same magnitude compared with placebo were present for all individual components, that is, progression to macroalbuminuria (HR 0.62, 95% CI 0.54–0.72), doubling of SCr accompanied by eGFR of ≤45 mL/min/1.73 m² (HR 0.56, 95% CI 0.39–0.79) or initiation
of renal replacement therapy (HR 0.45, 95% CI 0.21–0.97). Of note, rates of acute renal failure or hyperkalaemia episodes with empagliflozin were lower than or similar to those with placebo, regardless of whether patients had impaired kidney function at baseline.

In EMPA-REG OUTCOME, the total population did not resemble that of classical nephroprotective trials (i.e. proteinuric diabetic nephropathy) as the primary aim of the trial was assessment of cardiovascular effects. At baseline, there were 5201 patients with an eGFR ≥60 mL/min/1.73 m² of which 64% had no albuminuria, 27% had microalbuminuria and 8.5% had macroalbuminuria. There were 1819 patients with an eGFR <60 mL/min/1.73 m² (of which 47% had no albuminuria, 34% had microalbuminuria and 19% macroalbuminuria) [28]. The large number of patients in the three albuminuria categories ensured adequate power to assess significant differences in renal outcomes. However, differences in these composites were driven by doubling of SCr as events of renal replacement therapy (n = 27) and renal death (n = 3) were uncommon. This is the consequence of enrolling a population with less advanced CKD and could be considered as the main limitation of the study.

A similar effect of canagliflozin on renal outcomes was noted in CANVAS, where 20.1% of participants had an eGFR <60 mL/min/1.73 m² at baseline [36]. Although on the basis of pre-specified hypothesis testing sequence, the renal endpoints were not considered statistically significant, canagliflozin significantly decreased the pre-specified renal composite of 40% reduction in eGFR, need for renal replacement therapy or death from renal causes (HR 0.60, 95% CI 0.47–0.77). With regards to adverse effects, osmotic diuresis and volume depletion were more common with canagliflozin, but acute kidney injury (AKI) or hyperkalaemia were not. The reduction in renal composite with canagliflozin was consistent in patients with and without CKD and across the four eGFR subgroups (baseline eGFR ≥90, 60 to <90, 45 to <60 and <45 mL/min/1.73 m²) (P heterogeneity = 0.28 and >0.50, respectively) [37]. In a recent pre-specified renal analysis of CANVAS [29], canagliflozin was associated with reduction in doubling of SCr, ESRD and renal death (HR 0.53, 95% CI 0.33–0.84). These effects were consistent in subgroup analyses. Doubling of SCr was significantly reduced (HR 0.50, 95% CI 0.30–0.84), but ESRD was not affected (HR 0.77, 95% CI 0.30–1.97).

The recently reported DECLARE-TIMI 58 included as a secondary efficacy outcome a renal composite of ≥40% decrease in eGFR to <60 mL/min/1.73 m², ESRD or death from renal or cardiovascular causes; this occurred in 4.3 versus 5.6% of patients in dapagliflozin and placebo groups (HR 0.76, 95% CI 0.67–0.87) [30]. Inclusion of cardiovascular death in a pre-specified renal composite is rather not justified from a clinical point of view. However, the authors correctly reported a more appropriate composite of ≥40% decrease in eGFR to <60 mL/min/1.73 m², ESRD or renal death, which occurred in 1.5% versus 2.8% of patients (HR 0.53, 95% CI 0.43–0.66). HRs for the components of renal composites or albuminuria levels were not reported and are expected in subsequent reports. Subgroup analyses according to baseline eGFR (>90, 60–90 and <60 mL/min/1.73 m²) showed no differences in the above outcomes. Overall, although DECLARE-TIMI 58 included a population with less advanced CKD, which resulted in a smaller number of events, all three SGLT-2 inhibitors studies seem to have the same effect on the most appropriate renal composite of doubling of SCr (or relevant eGFR reduction), ESRD or renal death. With regards to albuminuria, in patients with normoalbuminuria at baseline in EMPA-REG OUTCOME, there was no significant between-group difference in the rate of incident albuminuria (51.5 and 51.2% with empagliflozin and placebo, respectively). However, overall progression to macroalbuminuria was reduced by 38%, indicating a different effect of the agent on patients with different levels of urinary albumin excretion [28]. An exploratory analysis on this effect [74] showed that after cessation of treatment for about 35 days, UACR was lower with empagliflozin compared with placebo in patients with baseline microalbuminuria (−22%; P = 0.0003) or macroalbuminuria (−29%; P = 0.0048), but not in patients with normoalbuminuria (+1%; P = 0.89). Similarly, in CANVAS, the risk of new-onset microalbuminuria decreased by 20% (HR 0.80, 95% CI 0.73–0.87) and that of macroalbuminuria by 42% (HR 0.58, 95% CI 0.50–0.68) with canagliflozin. Overall, mean UACR was 18% lower with canagliflozin compared with placebo [29].

Although EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 were not studies with primary renal endpoints, an objective reader cannot overlook that a 40–50% reduction in the composite outcome is much larger than relevant reductions in seminal trials in DKD. Indeed, in the aforementioned meta-analysis of the three trials, SGLT-2 inhibitors reduced the risk of worsening of renal function, ESRD or renal death by 45% (HR 0.55, 95% CI 0.48–0.64), with an identical effect in patients with and without atherosclerotic cardiovascular disease [40]. In the Reduction of Endpoints in NIDD already [76], studying the effects of combining aliskiren with ACEi or ARB, and the NEPHRON-D study examined the effects of losartan and lisinopril versus losartan alone [77] were prematurely stopped due to increased risk of complications, including hypotension, AKI and hyperkalaemia [11, 78]. Post hoc analyses of the RENAAAL and IDNT trials suggested that the magnitude of proteinuria reduction during follow-up was predictive of the primary outcome [79, 80]. Overall, renoprotection with RAS blockers is mainly attributed to reducing intraglomerular pressure and proteinuria; a similar
effect, via a different pathway, can be present with SGLT-2 inhibitors as discussed below.

**POTENTIAL MECHANISMS FOR THE NEPHROPROTECTIVE ACTIONS OF SGLT-2 INHIBITORS**

In physiological conditions, 180 g of glucose daily are freely filtered in the glomeruli and almost all is reabsorbed in the proximal convoluted tubule (PCT) through SGLTs 1 and 2, located in the apical surface of PCT cells. SGLT-2 is a high-capacity/low-affinity transporter found mainly in the S1-segment, responsible for 90% of glucose reabsorption, while SGLT-1 is a low-capacity/high-affinity transporter in the S2/S3 segment of the PCT, reabsorbing the remaining 10% [20, 81]. The maximal rate of glucose reabsorption is around 375 mg/min. When plasma glucose concentration exceeds 200–250 mg/dL, the co-transporters approach saturation, thus excreting excessive filtered glucose [82]. As SGLT-2 reabsors equimolar amounts of glucose and sodium, SGLT-2 inhibitors decrease PCT sodium reabsorption. Unlike the carbonic anhydrase inhibitor acetazolamide, which increases the distal tubular availability of sodium–bicarbonate, SGLT-2 inhibitors increase the distal availability of sodium–chloride [61]. The macula densa senses the increased chloride availability and restores the tubuloglomerular feedback by promoting afferent arteriolar vasoconstriction, thus decreasing intraglomerular pressure and GFR; this is a physiological mechanism aiming to avoid excess sodium loss in cases of proximal tubular damage (Figure 2) [83]. Thiazide diuretics act distal to the macula densa, and they lack this tubuloglomerular effect. Loop diuretics increase sodium–chloride at the macula densa, but they are short-lived diuretics and any effect is expected to be transient. The amount of extra sodium (and chloride) delivered as a direct result of SGLT-2 inhibition to the macula densa is huge, estimated from urinary glucose contents at 10 g sodium, equivalent to 25 g sodium chloride daily. As in the case of every diuretic, the distal tubules are responsible for fine regulation of sodium balance, and most of this sodium is reabsorbed, limiting the overall natriuretic effect [84].

Effects of SGLT-2 inhibitors on common risk factors, such as BP, fat mass or uric acid, could also promote nephroprotection. Other mechanisms involved could be the improvement of renal hypoxia observed in diabetic kidneys, due to reduction of activity and, thus, energy requirements of SGLT-2 [85]. Background data also suggest that SGLT-2 inhibitors have anti-inflammatory, anti-fibrotic and antioxidant effects, as they are able to suppress advanced glycation end products (AGEs) receptor axis, and nuclear factor kappa B activities and decrease the expression of inflammatory molecules, such as monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1 [86–88]. However, the unique nephroprotective properties of SGLT-2 inhibitors can be largely attributed to their direct ability to decrease glomerular hyperfiltration. Animals and humans with DM express higher number of renal SGLT-2 co-transporters than healthy individuals, leading to ~20% increase in glucose reabsorption [89, 90], as an attempt by the body to conserve glucose. However, this is a maladaptive response in the setting of DM and an additional factor favouring inadequate glycaemic control. Furthermore, this increase in SGLT-2 concentration leads to decreased delivery to the macula densa of sodium and chloride, thus promoting hyperfiltration [91, 92]. Hyperfiltration and glomerular hypertension are common features of early diabetic nephropathy and are known factors promoting initiation and progression of all proteinuric nephropathies, through increased filtration of many molecules, including albumin [93, 94].

Animal studies showed that SGLT-2 inhibitors can slow down the progression of diabetic nephropathy and ameliorate the associated histological features (mesangial matrix accumulation, glomerular enlargement and interstitial fibrosis) [95]. An elegant human study [61] showed that empagliflozin could reverse glomerular hyperfiltration through modulation of the afferent arteriole tone. The authors measured inulin and para-aminohippurate clearance in patients with type 1 DM with (GFR > 135 mL/min/1.73 m²) and without hyperfiltration during hyperinsulinaemic–euglycaemic clamp. In hyperfiltrating patients, treatment with empagliflozin for 8 weeks resulted in a reduction of GFR from 172 ± 23 to 139 ± 25 mL/min/1.73 m² (P < 0.001). This was accompanied by a significant reduction in RBF from 1641 ± 458 to 1156 ± 219 mL/min/1.73 m² and increase in renal vascular resistance, suggesting that this was due to decreased afferent arteriole vasodilatation (Figure 2) [61]. An estimated reduction of intraglomerular pressure of ~10% or 7–8 mmHg also occurred [96]. In patients without hyperfiltration, GFR and other renal function, parameters were not significantly changed. However, this study excluded patients with macroalbuminuria as authors aimed to study the early stage of hyperfiltration; thus, mean UACR was within the normal range at baseline and did not change during follow-up. This effect is consistent with the above findings on UACR depending on the baseline level of albuminuria.

These effects of SGLT-2 inhibitors on reduction of glomerular hyperfiltration and intraglomerular pressure are supported by the EMPA-REG OUTCOME and CANVAS trials, as well as several other studies, showing decrease in urine albumin excretion [97, 98]. Further support is provided by their effect on eGFR. In early studies, SGLT-2 inhibitors produced a quick-onset reduction of 6–7 mL/min/1.73 m² over the first 2–3 weeks [92, 99], attributed to hypovolaemia and considered a possible side effect. However, it was soon postulated to be related to potential nephroprotection [92]. The EMPA-REG OUTCOME renal analysis [28] examined the effect of treatment on eGFR over time using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. From baseline to Week 4, weekly decreases of −0.62 ± 0.04 mL/min/1.73 m² and −0.82 ± 0.04 mL/min/1.73 m² with empagliflozin 10 and 25 mg were noted versus 0.01 ± 0.04 mL/min/1.73 m² (P < 0.001) with placebo. However, from Week 4 of treatment to end, eGFR stabilized in both empagliflozin groups (annual decreases of −0.19 ± 0.11 mL/min/1.73 m²) and declined steadily with placebo (−1.67 ± 0.13 mL/min/1.73 m², P < 0.001). After cessation of the study drug (last week of treatment to end of follow-up), eGFR increased in patients previously treated with empagliflozin (weekly increases of 0.48 ± 0.04 and
0.55 ± 0.04 mL/min/1.73 m² in empagliflozin groups versus −0.04 ± 0.04 mL/min/1.73 m² with placebo, P < 0.001). A similar effect was noted in CANVAS as the annual eGFR decline was slower with canagliflozin (slope difference between groups 1.2 mL/min/1.73 m²/year, 95% CI 1.0–1.4) [29]. This effect is typical of the initial, functional ‘dip’ in eGFR that resembles the effect of RAS blockers, is associated with long-term nephroprotection and is reversible upon discontinuation of the drug [100]. Occurrence of this ‘dip’ on top of RAS blockers further supports that SGLT-2 inhibitors act on the afferent arteriole.

Of greater importance is that empagliflozin was able to ‘stabilize’ eGFR after the initial functional ‘dip’ across all albuminuria categories. In the relevant exploratory analysis [74], the difference between empagliflozin and placebo groups in eGFR over time was much more pronounced in patients with macra-albuminuria at baseline (Figure 3); in this category, eGFR dropped during follow-up from around 67 mL/min/1.73 m² to 58 mL/min/1.73 m² in the empagliflozin group (with 5 mL/min/1.73m² being relevant to functional dip), but to 47 mL/min/1.73m² with placebo. Thus, in patients with DKD and macroalbuminuria (those at the highest risk for progression), SGLT-2 inhibitors are able to reduce the rate of eGFR decline by around 75%, and that occurs on the top of RAS blockade.

SAFETY OF SGLT-2 INHIBITORS

Although the rates of adverse effects were significantly lower in the SGLT-2 inhibitor groups than placebo [23, 24, 30] in EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58, use of SGLT-2 inhibitors is associated with certain adverse reactions [101, 102]. Some of them relate to their mode of action, such as urinary frequency, volume depletion and genitourinary tract infections. Increased frequency due to osmotic diuresis (34.5 versus 13.3 events/1000 patient-years, P < 0.001) and volume depletion-related adverse events (26.0 versus 18.5/1000 patient-years, P = 0.009) were more frequent with canagliflozin compared with placebo in CANVAS [24]. In contrast, volume depletion was similar between empagliflozin and placebo groups in EMPA-REG OUTCOME (5.1% versus 4.9%) and in DECLARE-TIMI 58 (2.5% versus 2.4%) [23, 30]. In a study in type 1 DM, volume depletion with sotagliflozin, a new oral SGLT-1 and SGLT-2 inhibitor, were slightly higher than placebo after 24 weeks of treatment (1.9% versus 0.5%) [103]. AKI reports with SGLT-2 inhibitors previously led the FDA to issue an alert for canagliflozin and dapagliflozin. Most reported incidences occurred in the first month of treatment and improved following drug discontinuation [102]; thus, this could be associated with the GFR ‘dip’. In EMPA-REG OUTCOME, both acute renal failure (5.2% versus 6.6%, P < 0.001) and strictly defined AKI (1.6% versus 1% P < 0.01) were lower with empagliflozin [23]; this was consistent in eGFR subgroups [28]. In CANVAS, AKI was non-significantly lower with canagliflozin (3.0 versus 4.1 events/1000 patient-years, P = 0.33) [24] and in DECLARE-TIMI 58 lower with dapagliflozin (1.5% versus 2%, P = 0.002) [30]. A recent propensity-matched analysis also found that AKI does not increase with SGLT-2 inhibitors [104]. Concerns for bladder cancer due to glucosuria have been mentioned in a meta-analysis suggesting increased risk with SGLT-2 inhibitors (odds ratio 3.87, 95% CI 1.48–10.08), compared with placebo or active treatment; however, the overall risk of cancer was not elevated (odds ratio 1.14, 95% CI 0.96–1.36) [105]. Of note, in DECLARE-TIMI 58, not included in the aforementioned meta-analysis, the incidence of bladder cancer...
was lower with dapagliflozin than with placebo (0.3 versus 0.5\%, \(P = 0.02\)) [30].

Genital mycotic infections are the most common side effects of SGLT-2 inhibitors. In EMPA-REG OUTCOME, they were noted in 5\% versus 1.5\% of men and 10\% versus 2.6\% of women with empagliflozin and placebo, respectively (\(P < 0.001\)) [23]. In DECLARE-TIMI 58, genital infections leading to discontinuation were also higher than placebo (0.9\% versus 0.1\%, \(P < 0.001\)) [30]. Mycotic infections are linked to increased glucosuria and are generally mild to moderate in severity; they commonly resolve with topical anti-fungal treatment and do not require discontinuation of the drug. Urinary tract infections (including pyelonephritis and urosepsis) do not appear to increase with SGLT-2 inhibitors (18.1\% versus 18\% in EMPA-REG OUTCOME) [23].

Diabetic ketoacidosis (DKA) is a rare but serious complication of SGLT-2 inhibitors for which the FDA issued a warning in 2015 [101]. It occurs more frequently in individuals with type 1 DM treated off-label with these agents [106]. In CANVAS and DECLARE-TIMI 58, DKA events were rare but more frequent with canagliflozin (0.6 versus 0.3/1000 patient-years; HR 2.33, 95\% CI 0.76–7.17) or dapagliflozin (0.3\% versus 0.1\%, \(P = 0.02\)) [24, 30]. The rates were even lower and similar between groups in EMPA-REG OUTCOME (0.09\% versus 0.04\%) [23]. However, real-world data suggest that the rate of DKA within 180 days after the initiation of an SGLT-2 inhibitor compared with a DPP-4 inhibitor can be higher (4.9 versus 2.3 events/1000 person-years; HR 2.1, 95\% CI 1.5–2.9) [106].

Canagliflozin was associated with a higher risk of lower extremity amputation in CANVAS (6.3 versus 3.4/1000 person-years, \(P < 0.001\)) [24]. This finding was not present in empagliflozin [107] or dapagliflozin trials [30]. It was suggested but not proven that this may be the result of greater volume depletion and haemoconcentration due to dual SGLT-1/2 inhibition with canagliflozin [101]. Furthermore, sotagliflozin, a dual SGLT-1/2 inhibitor, was also not associated with increased risk of amputations in patients with type 1 DM [108]. In the CANVAS programme, bone fractures were also more frequent with canagliflozin versus placebo (15.4 versus 11.9/1000 person-years, \(P = 0.02\)) [24], a difference observed in CANVAS but not in the CANVAS-R study. This effect was not seen with other SGLT-2 inhibitors. Volume depletion with orthostatic hypotension and decrease in bone mineral density with canagliflozin are between the proposed mechanisms [102], but additional data are needed.
CARDIOPROTECTIVE PROPERTIES OF GLP-1 RECEPTOR AGONISTS

The results observed in the cardiovascular outcome trials with GLP-1 receptor agonists have been less consistent (Table 2) [112–114] than those in SGLT-2 inhibitor trials. In the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, 6068 patients with type 2 DM with either a MI or hospitalized for unstable angina in the preceding 180 days were randomized to receive either lixisenatide 10–20 ìg or placebo [115]. The primary endpoint was a composite of cardiovascular death, MI, stroke or hospitalization for heart failure. After a median follow-up of 25 months, 406 (13.4%) patients receiving lixisenatide and 399 (13.2%) receiving placebo reached the primary endpoint (HR 1.02, 95% CI 0.89–1.17). Thus, the trial showed the non-inferiority of lixisenatide to placebo (P < 0.001) but did not show its superiority (P = 0.81). There was no difference between groups in any of the cardiovascular outcomes when considered individually, or in all-cause mortality. No significant interactions were observed for the primary endpoint and renal function.

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9380 patients with type 2 DM and high cardiovascular risk were randomized to receive either liraglutide or placebo [25]. The primary endpoint was a composite of cardiovascular death, MI or stroke, and the trial was designed to test the non-inferiority of liraglutide to placebo. After a median follow-up of 3.8 years, 608 (13.0%) patients receiving liraglutide and 694 (14.9%) patients receiving placebo reached the primary endpoint (HR 0.87, 95% CI 0.78–0.97; P < 0.001 for non-inferiority and P = 0.01 for superiority). All-cause mortality (HR 0.85, 95% CI 0.74–0.97) and cardiovascular death (HR 0.78, 95% CI 0.66–0.93) were lower with liraglutide. Rates of non-fatal MI, non-fatal stroke and hospitalization for heart failure were non-significantly lower in the liraglutide group. Patients with CKD (eGFR <60 mL/min/1.73 m²) appeared to derive greater benefit (HR 0.69, 95% CI 0.57–0.85) than patients with eGFR >60 mL/min/1.73 m² (HR 0.94, 95% CI 0.83–1.07) from liraglutide treatment. Part of this difference may have been driven by the higher cardiovascular event rate in CKD patients [25].

In the Trial to Evaluate Cardiovascular and Other Long term Outcomes with Semaglutide in Subjects with Type 2 DM (SUSTAIN-6), 3297 patients with type 2 DM and established cardiovascular disease were randomized to once-weekly semaglutide (0.5 or 1.0 mg) or placebo for 104 weeks [26]. The primary composite outcome included cardiovascular death, non-fatal MI or non-fatal stroke. The trial was designed to test the non-inferiority of semaglutide to placebo. Part of this difference may have been driven by the higher cardiovascular event rate in CKD patients [25].

In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), 14 752 patients with type 2 DM with and without pre-existing cardiovascular disease were randomized to once-weekly 2 mg extended-release exenatide or placebo [110]. The primary outcome was a composite of cardiovascular death, MI or stroke. The trial was designed and statistically powered to test for non-inferiority and superiority of exenatide to placebo. After a median follow-up of 3.2 years, the primary outcome occurred in 839 (11.4%) patients receiving exenatide and in 905 (12.2%) receiving placebo (HR 0.91, 95% CI 0.83–1.00; non-inferiority P < 0.001; superiority P = 0.06). The rates for the individual cardiovascular outcomes described directly above and for hospitalization for heart failure did not differ between groups. All-cause mortality was significantly lower with exenatide (HR 0.86, 95% CI 0.77–0.97). Although not fully reported yet, the Phase 3 FREEDOM-CVO trial evaluated the continuous delivery of exenatide and was designed to accrue a limited number of cardiovascular events. A press release reported that the primary objective in achieving an HR upper limit <1.8 had been met [116].

In the HARMONY OUTCOMES Trial [27], 9463 patients with type 2 DM and cardiovascular disease were randomized to weekly albiglutide (30–50 mg) or placebo. The primary outcome was a composite of cardiovascular death, MI or stroke. After a median follow-up of 1.6 years, the primary outcome occurred in 338 (7%) patients receiving albiglutide and in 428 (9%) patients receiving placebo (HR 0.78, 95% CI 0.68–0.90). The trial thus showed the non-inferiority (P < 0.001) and superiority (P = 0.0006) of albiglutide to placebo. Use of albiglutide was associated with a lower rate of MI (HR 0.75, 95% CI 0.61–0.90) but not of stroke, cardiovascular death or all-cause mortality.

The Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial evaluated major cardiovascular outcomes with weekly dulaglutide in 9901 patients with type 2 DM, 69% of whom did not have prior cardiovascular disease [117]. The study had a median follow-up of >5 years, which is longer than other GLP-1 receptor agonist trials. It was recently announced that the study met its primary efficacy objective, that is, dulaglutide significantly reduced the composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke compared with placebo [118]. The Peptide InnOvatioN for Early DiabEtes Treatment 6 (PIONEER-6) study randomized 3183 patients with type 2 DM and high risk of cardiovascular events to once-daily oral semaglutide or placebo [119]. A press release reported that the trial achieved its primary endpoint by demonstrating non-inferiority to placebo in the composite of cardiovascular death, non-fatal MI or non-fatal stroke. The study showed a 21% reduction in the primary outcome in favour of semaglutide not reaching statistical significance in superiority analysis, but significant decreases in cardiovascular mortality (HR 0.49, P = 0.03) and all-cause mortality (HR 0.51, P = 0.008) in semaglutide-treated patients [120].

A meta-analysis of 236 trials enrolling 176 310 patients with type 2 DM demonstrated that SGLT-2 inhibitors and GLP-1 receptor agonists were associated with lower all-cause and cardiovascular mortality compared with DPP-4 inhibitors [121]. Use of SGLT-2 inhibitors was associated with reductions in hospitalization for heart failure compared with GLP-1 receptor agonists and for MI compared with placebo [121]. This, together with the more favourable adverse event profile of SGLT-2
<table>
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<tr>
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<td>1:1 ratio linsencatide 10–20 μg/day or placebo</td>
<td>25 months</td>
<td>Cardiovascular death, MI, stroke, hospitalization for unstable angina</td>
<td>Primary outcome: HR 1.02, 95% CI 0.89–1.12</td>
<td>Mean Age 60 years, Mean eGFR: 67.0 eGFR &lt; 60 22.5%</td>
<td>Percentage change in ACR at 24 months</td>
<td>34% versus 24% P = 0.004 adjusted for baseline, treatment, region, ACEi/ARB use (NS after adjusting for HbA1c)</td>
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<td>LEADER [25, 109]</td>
<td>Double-blind RCT</td>
<td>Type 2 DM with at least one cardiovascular risk factor</td>
<td>9380</td>
<td>1:1 ratio, 1.8 mg (or the maximum tolerated dose) of liraglutide once daily as a subcutaneous injection</td>
<td>Median of 3.8 years</td>
<td>Cardiovascular death, non-fatal (including silent) MI or non-fatal stroke</td>
<td>Primary outcome: HR 0.87, 95% CI 0.78–0.97; cardiovascular death: HR 0.78, 95% CI 0.66–0.93; all-cause mortality: HR 0.85, 95% CI 0.74–0.97; heart failure hospitalization: HR 0.87, 95% CI 0.73–1.05; stroke: HR 0.64, 95% CI 0.34–1.19 Subgroup analyses showed increased benefit if baseline eGFR &lt; 60 mL/min/1.73 m² excluded</td>
<td>Mean Age: 64.3 years, eGFR &lt; 60 mL/min/1.73 m²: 24.7% Microalbuminuria: 26.3% Macroalbuminuria: 10.5%</td>
<td>New onset macroalbuminuria, doubling of Scr, ESRD or death from renal disease</td>
<td>Renal composite: HR 0.78, 95% CI 0.67–0.92 New-onset macroalbuminuria: HR 0.74, 95% CI 0.60–0.91 Doubling of Scr: HR 0.89, 95% CI 0.67–1.19 ESRD: HR 0.87, 95% CI 0.61–1.24 Death from renal disease: HR 1.99, 95% CI 0.52–4.87</td>
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<td>SUSTAIN-6 [26]</td>
<td>Double-blind RCT</td>
<td>Type 2 DM with established cardiovascular disease</td>
<td>3297</td>
<td>1:1:1:1 ratio 0.5 or 1.0 mg once-weekly semaglutide or volume-matched placebo</td>
<td>Median of 2.1 years</td>
<td>Composite of cardiovascular death, MI or stroke</td>
<td>Primary outcome: HR 0.74, 95% CI 0.58–0.95; cardiovascular death: HR 0.98, 95% CI 0.65–1.48; all-cause mortality: HR 1.05, 95% CI 0.74–1.50; MI: HR 0.74, 95% CI 0.51–1.08; stroke: HR 0.61, 95% CI 0.38–0.99; HF hospitalization: HR 1.11, 95% CI 0.77–1.61</td>
<td>Mean Age 64.6 years, eGFR &lt; 60 mL/min/1.73 m²: 24.1%</td>
<td>Persistent macroalbuminuria, doubling of Scr and eGFR: 45 mL/min/1.73 m² or the need for dialysis</td>
<td>Renal composite: HR 0.64, 95% CI 0.46–0.88 Persistent macroalbuminuria: HR 0.54, 95% CI 0.37–0.77 Doubling Scr level and eGFR: 45 mL/min/1.73 m²: HR 1.28, 95% CI 0.64–2.58 Need for dialysis: HR 0.91, 95% CI 0.40–2.07</td>
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<td>Type 2 DM with 70% of participants having a previous cardiovascular event</td>
<td>14752</td>
<td>1:1 ratio extended-release exenatide 2 mg weekly or matching placebo</td>
<td>Median of 3.2 years</td>
<td>Composite of cardiovascular death, MI or stroke</td>
<td>Primary outcome: HR 0.91, 95% CI 0.83–1.00; cardiovascular death: HR 0.88, 95% CI 0.73–1.05; MI: HR 0.95, 95% CI 0.84–1.09; stroke: HR 0.86, 95% CI 0.70–1.07; HF hospitalization: HR 0.94, 95% CI 0.78–1.13</td>
<td>Mean Age 62 years, eGFR &lt; 60 mL/min/1.73 m²: 22%</td>
<td>40% decline in eGFR, ESRD, renal death or new-onset macroalbuminuria</td>
<td>Renal composite: HR 0.85, 95% CI 0.73–0.98 Result driven by new-onset macroalbuminuria</td>
</tr>
<tr>
<td></td>
<td>Type 2 DM with established</td>
<td></td>
<td>9463</td>
<td>Median of 1.6 years</td>
<td></td>
<td></td>
<td>Primary outcome: HR 0.78, 95% CI 0.68–0.90; 19% of patients had nephropathy</td>
<td>Only renal safety data published</td>
<td></td>
<td></td>
</tr>
</tbody>
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Continued
inhibitors, suggests that these agents may be preferred to GLP-1 receptor agonists to lower cardiovascular risk [114, 121]. Furthermore, doubt remains as to whether beneficial cardiovascular effects of GLP-1 receptor agonists are a class effect or limited to individual agents [122–125].

**POTENTIAL MECHANISMS FOR THE CARDIOPROTECTIVE ACTIONS OF GLP-1 RECEPTOR AGONISTS**

The cardiovascular benefits of GLP-1 receptor agonists in the trials showing superiority over placebo are rather unlikely to be driven by the modest glycaemic differences achieved between treatment and placebo arms (HbA1c difference of 0.4% LEADER [25], 0.8% SUSTAIN-6 [26] and 0.6% HARMONY OUTCOMES [27]) and are generally considered to be due to improvements in other cardiovascular risk factors including weight, lipids and renal function [112, 113].

GLP-1 receptor agonists reduced body weight and waist circumference compared with placebo and anti-hyperglycaemic drugs that increased weight, albeit with much variation in individual responses and within-class differences [126–128]. This body weight decrease is associated with reduction in total fat, rather than in lean tissue mass [129, 130]. Weight loss with GLP-1 receptor agonists is generally greater than that observed with SGLT-2 inhibitors and is due to reduced calorie intake [112]. GLP-1 receptors are expressed in the hypothalamus and intestine and may be responsible for the promotion of satiety, appetite suppression and delayed gastric emptying [131–134].

The major adverse effects of GLP-1 receptor agonists are gastrointestinal including nausea, vomiting and diarrhoea, all of which may also contribute to reduced calorie intake [131, 133, 134].

Modest improvements in BP have been observed with GLP-1 receptor agonists in some but not all studies. A previous meta-analysis showed SBP reductions with liraglutide and albiglutide, albeit non-significantly with exenatide and dulaglutide [135]. In addition to weight loss, proposed mechanisms include GLP-1-mediated release of atrial natriuretic peptide by cardiomyocytes leading to vasodilatation, improved endothelial function and natriuresis [124, 136, 137]. Exogenous GLP-1 has been shown to dose-dependently increase natriuresis and diuresis probably by direct actions on the proximal renal tubule [126, 138–142]. GLP-1 receptor agonists may be able to increase absolute and fractional sodium excretion [143, 144] and may also reduce circulating levels of components of the RAS system [144, 145]. An elegant uncontrolled study in 31 patients with type 2 DM included 11 ambulatory BP measurements within 70 days. Initiation of liraglutide at 0.6 mg/day was associated with an initial increase in 24-h SBP, followed by a 7 mmHg reduction after escalation to 1.8 mg/day, which again disappeared after 4 weeks of maximum dose [146]. These data suggest that the effect of GLP-1 agonist on BP may be related to the actual dose of the agent acting in an antagonist or agonist fashion to produce natriuretic effects, followed by compensatory mechanisms, and may explain the discrepancy between studies in the field. These results must be confirmed in randomized studies.
Studies consistently demonstrate beneficial effects of GLP-1 receptor agonists on lipid profiles [132]. Proposed mechanisms include reductions in post-prandial chylomicron synthesis and reduced triglyceride absorption [147, 148], as well as increased post-prandial insulin production and reduction in glucagon release leading to inhibition of adipose tissue lipolysis [149, 150]. In pre-clinical studies, GLP-1 receptor agonists prevented atherosclerosis in non-diabetic mice [151]. The infusion of liraglutide into apoE−/− mice significantly retarded atherosclerotic lesions in the aortic wall and suppressed macrophage foam cell formation [152]. In rabbits with fully developed atherosclerotic plaques, these agents inhibited plaque growth and modified the plaque components; both macrophage infiltration and calcium deposition were reduced [153]. Furthermore, GLP-1 receptor agonists may reduce the systemic and vascular inflammation. Incubation of endothelial cells with liraglutide reduced the expression of several inflammatory and pro-inflammatory proteins involved in the atherosclerosis development and progression [154]. Liraglutide reduced plasma concentrations of both plasminogen activator inhibitor-1 and C-reactive protein in patients with DM [137]; exenatide exerted anti-inflammatory effects in diabetic patients without micro- or macrovascular complications [155].

The effect of the GLP-1 receptor agonists on heart failure is still to be elucidated. In an animal model of dilated cardiomyopathy, administration of recombinant GLP-1 dramatically improved cardiac output, and decreased heart rate and vascular resistance [156]. Hospitalization for heart failure was not improved in any of the above major studies with GLP-1 receptor agonists. Liraglutide did not improve heart failure hospitalization or functional status in patients with reduced left ventricular function [157]. However, 5-week treatment with GLP-1 improved left ventricular function, functional status and quality of life in patients with severe heart failure, benefits were seen in both diabetic and non-diabetic patients [158]. In the setting of acute MI, injection of GLP-1 receptor agonist improved left ventricular function in patients with severe systolic dysfunction after successful primary angioplasty [159]. Mechanisms beyond these actions may include the natriuretic effects of GLP-1 [138] or a beneficial effect on myocardial cells apoptosis and cardiac fibrosis independently of glucose lowering [160, 161].

**Nephroprotective Properties of GLP-1 Receptor Agonists**

In the LEADER trial, a composite of new-onset persistent macroalbuminuria, persistent doubling of Scr, ESRD or death due to renal disease (Table 2) was lower in the liraglutide group (HR 0.78, 95% CI 0.67–0.92) [25, 109]. This result was driven by the reduction in new-onset macroalbuminuria (HR 0.74, 95% CI 0.60–0.91), as all the other components did not change significantly. The result was similar when patients with a baseline eGFR <60 mL/min/1.73 m² were considered separately [109]. The eGFR declined continuously in both groups of patients, but the decline was 2% less in the liraglutide group (estimated trial group ratio 1.02; 95% CI 1.00–1.03). This effect was more pronounced in patients with baseline eGFR 30–59 mL/min/1.73 m² (estimated trial-group ratio 1.07; 95% CI 1.04–1.10). The UACR increased less in the liraglutide group with a 17% lower UACR at 36 months; this was independent of baseline eGFR or UACR. Incidence of microalbuminuria was also lower with liraglutide (HR 0.87; 95% CI 0.83–0.93). There were no differences in the rates of renal adverse events (including AKI) between the two groups [109].

The SUSTAIN-6 study evaluated a pre-specified secondary renal composite of microalbuminuria, doubling of Scr, creatinine clearance >45 mL/min/1.73 m² or the need of maintenance dialysis. This composite outcome was lower in patients on semaglutide than placebo (3.8% versus 6.1%; HR 0.64, 95% CI 0.46–0.88) [26]. As in the LEADER trial [109], this was driven mainly by a reduction in new-onset macroalbuminuria (2.5% versus 4.9%). Doubling of Scr, ESRD or renal death were unaffected and the total event rate was very low (<1%).

In the ELIXA trial, treatment with lixisenatide was associated with a lower increase in median UACR compared with placebo (24% versus 34%, P = 0.004) although the median values at baseline (ratio 10 in both groups) and follow-up (ratio 12 in lixisenatide group and 13 in placebo group) were clinically similar [115]. Adjustment for HbA1c at baseline and at 3 months after randomization attenuated the difference (P = 0.07). In a recent analysis of opportunistic laboratory data from the EXSCEL study [111], a composite of 40% decline in eGFR, need for renal replacement therapy, renal death and new-onset macroalbuminuria was lower in the exenatide group (HR 0.85, 95% CI 0.73–0.98). Again, this result was mainly driven by new-onset macroalbuminuria. Although renal outcomes data from the HARMONY OUTCOMES study have not yet been published, safety data suggest that there were no differences in eGFR between groups at 16 months (HR −0.43, 95% CI −1.26 to 0.41 mL/min/1.73 m²) [27].

In small previous studies, liraglutide was associated with reductions in albuminuria around 30%, which were independent of BP or eGFR [162, 163]. In the SCALE Diabetes Randomized Trial, a maximum daily dose of 3 mg of liraglutide showed an 18% reduction in albuminuria compared with placebo [164]. A recent multicentre study evaluated the effect of dulaglutide 0.75 or 1.5 mg once-weekly or daily insulin glargine during 52 weeks in almost 500 patients with type 2 DM and CKD Stages 3 and 4, on a maximum tolerated dose of an ACEi or an ARB [165]. Between baseline and Week 52, eGFR by CKD-EPI equation based on cystatin-c showed minor changes in patients with any dose of dulaglutide but declined in those with insulin (−0.7 mL/min/1.73 m² versus −3.3 mL/min/1.73 m², P < 0.0001). Interestingly, these differences were not apparent when eGFR was estimated with the creatinine-based CKD-EPI formula, which may reflect the error of estimated GFR in the diabetic population [166]. Dulaglutide reduced albuminuria compared with insulin only in the subgroup of patients with microalbuminuria [165, 167].

Overall, there is now considerable evidence demonstrating that the treatment with GLP-1 receptor agonists reduces albuminuria. Therefore, it can be suggested that these agents are renoprotective. However, evidence of direct benefit on hard renal outcomes is still lacking.
POTENTIAL MECHANISMS FOR THE NEPHROPROTECTIVE ACTIONS OF GLP-1 RECEPTOR AGONISTS

Similar to the actions of GLP-1 receptor agonists on the cardiovascular system, it is likely that the renal effects of GLP-1 receptor agonists are multifactorial, mediated by actions on body weight, BP and dyslipidaemia. In addition, pre-clinical studies have shown that GLP-1 receptor agonists reduce proteinuria and glomerular sclerosis associated with protection from endothelial injury and reductions in oxidative stress and inflammation in a glucose-independent manner [168, 169].

The tubular effects of GLP-1 receptor agonists promoting natriuresis and diuresis are described above [126, 138–142]. The impact of GLP-1 agonism on renal haemodynamics and glomerular filtration rate is controversial [170]. Under physiological conditions, GLP-1 agonists have either no effect or influence glomerular hyperfiltration by reducing afferent arteriolar resistance [126, 138, 171]. In diabetic patients, GLP-1-related natriuresis might restore disrupted tubulo-glomerular feedback, resulting in relative vasoconstriction of afferent arteriole leading to decreased glomerular hydraulic pressure [172]. In the aforementioned study from von Scholten et al. [146], despite the variance in BP levels over follow-up, escalation of liraglutide to a maximum dose of 1.8 mg/day was associated with progressive reductions in eGFR (up to 10 mL/min), UACR and fractional albumin excretion (up to 30%), which were reversible after drug withdrawal. Other studies suggested that these agents reduced GFR rate in hyperfiltrating type 2 diabetic patients [138, 170]. The presence of glomerular hyperfiltration might therefore be required for GLP-1 receptor agonists to confer renoprotective alterations in renal haemodynamics [173].

SAFETY OF GLP-1 RECEPTOR AGONISTS

Several concerns have been raised regarding the use of GLP-1 receptor agonists, including retinopathy, acute gallstone disease, pancreatitis, medullary thyroid cancer and increased heart rate. In SUSTAIN-6, diabetic retinopathy complications occurred in 3% of patients taking semaglutide and 1.8% taking placebo (HR 1.76, 95% CI 1.11–2.78) [26]. A similar, but non-statistically significant increase was observed in LEADER (HR 1.15, 95% CI 0.87–1.52) [25]. A large meta-analysis of relevant trials with 21782 participants did not find increase in retinopathy events [174]. Indeed, use of GLP-1 receptor agonists was associated with a lower retinopathy risk compared with sulphonylureas [174]. This finding would suggest that any effect on worsening of retinopathy is either specific to semaglutide or a type 1 error, rather than a drug class effect. It is possible that the effect of semaglutide on retinopathy in the SUSTAIN-6 trial was due to rapid reduction of blood glucose as reported in other studies [175].

Acute gallstone disease was more common with liraglutide than placebo in the LEADER trial [25]. A similar finding was observed in a large population study with exenatide and liraglutide [176]. Proposed mechanisms for this include fast weight loss leading to supersaturation of bile acid cholesterol, diminished gall bladder emptying and cholangiocyte proliferation [176]. However, in SUSTAIN-6, the frequency of gall bladder disorders was not different between semaglutide and placebo [26]. Early concerns about increased pancreatitis [177, 178] and medullary thyroid cancer risk [177, 179] with GLP-1 receptor agonists have not been substantiated in the large outcome studies [25–27, 115], nor in recent meta-analyses of RCTs [180, 181].

GLP-1 receptor agonists induce an increase in heart rate [182] that theoretically could represent a safety concern [183, 184]. The mechanism for this is currently unknown, but may be mediated by direct actions of these drugs on sinoatrial node [185] or activation of the sympathetic nervous system [186]. Increased heart rate could be associated with adverse clinical outcomes in patients with heart failure. In the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial 300 patients with heart failure and reduced ejection fraction were randomized to liraglutide or placebo [157]. Although a small study, patients on liraglutide did not have an increased risk of hospitalization for heart failure (HR 1.30, 95% CI 0.89–1.88). Liraglutide in the LEADER trial showed a non-significant reduction, whereas semaglutide in SUSTAIN-6 showed a non-significant increase in heart failure hospitalizations [25, 26]. However, it should be noted that both LEADER (18%) and SUSTAIN-6 (24%) had low numbers of patients with mild-to-moderate heart failure (New York Heart Association II–III). Although GLP-1 receptor agonists are not contraindicated for use in patients with type 2 DM and heart failure, SGLT-2 inhibitors appear to have more demonstrable benefits in such patents.

ONGOING STUDIES WITH OF NEPHROLOGY INTEREST WITH SGLT-2 INHIBITORS AND GLP-1 RECEPTOR AGONISTS

Following pilot observations and renal outcome data from EMPA-REG OUTCOME and CANVAS studies, three Phase 3 trials with SGLT-2 inhibitors and renal primary endpoints are currently running. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation trial (CREDiTE) [187] was designed to compare the efficacy and safety of canagliflozin versus placebo (on top of maximum labelled or tolerated dose of an ACEi or an ARB) in preventing clinically important kidney and cardiovascular outcomes in 4401 patients with type 2 DM and CKD (eGFR 30–90 mL/min/1.72 m² and UACR >300 to ≤5000 mg/g) [188] with projected duration of ~5.5 years. The primary endpoint is the composite of ESRD, doubling of Scr and renal or cardiovascular death (non-dialysed). In July 2018, that study was stopped early [189] based on achieved pre-specified criteria for the primary composite endpoint during a planned interim analysis. Full data from the study are expected in the following months.

Of importance, the other two renal outcome studies with SGLT-2 inhibitors are recruiting patients with or without DM. The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD) is an event-driven, randomized, double-blind study, evaluating the effect of dapagliflozin versus placebo in addition to standard
of care (maximum tolerated labelled dose with ACEi or ARB) to prevent the progression of CKD or cardiovascular/renal death in patients with eGFR $\geq 25$ and $<75$ mL/min/1.73 m$^2$, and UACR $\geq 200$ and $\leq 5000$ mg/g [190]. The primary outcome is a composite of $\geq 50\%$ sustained decline in eGFR or reaching ESRD or cardiovascular death or renal death. The study started in February 2017, is planned to enrol 4000 participants and is to be completed in November 2020.

Finally, the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) [191] aims to investigate the effect of empagliflozin on kidney disease progression or cardiovascular death versus placebo on top of standard treatment in patients with CKD (eGFR $\geq 20$ to $<45$ mL/min/1.73 m$^2$ or eGFR $\geq 45$ to $<90$ mL/min/1.73 m$^2$ with UACR $\geq 200$ mg/g or protein:creatinine ratio $\geq 300$ mg/g). The composite primary outcome consists of time to first occurrence of (i) kidney disease progression (defined as ESRD, a sustained decline in eGFR to $<10$ mL/min/1.73 m$^2$, renal death or a sustained decline of $\geq 40\%$ in eGFR from randomization) or (ii) cardiovascular death. The study plans to enrol 5000 participants from November 2018 and is to be completed in June 2022.

With regards to GLP-1 receptor agonists, no trial with primary hard renal outcome seems currently under way. Renal endpoints are included in the REWIND [117] and the PIONEER-6 [119] studies and are expected to be described in the relevant full reports. Furthermore, as beneficial effects of GLP-1 receptor agonists might not be mediated through glycaemic control, trials of these agents in patients with cardiovascular disease without diabetes are under way [e.g. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT) trial NCT03574597] [192].

**CONSENSUS ON SGLT-2 INHIBITOR AND GLP-1 RECEPTOR AGONIST USE AND CONCLUSIONS**

A multifactorial intervention in patients with type 2 DM, including improving glycaemic control, treating BP with RAS blockers, using statins and implementing lifestyle interventions is able, among other things, to slow CKD progression [193, 194]. In light of the aforementioned data, suggesting for the first time beneficial effects of an anti-diabetic class on survival and progression to ESRD, the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) published an updated Consensus Report for management of hyperglycaemia in type 2 DM in September 2018, with major changes in recommendations for anti-diabetic drug use [195].

As first-line treatment, ADA/EASD recommends metformin together with comprehensive lifestyle measures (weight loss and physical activity), as in previous recommendations [196]. The rationale for metformin is based on its low cost, proven safety record, weight neutrality and some indirect data on possible cardiovascular benefit deriving mainly from the UKPDS study [197]. Discussing the major issue of metformin use, that is the potential for increased levels and adverse effects in patients with GFR $<60$ mL/min/1.73 m$^2$ [196], is beyond the scope of this document; the reader is referred to a previous Clinical Practice Guideline from ERA-EDTA [198]. The major change in the recent ADA/EASD report is the differentiation of patients into those that have established atherosclerotic cardiovascular disease (ASCVD) or heart failure or CKD, and those that do not. In the latter, the various anti-diabetic agents are proposed depending on the underlying clinical needs (to reduce HbA1c or weight or cost). In patients with ASCVD, the authors recommend to use after metformin a GLP-1 receptor agonist or an SGLT-2 inhibitor with proven cardiovascular benefit, suggesting that for GLP-1 receptor agonist the strongest evidence is for liraglutide > semaglutide > exenatide extended release, and for SGLT-2 inhibitors moderately stronger for empagliflozin > canagliflozin. For patients in whom heart failure or CKD predominate, the authors recommend an SGLT-2 inhibitor with the evidence of reducing heart failure or CKD progression and, if this is not tolerated or is contraindicated, a GLP-1 receptor agonist. In every case, use of SGLT-2 inhibitor is recommended if eGFR is adequate (i.e. to the indicated level of initiation and continuation of use in every region) [196].

The present consensus report examined recent evidence on the use of SGLT-2 inhibitors and GLP-1 receptor agonists in diabetic patients with CKD, that is with eGFR $<60$ mL/min/1.73 m$^2$ or with eGFR $>60$ mL/min/1.73 m$^2$ and micro- or microalbuminuria and those without CKD. Evidence from EMPA-REG OUTCOME and CANVAS studies suggest that the observed cardiovascular and mortality benefits were similar for patients with eGFR $<60$ and $>60$ mL/min/1.73 m$^2$ or in further eGFR subgroups [35, 37]. With regards to nephroprotection, current evidence clearly suggests that SGLT-2 inhibitors are able to reduce glomerular hyperfiltration, intraglomerular pressure and thus albumin excretion, by a mechanism that is unique and different to the current established treatment with RAS blockers. In particular, SGLT-2 inhibitors reverse the vasodilation of the afferent arteriole, whereas RAS blockers act through inhibiting the effects of angiotensin-II on the efferent arteriole and promoting its vasoconstriction [11, 199]. As patients with proteinuric CKD commonly progress to ESRD via single-nephron hyperfiltration [200], this mode of action of SGLT-2 inhibitors offers a unique opportunity for nephroprotection. Although trials with hard renal endpoints are currently under way, the observed renal benefit in EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 is clear, especially as in EMPA-REG OUTCOME the reduction in all components of the composite renal outcome was significant and of large magnitude. Again, the nephroprotective properties were evident in all eGFR subgroups and appeared to be more potent in patients with macroalbuminuria. Thus, the recommendation of this report (Figure 4) is that in patients with type 2 DM and CKD not on HbA1c target on recommended metformin therapy or for those whom metformin is not tolerated or is contraindicated, to use an SGLT-2 inhibitor with evidence for cardio- and nephroprotection, given that eGFR is within licenced range. Patients with CKD achieving HbA1c target on
Patients with type 2 DM and CKD (eGFR <60 ml/min/1.73m² or eGFR >60 ml/min/1.73m² and micro- or microalbuminuria) not on HbA1c target (HbA1c >7%) on recommended metformin dose or not on HbA1c target (HbA1c >7%) and metformin is not tolerated or is contraindicated

Use SGLT-2 inhibitor with evidence for cardio- and nephroprotection¹

If HbA1c remains above target or SGLT-2 inhibitor is not tolerated or is contraindicated

Use GLP-1 receptor agonist with evidence for cardio- and nephroprotection²

If HbA1c remains above target or GLP-1 receptor agonist is not tolerated or is contraindicated

Use another antidiabetic agent (DDP-4 i, TZD, SU, or basal insulin) according to current recommendations for Type 2 DM³

¹ SGLT-2 inhibitors have been used in EMPA-REG OUTCOME and CANVAS studies up to 30 ml/min/1.73m² but their current indication for use is >45 ml/min/1.73m² for empagliflozin and canagliflozin and >60 ml/min/1.73m² for dapagliflozin (see text for prescribing information)
² Consult licensing indications for GLP-1 receptor agonists regarding combination treatment and use according to renal function
³ Follow recent ADA/EASD recommendations and current licensing data for combining antidiabetic agents and use according to renal function

FIGURE 4: Recommendations for SGLT-2 inhibitor and GLP-1 receptor agonist use for patients with type 2 DM and CKD not on HbA1c target after first-step treatment.

Reassess HbA1c in 3-months interval and adjust the treatment if above target³

1. SGLT-2 inhibitors have been used in EMPA-REG OUTCOME and CANVAS studies up to 30 ml/min/1.73m² but their current indication for use is >45 ml/min/1.73m² for empagliflozin and canagliflozin and >60 ml/min/1.73m² for dapagliflozin (see text for prescribing information)
2. Consult licensing indications for GLP-1 receptor agonists regarding combination treatment and use according to renal function
3. Follow recent ADA/EASD recommendations and current licensing data for combining antidiabetic agents and use according to renal function

FIGURE 5: Recommendations for SGLT-2 inhibitor and GLP-1 receptor agonist use for patients with type 2 DM and CKD on HbA1c target after first-step or combination treatment.
combined therapy with metformin, and one or more additional anti-diabetic agents (Figure 5) would benefit from switching one of the glucose-lowering drugs that does not confer cardio- or nephroprotection with an SGLT-2 inhibitor (in line with current diabetes recommendations [196]).

An important issue relevant to renal function is the current licencing indications of these drugs. This report recommends following prescribing rules in the individual countries. In Europe, both empagliflozin and canagliflozin should not be initiated in eGFR <60 mL/min/1.73 m²; if eGFR falls below this levels, their doses should be reduced to 10 and 100 mg daily and they should be discontinued in eGFR persistently <45 mL/min/1.73 m² [201, 202]. In the USA, empagliflozin and canagliflozin should not be used in patients with eGFR <45 mL/min/1.73 m² [203, 204]. In Europe, dapagliflozin should not be started in patients with eGFR <60 and should be discontinued in patients with eGFR <45 mL/min/1.73 m²; in the USA, it should not be used in patients with eGFR <60 mL/min/1.73 m² [205, 206]. Importantly, the above recommendations are based on the effects of SGLT-2 inhibitors on blood glucose, which are much weaker below 45 mL/min/1.73 m². Both EMPA-REG OUTCOME and CANVAS recruited patients up to 30 mL/min/1.73 m², with the cardio- and nephroprotective properties being at least equally, if not more, evident in patients with CKD. DECLARE-TIMI 58 included patients with creatinine clearance >60 mL/min/1.73 m², but again, no differences in outcomes were noted in the few patients with eGFR <60 mL/min/1.73 m².

Outcome trials with liraglutide [25, 109], semaglutide [26], extended-release exenatide [110] and, recently, albiglutide [27] have clearly shown reductions in cardiovascular events that were similar across eGFR subgroups. Importantly, the LEADER, SUSTAIN-6 and EXSCEL trials included also patients with eGFR <30 mL/min/1.73 m², whereas HARMONY OUTCOMES included patients up to these levels. With regards to renal outcomes, in the first three of the above trials, a significant reduction in the renal composite was noted in the active treatment groups. This was mainly driven by reduction in new-onset macroalbuminuria, whereas the other components did not change [25–27, 109, 110]. In addition, there are currently no background or clinical data supporting a clear mechanism for nephroprotection. However, reduction of progression to macroalbuminuria is a meaningful outcome since pharmacologically induced reductions in albuminuria by 30% translate into a long-term reduction in the risk of ESRD by 23.7% [207]. Thus, we recommend that GLP-1 receptor agonists should be used in patients with type 2 DM and CKD immediately after SGLT-2 inhibitors to maximize cardio- and nephroprotection (Figures 4 and 5).

Overall, RCTs published in recent years have provided important evidence on the effects of SGLT-2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes, changing the landscape in treatment of DM. This report advocates the preferred use of these agents in patients with type 2 DM and CKD, within their licenced indications. Future trials are awaited to offer more data in this important field.

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CONFLICT OF INTEREST STATEMENT

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