ndt
Nephrology Dialysis Transplantation

SPECIAL REPORT

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

Pantelis Sarafidis[1], Charles J. Ferro[2], Enrique Morales[3], Alberto Ortiz[4], Jolanta Malyszko[5], Radovan Hojs[6], Khaled Khazim[7], Robert Ekart[6], Jose Valdivielso[8], Denis Fouque[9], Gérard M. London[10], Ziad Massy[11], Petro Ruggenenti[12], Esteban Porrini[13], Andrej Wiecek[14], Carmine Zoccali[15], Francesca Mallamaci[15] and Mads Hornum[16]

[1]Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2]Department of Renal Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, [3]Department of Nephrology, Hospital Universitario 12 de Octubre and Research Institute i+12, Madrid, Spain, [4]IIS-Fundacion Jimenez Diaz, School of Medicine, University Autonoma of Madrid, FRIAT and REDINREN, Madrid, Spain, [5]Department of Nephrology, Dialysis and Internal Medicine, Warsaw Medical University, Warsaw, Poland, [6]Department of Nephrology, University Medical Center and Faculty of Medicine, Maribor University, Maribor, Slovenia, [7]Department of Nephrology and Hypertension, Galilee Medical Center, Nahariya, Israel, [8]Vascular and Renal Translational Research Group, Institut de Recerca Biomedica de Lleida, IRBLleida, Lleida and RedInRen, ISCIII, Spain, [9]Department of Nephrology, Centre Hospitalier Lyon Sud, University of Lyon, Lyon, France, [10]Manhes Hospital and FCRIN INI-CRCTC, Manhes, France, [11]Hopital Ambroise Paré, Paris Ile de France Ouest (UVSQ) University, Paris, France, [12]IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Nephrology and Dialysis Unit, Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy, [13]Faculty of Medicine, University of La Laguna, Instituto de Tecnología Biomédicas (ITB) Hospital Universitario de Canarias, Tenerife, Canary Islands, Spain, [14]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, [15]CNR-IFC, Clinical Epidemiology and Pathophysiology of Hypertension and Renal Diseases Unit, Ospedali Riuniti, Reggio Calabria, Italy and [16]Department of Nephrology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

Correspondence and offprint requests to: Pantelis A. Sarafidis; E-mail: psarafidis@auth.gr; Twitter handle: @carminezoccali

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 1. Cardiovascular and renal outcomes in major studies with SGLT-2 inhibitors

Study	Type of study	Type of subjects	N	Comparisons	Duration	Primary composite endpoint	Main cardiovascular outcomes	Population characteristics of renal interest	Renal composite endpoint	Main renal outcomes
EMPA-REG OUTCOME [23, 28]	Double-blind, RCT	Type 2 DM with established cardiovascular disease	7028	1:1:1 ratio: empagliflozin 10 mg, empagliflozin 25 mg, placebo	Median of 3.1 years	3-point MACE (cardiovascular mortality, non-fatal MI and non-fatal stroke)	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	Mean Age: 63.1 years; eGFR: 74 mL/min/1.73 m²; Mean eGFR <60 mL/min/1.73 m²: 26%; UACR >300 mg/g: 11.1%; eGFR <30 mL/min/1.73 m² excluded	Progression to macroalbuminuria, doubling of SCr, initiation of RRT or death from renal disease	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
CANVAS [24, 29]	Double-blind RCT	Type 2 DM with high cardiovascular risk	10 142	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	Mean of 188.2 weeks	Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke	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	Mean Age: 63.3 years; eGFR: 76.5 mL/min/1.73 m²; eGFR <60 mL/min/1.73 m²: 20% Macroalbuminuria: 7.6% eGFR <30 mL/min/1.73 m² excluded	40% reduction in eGFR, need for RRT or death from renal causes	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; Ad hoc: Doubling of SCr ESRD or death from renal causes: HR 0.53, 95% CI 0.33–0.84
DECLARE-TIMI 58 [30]	Double-blind RCT	Type 2 DM with risk factors for or established cardiovascular disease	17 160	1:1 ratio dapagliflozin 10 mg or placebo	Median of 4.2 years	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	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	Mean Age: 64 years; Creatinine clearance <60 mL/min excluded	≥40% decrease in eGFR to <60 mL/min/1.73 m², ESRD or death from renal or cardiovascular causes	Renal composite: HR 0.76, 95% CI 0.67–0.87; Ad hoc: ≥40% decrease in eGFR to <60 mL/min/1.73 m², ESRD or death from renal causes: HR 0.53, 95% CI 0.43–0.66

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.

P. Sarafidis *et al.*

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 m^2 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 1:1:1 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 m^2, and according to baseline kidney function categories (eGFR <45, 45 to <60, 60 to <90 and ≥ 90 mL/min/1.73 m^2). 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 patients 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 m^2 (HR 0.79, 95% CI 0.66–0.95) and in the few patients ($n = 189$) with eGFR <60 mL/min/1.73 m^2 (HR 0.78, 95% CI 0.55–1.09), but not in patients with eGFR > 90 mL/min/1.73 m^2 (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 m^2); 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,

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 Prevent Heart Attack Trial (ALLHAT) enrolled 33 357 patients with hypertension and showed that chlorothalidone, lisinopril and amlodipine 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 normofiltrating 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

P. Sarafidis *et al.*
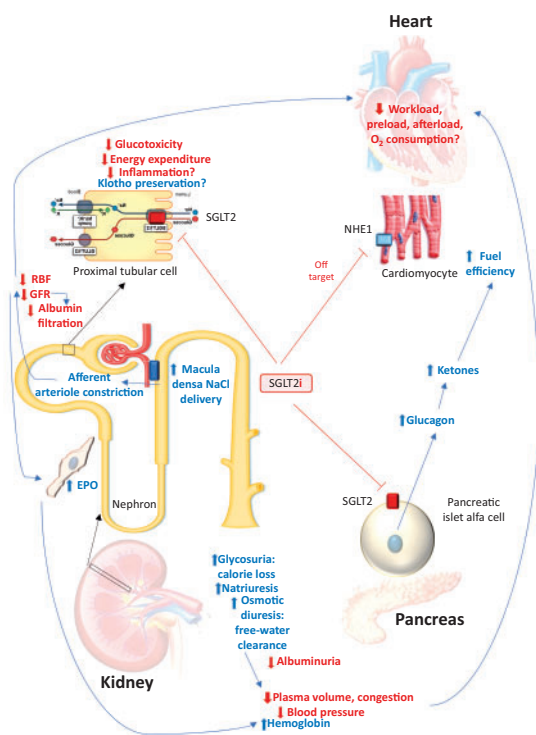
FIGURE 1: Potential mechanisms of the cardioprotective actions of SGLT-2 inhibitors. Three key direct target organs have been identified. Proximal tubular cells in the kidney and alpha-cells in the pancreatic islets express SGLT-2 in their cell membrane, while off-target effects in cardiomyocyte sodium–hydrogen antiporter 1 (NHE-1) have been proposed. Inhibition of proximal tubular cell SGLT-2 prevents glucose entry into these cells, limiting glucotoxicity potentially leading to an inflammatory response and downregulation of the expression of the anti-ageing and cardioprotective factor Klotho. It additionally is expected to decrease energy expended by the basolateral Na^+/K^+ ATPse and increases delivery of sodium (not absorbed with glucose) and chloride (accompanying sodium) to the macula densa, where chloride activates the tubuloglomerular feedback to promote afferent arteriole vasoconstriction, a decreased RBF (which may decrease cardiac workload), a decreased GFR (nephroprotective) and decreased glomerular albumin filtration. Decreased RBF may also contribute to increase erythropoetin production and increase red blood cell mass, which is a factor in the increased haemoglobin concentration, together with decreased plasma volume dependent on osmotic diuresis and natriuresis. The latter contribute to lower BP and congestion, thus decreasing the heart workload, together with increased oxygen delivery by higher haemoglobin levels. In the pancreas, SGLT-2 inhibition leads to increased glucagon secretion, which may contribute to a higher availability of ketones, leading to their preferential use by cardiomyocytes over fatty acids, the substrate accounting to the most of energy generation, but that are less efficient regarding oxygen consumption than ketones. Finally, off-target inhibitory effects on NHE1 have been proposed to directly protect cardiomyocytes. Clinical trials in non-diabetic patients may provide additional insights.

densa. In individuals with genetic defects in SGLT-2 and in diabetics 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 ketoacidosis) [67]. Increased circulating ketone levels are thought to be an efficient source of adenosine triphospate (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 also had 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 $\leq 45\,mL/min/1.73\,m^2$ (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 $\geq$60 mL/min/1.73 m^2 of which 64% had no albuminuria, 27% had microalbuminuria and 8.5% had macroalbuminuria. There were 1819 patients with an eGFR <60 mL/min/1.73 m^2 (of which 47% had no albuminuria, 34% had microalbuminuria and 19% macroalbuminuria) [28]. The large number of patients in the three albuminuria categories ensured adequate power to assess significant differences in renal outcomes. However, differences in these composites were driven by doubling of SCr as events of renal replacement therapy ($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 m^2 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 $\geq$90, 60 to <90, 45 to <60 and <45 mL/min/1.73 m^2) (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 $\geq$40% decrease in eGFR to <60 mL/min/1.73 m^2, 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 $\geq$40% decrease in eGFR to <60 mL/min/1.73 m^2, 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 m^2) 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 NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, losartan treatment was associated with 16% reduction in doubling of SCr, ESRD or death [12]; in the Irbesartan Diabetic Nephropathy Trial (IDNT), irbesartan resulted in a 20% reduction compared with placebo and 23% reduction compared with amlodipine in the same composite outcome. In these studies, the point estimates of doubling of SCr and ESRD were also much less than those observed in EMPA-REG OUTCOME [75]. Of note, effects of SGLT-2 inhibitors were additional RAS blockade as 80% of EMPA-REG OUTCOME patients, and a similar percentage of CANVAS patients, were taking ACEis or ARBs at baseline [29, 75]. This is of utmost importance since both major trials examining the effect of combined RAS blockade in DKD (i.e. the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) [76], studying the effects of combining aliskiren with ACEi or ARB, and the NEPHRON-D study examining 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 RENAAL 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

P. Sarafidis et al.

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 SGTL-2 reabsorbs 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 arteriole 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 $\geq$135 mL/min/1.73 m^2) and without hyperfiltration during hyperinsulinaemic–euglycaemic clamp. In hyperfiltrating patients, treatment with empagliflozin for 8 weeks resulted in a reduction of GFR from 172 $\pm$ 23 to 139 $\pm$ 25 mL/min/1.73 m^2 (P < 0.01). This was accompanied by a significant reduction in RBF from 1641 $\pm$ 458 to 1156 $\pm$ 219 mL/min/1.73 m^2 and increase in renal vascular resistance, suggesting that this was due to decreased afferent arteriole vasodilation (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 m^2 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 m^2 and -0.82 ± 0.04 mL/min/1.73 m^2 with empagliflozin 10 and 25 mg were noted versus 0.01 $\pm$ 0.04 mL/min/1.73 m^2 (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 m^2) and declined steadily with placebo (-1.67 ± 0.13 mL/min/1.73 m^2, 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 $\pm$ 0.04 and
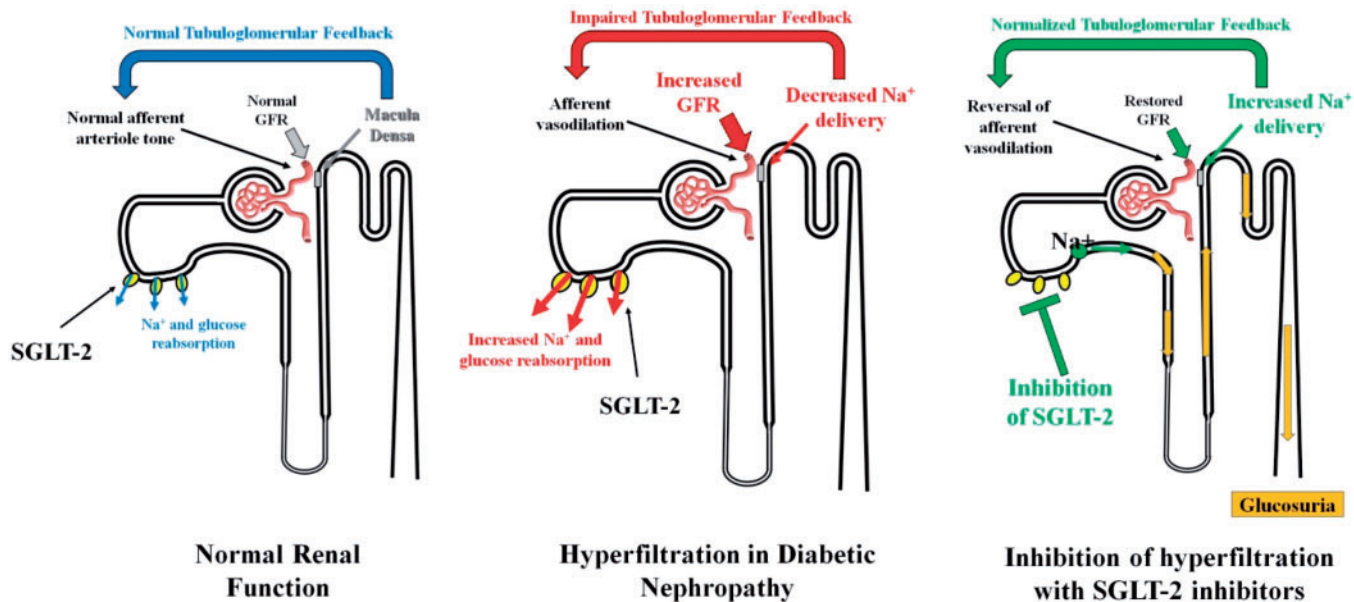
FIGURE 2: Actions of SGLT-2 inhibitors on the renal microcirculation in patients with DM. Under physiological conditions, SGLT-2 co-transporters reabsorb around 90% of the filtered glucose and relevant amounts of sodium, the macula densa is orchestrating normal tubulo-glomerular feedback and GFR is normal. In patients with DM, the number and activity of SGLT-2 co-trasporters are increased, thus the macula densa senses relatively lower sodium and chloride concentrations, leading to afferent arteriole vasodilation and hyperfiltration. Inhibition of SGLT-2 blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium and chloride delivery to the macula densa, restoration of normal tubulo-glomerular feedback and afferent vasoconstriction, which in turn reduces renal plasma flow and GFR.

0.55 ± 0.04 mL/min/1.73 m^2 in empagliflozin groups versus -0.04 ± 0.04 mL/min/1.73 m^2 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 m^2/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 macroalbuminuria at baseline (Figure 3); in this category, eGFR dropped during follow-up from around 67 mL/min/1.73 m^2 to 58 mL/min/1.73 m^2 in the empagliflozin group (with 5 mL/min/1.73 m^2 being relevant to functional dip), but to 47 mL/min/1.73m^2 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

P. Sarafidis *et al.*
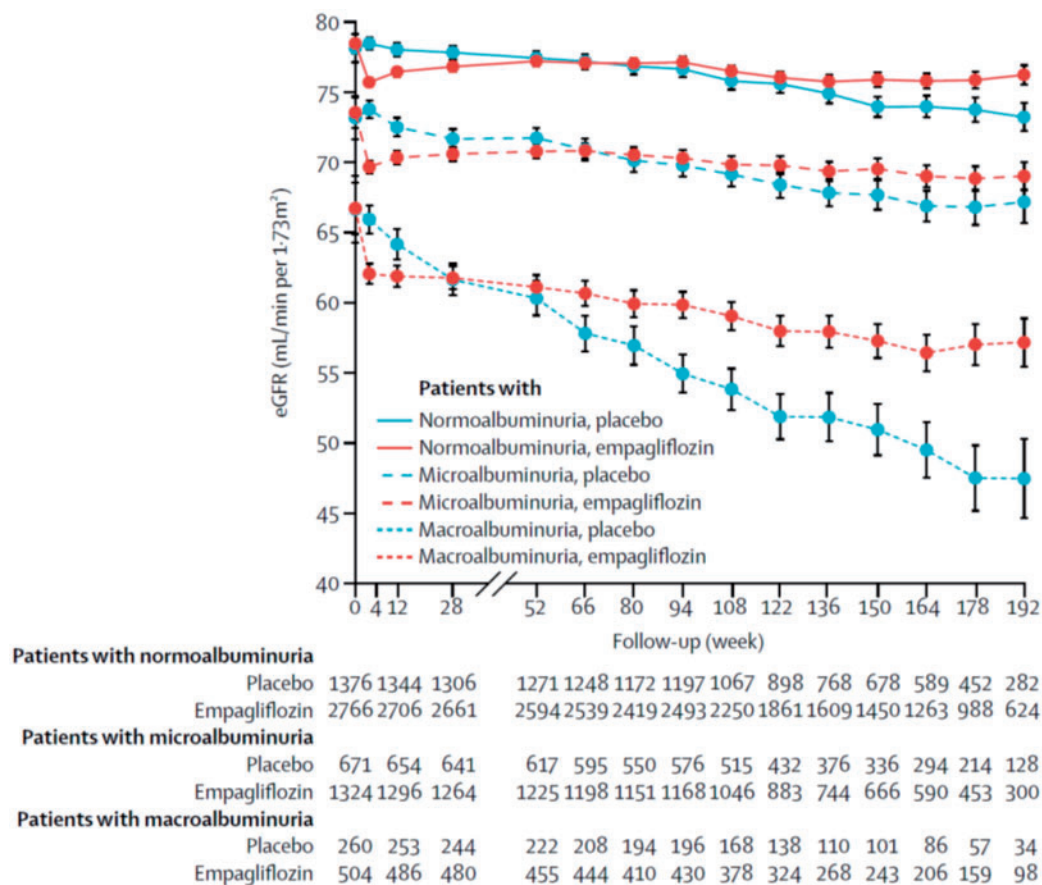
FIGURE 3: Trends in eGFR calculated according to CKD-EPI formula during follow-up in the EMPA-REG OUTCOME trial stratified by the level of UACR. Normoalbuminuria: UACR <30 mg/g. Microalbuminuria: UACR ≥30 to ≤300 mg/g. Macroalbuminuria: UACR >300 mg/g. Data are adjusted means; error bars show 95% CIs. Mixed model repeated measures analysis using all data obtained until study end in patients treated with at least one dose of study drug. Only patients with baseline and post-randomization measurements are included in the figure. Reprinted with permission from Cherney *et al.* [74].

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 µg 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 m^2) appeared to derive greater benefit (HR 0.69, 95% CI 0.57–0.85) than patients with eGFR >60 mL/min/1.73 m^2 (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. The primary outcome occurred in 108 (6.6%) patients receiving semaglutide and 146 (8.9%) patients receiving placebo (HR 0.74, 95% CI 0.58–0.95; P < 0.001 for non-inferiority and P = 0.02 for superiority). Rates of MI were non-significantly lower (HR 0.74, 95% CI 0.51–1.08), and rates of stroke were significantly lower (HR 0.61, 95% CI 0.38–0.99) with semaglutide.

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 albigltutide (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

P. Sarafidis *et al.*

Table 2. Cardiovascular and renal outcomes in major studies with GLP-1 receptor agonists

Study	Type of study	Type of subjects	N	Comparisons	Duration	Primary composite endpoint	Main cardiovascular outcomes	Population characteristics of renal interest	Renal composite endpoint	Main renal outcomes
ELIXA [25]	Double-blind, event-driven RCT	Type 2 DM with recent acute coronary syndrome	6068	1:1 ratio lixisenatide 10–20 µg/day or placebo	25 months	Cardiovascular death, MI, stroke, hospitalization for unstable angina	Primary outcome: HR 1.02, 95% CI 0.89–1.12	Mean Age 60 years Mean eGFR: 67.0 eGFR <60 22.5% Median ACR 10.4 mg/g eGFR <30 mL/min/1.73 m² excluded	Percentage change in ACR at 24 months	34% versus 24% P = 0.004 adjusted for baseline, treatment, region, ACEi/ARB use (NS after adjusting for HbA1c)
LEADER [25, 109]	Double-blind RCT	Type 2 DM with at least one cardiovascular risk factor	9380	1:1 ratio, 1.8 mg (or the maximum tolerated dose) of liraglutide or placebo once daily as a subcutaneous injection	Median of 3.8 years	Cardiovascular death, non-fatal (including silent) MI or non-fatal stroke	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 <60 mL/min/1.73 m² HR 0.67, 95% CI 0.54–0.83	Mean Age: 64.3 years eGFR <60 mL/min/1.73 m²: 24.7% Microalbuminuria 26.3% Macroalbuminuria: 10.5%	New onset macroalbuminuria, doubling of SCr, ESRD or death from renal disease	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 1.59, 95% CI 0.52–4.87
SUSTAIN-6 [26]	Double-blind RCT	Type 2 DM with established cardiovascular disease	3297	1:1:1:1 ratio 0.5 or 1.0 mg once-weekly semaglutide or volume-matched placebo	Median of 2.1 years	Composite of cardiovascular death, MI or stroke	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	Mean Age 64.6 years eGFR <60 mL/min/1.73 m² 24.1%	Persistent macroalbuminuria, doubling of SCr and eGFR <45 mL/min/1.73 m² or the need for dialysis	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
EXSCEL [110, 111]	Double-blind event-driven RCT	Type 2 DM with 70% of participants having a previous cardiovascular event	14 752	1:1 ratio extended-release exenatide 2 mg weekly or matching placebo	Median 3.2 years	Composite of cardiovascular death, MI or stroke	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	Mean Age 62 years eGFR <60 mL/min/1.73 m² 22%	40% decline in eGFR, ESRD, renal death or new-onset macroalbuminuria	Renal composite: HR 0.85, 95% CI 0.73–0.98 Result driven by new-onset macroalbuminuria
		Type 2 DM with established	9463		Median 1.6 years		Primary outcome: HR 0.78, 95% CI 0.68–0.90;	19% of patients had nephropathy	Only renal safety data published	

Continued

SGLT-2 inhibitors and GLP-1 agonists for nephro- and cardioprotection

219

Table 2. Continued

Study	Type of study	Type of subjects	N	Comparisons	Duration	Primary composite endpoint	Main cardiovascular outcomes	Population characteristics of renal interest	Renal composite endpoint	Main renal outcomes
HARMONY OUTCOMES [27]	Double-blind event-driven RCT	cardiovascular disease		1:1 albiglutide 30–50 mg or matching placebo		Composite of cardiovascular death, MI or stroke	cardiovascular death: HR 0.93, 95% CI 0.73–1.19; MI: HR 0.75, 95% CI 0.61–0.90; stroke: HR 0.86, 95% CI 0.66–1.14; composite of death or hospitalization for heart failure: HR 0.85, 95% CI 0.70–1.04 Subgroup analysis showed no interaction between baseline eGFR and primary outcome	eGFR <30 mL/min/1.73 m² excluded		No difference in eGFR between groups at 16 months −0.43 95% CI −1.26 to 0.41 mL/min/1.73 m²

RCT, randomized controlled trial; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval; HF, heart failure; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; ESRD, end-stage renal disease.

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.

P. Sarafidis *et al.*

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 m^2 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 m^2 (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 m^2 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 m^2) [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 m^2 versus −3.3 mL/min/1.73 m^2, 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 induce 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 reno-protective 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 21 782 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 (CREDENCE) [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 m^2 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 ≥25 and ≤75 mL/min/1.73 m², and UACR ≥200 and ≤5000 mg/g [190]. The primary outcome is a composite of ≥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 ≥20 to <45 mL/min/1.73 m² or eGFR ≥45 to <90 mL/min/1.73 m² with UACR ≥200 mg/g or protein:creatinine ratio ≥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 m², renal death or a sustained decline of ≥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].

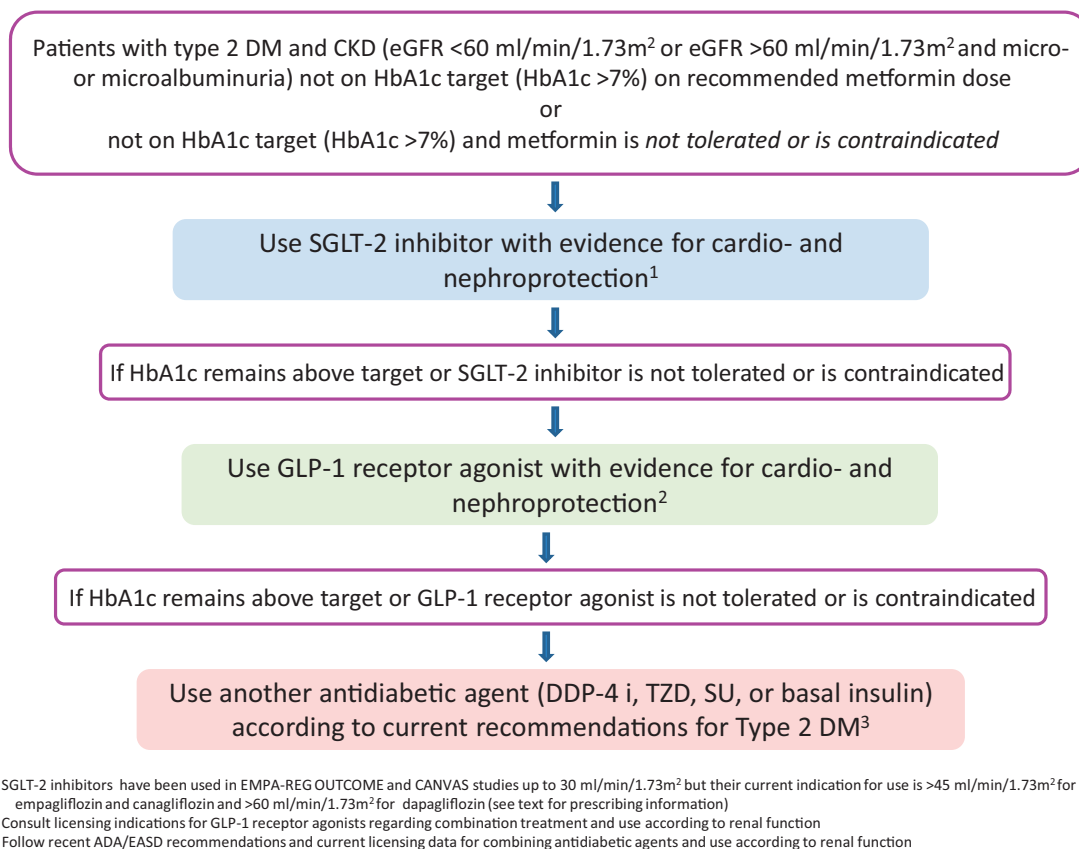## CONSENSUS ON SGLT-2 INHIBITOR AND GLP-1 RECEPTOR AGONIST USE AND CONCLUSIONS

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 UKDPS study [197]. Discussing the major issue of metformin use, that
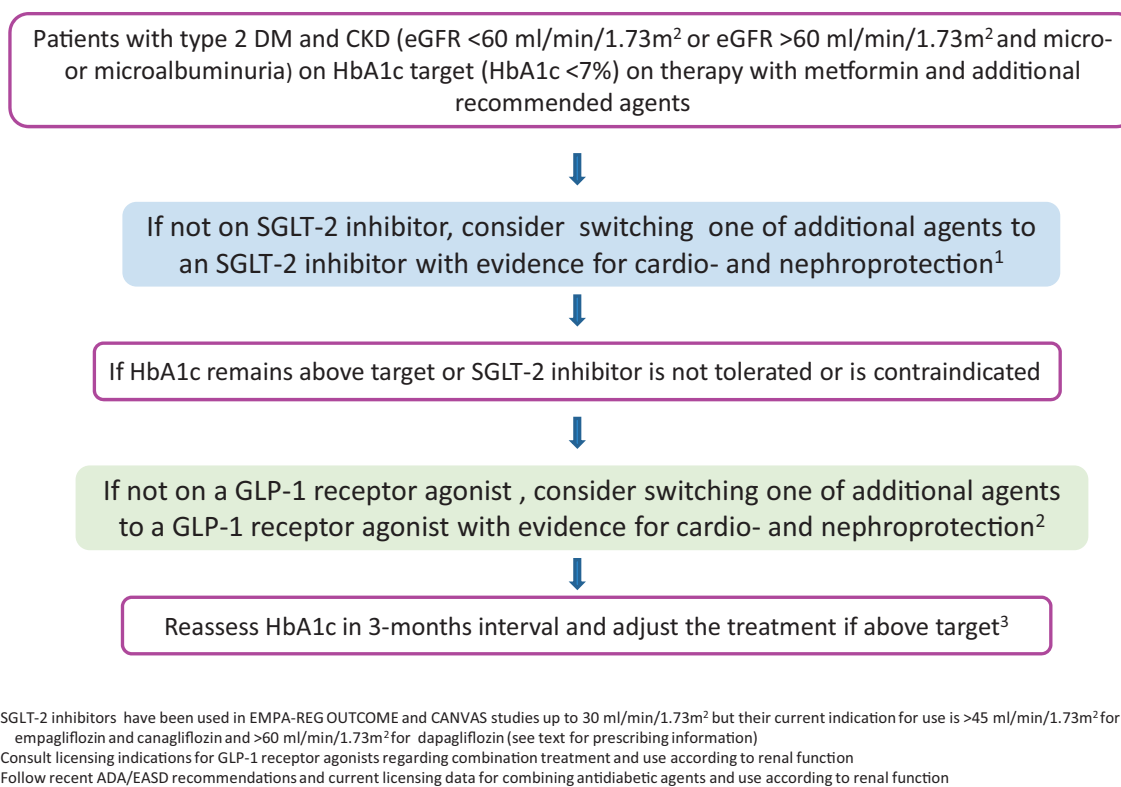
is the potential for increased levels and adverse effects in patients with GFR <60 mL/min/1.73 m² [196], is beyond the scope of this document; the reader is referred to a previous Clinical Practice Guideline from ERA-EDTA [198]. The major change in the recent ADA/EASD report is the differentiation of 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 predominates, 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 m² or with eGFR >60 mL/min/1.73 m² 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 m² 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 vasodilation [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/1.73m^2 or eGFR >60 ml/min/1.73m^2 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 nephroprotection[1]

↓

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 nephroprotection[2]

↓

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 DM[3]

1. SGLT-2 inhibitors have been used in EMPA-REG OUTCOME and CANVAS studies up to 30 ml/min/1.73m^2 but their current indication for use is >45 ml/min/1.73m^2 for empagliflozin and canagliflozin and >60 ml/min/1.73m^2 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.

Patients with type 2 DM and CKD (eGFR <60 ml/min/1.73m^2 or eGFR >60 ml/min/1.73m^2 and micro- or microalbuminuria) on HbA1c target (HbA1c <7%) on therapy with metformin and additional recommended agents

↓

If not on SGLT-2 inhibitor, consider switching one of additional agents to an SGLT-2 inhibitor with evidence for cardio- and nephroprotection[1]

↓

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

↓

If not on a GLP-1 receptor agonist, consider switching one of additional agents to a GLP-1 receptor agonist with evidence for cardio- and nephroprotection[2]

↓

Reassess HbA1c in 3-months interval and adjust the treatment if above target[3]

1. SGLT-2 inhibitors have been used in EMPA-REG OUTCOME and CANVAS studies up to 30 ml/min/1.73m^2 but their current indication for use is >45 ml/min/1.73m^2 for empagliflozin and canagliflozin and >60 ml/min/1.73m^2 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.

P. Sarafidis *et al.*

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 m^2; 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 m^2 [201, 202]. In the USA, empagliflozin and canagliflozin should not be used in patients with eGFR <45 mL/min/1.73 m^2 [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 m^2; in the USA, it should not be used in patients with eGFR <60 mL/min/1.73 m^2 [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 m^2. Both EMPA-REG OUTCOME and CANVAS recruited patients up to 30 mL/min/1.73 m^2, 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 m^2, but again, no differences in outcomes were noted in the few patients with eGFR <60 mL/min/1.73 m^2.

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 m^2, 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.

REFERENCES

1. WHO. *Global Report on Diabetes*. 2016. http://www.who.int/diabetes/global-report/en/ (7 November 2016, date last accessed)
2. Group IDFDA. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. *Diabetes Res Clin Pract* 2015; 109: 461–465
3. Sarwar N, Gao P, Seshasai SR. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375: 2215–2222
4. Papadopoulou E, Angeloudi E, Karras S *et al*. The optimal blood pressure target in diabetes mellitus: a quest coming to an end? *J Hum Hypertens* 2018; 32: 641–650
5. Haffner SM, Lehto S, Ronnemaa T *et al*. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339: 229–234
6. Stamler J, Vaccaro O, Neaton JD *et al*. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; 16: 434–444
7. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305
8. White SL, Chadban SJ, Jan S *et al*. How can we achieve global equity in provision of renal replacement therapy? *Bull World Health Organ* 2008; 86: 229–237
9. Adler AI, Stevens RJ, Manley SE. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003; 63: 225–232
10. KDIGO. Clinical Practice Guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012; 2: 337
11. Sarafidis PA, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? *Kidney Int* 2014; 85: 536–546
12. Brenner BM, Cooper ME, de Zeeuw D *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861–869
13. Lewis EJ, Hunsicker LG, Clarke WR *et al*. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345: 851–860
14. American Diabetes Association. Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018; 41: S1–S153
15. Whelton PK, Carey RM, Aronow WS *et al*. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension 2018* 2017; 71: e13–e115
16. Williams B, Mancia G, Spiering W *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36: 1953–2041

17. Sarafidis PA, Ruilope LM. Cardiorenal disease development under chronic renin-angiotensin-aldosterone system suppression. *J Renin Angiotensin Aldosterone Syst* 2012; 13: 217–219

18. Hoerger TJ, Segel JE, Gregg EW *et al*. Is glycemic control improving in U.S. adults? *Diabetes Care* 2008; 31: 81–86

19. Aylsworth A, Dean Z, VanNorman C *et al*. Dapagliflozin for the treatment of type 2 diabetes mellitus. *Ann Pharmacother* 2014; 48: 1202–1208

20. Imprialos KP, Sarafidis PA, Karagiannis AI. Sodium-glucose cotransporter-2 inhibitors and blood pressure decrease: a valuable effect of a novel antidiabetic class? *J Hypertens* 2015; 33: 2185–2197

21. Kalaitzidis R, Sarafidis PA, Bakris GL. Effects of thiazolidinediones beyond glycaemic control. *Curr Pharm Des* 2009; 15: 529–536

22. Schernthaner G, Schernthaner-Reiter MH, Schernthaner GH. EMPA-REG and other cardiovascular outcome trials of glucose-lowering agents: implications for future treatment strategies in type 2 diabetes mellitus. *Clin Ther* 2016; 38: 1288–1298

23. Zinman B, Wanner C, Lachin JM *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128

24. Mahaffey KW, Neal B, Perkovic V *et al*. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; 137: 323–334

25. Marso SP, Daniels GH, Brown-Frandsen K *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375: 311–322

26. Marso SP, Bain SC, Consoli A *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834–1844

27. Hernandez AF, Green JB, Janmohamed S *et al*. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018; 392: 1519–1529

28. Wanner C, Inzucchi SE, Lachin JM *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334

29. Perkovic V, de Zeeuw D, Mahaffey KW *et al*. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018; 6: 691–704

30. Wiviott SD, Raz I, Bonaca MP *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2018 (e pub ahead of print)

31. US Food and Drug Administration. FDA approves Jardiance to Reduce Cardiovascular Death in Adults with Type 2 Diabetes [news release]. 2016. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm (15 August 2018, date last accessed)

32. Fitchett D, Butler J, van de Borne P *et al*. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2018; 39: 363–370

33. Verma S, Mazer CD, Fitchett D *et al*. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME(R) randomised trial. *Diabetologia* 2018; 61: 1712–1723

34. Zinman B, Inzucchi SE, Wanner C *et al*. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME(R). *Diabetologia* 2018; 61: 1522–1527

35. Wanner C, Lachin JM, Inzucchi SE *et al*. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. *Circulation* 2018; 137: 119–129

36. Neal B, Perkovic V, Mahaffey KW *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657

37. Neuen BL, Ohkuma T, Neal B *et al*. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation* 2018; 138: 1537–1550

38. Radholm K, Figtree G, Perkovic V *et al*. Canagliflozin and heart failure in type 2 diabetes mellitus. *Circulation* 2018; 138: 458–468

39. Wiviott SD, Raz I, Bonaca MP *et al*. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. *Am Heart J* 2018; 200: 83–89

40. Zelniker TA, Wiviott SD, Raz I *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2018 (e pub ahead of print)

41. Kosiborod M, Cavender MA, Fu AZ *et al*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017; 136: 249–259

42. Lytvyn Y, Bjornstad P, Udell JA *et al*. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation* 2017; 136: 1643–1658

43. Flores E, Santos-Gallego CG, Diaz-Mejía N *et al*. Do the SGLT-2 inhibitors offer more than hypoglycemic activity? *Cardiovasc Drugs Ther* 2018; 32: 213–222

44. Ferrannini E. Sodium-glucose co-transporters and their inhibition: clinical physiology. *Cell Metab* 2017; 26: 27–38

45. Scheen AJ. Cardiovascular effects of new oral glucose-lowering agents: DPP-4 and SGLT-2 inhibitors. *Circ Res* 2018; 122: 1439–1459

46. White WB, Saag KG, Becker MA *et al*. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018; 378: 1200–1210

47. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 317: 703–713

48. Patel A, MacMahon S, Chalmers J *et al*. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; 370: 829–840

49. Sarafidis PA, Lazaridis AA, Ruiz-Hurtado G *et al*. Blood pressure reduction in diabetes: lessons from ACCORD, SPRINT and EMPA-REG OUTCOME. *Nat Rev Endocrinol* 2017; 13: 365–374

50. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 1996; 27: 1214–1218

51. Fitchett D, Zinman B, Wanner C *et al*. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2016; 37: 1526–1534

52. Faris RF, Flather M, Purcell H *et al*. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012; 2: Cd003838

53. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997

54. Franse LV, Pahor M, Di Bari M *et al*. Hypokalemia associated with diuretic use and cardiovascular events in the systolic hypertension in the elderly program. *Hypertension* 2000; 35: 1025–1030

55. Sarafidis PA, Georgianos PI, Lasaridis AN. Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opin Drug Saf* 2010; 9: 259–273

56. Hallow KM, Helmlinger G, Greasley PJ *et al*. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab* 2018; 20: 479–487

57. Kenchaiah S, Evans JC, Levy D *et al*. Obesity and the risk of heart failure. *N Engl J Med* 2002; 347: 305–313

58. Navarro-Gonzalez JF, Sanchez-Nino MD, Donate-Correa J *et al*. Effects of pentoxifylline on soluble klotho concentrations and renal tubular cell expression in diabetic kidney disease. *Diabetes Care* 2018; 41: 1817–1820

59. Sanchez-Nino MD, Bozic M, Cordoba-Lanus E *et al*. Beyond proteinuria: VDR activation reduces renal inflammation in experimental diabetic nephropathy. *Am J Physiol Renal Physiol* 2012; 302: F647–F657

60. Ortiz A, Ziyadeh FN, Neilson EG. Expression of apoptosis-regulatory genes in renal proximal tubular epithelial cells exposed to high ambient glucose and in diabetic kidneys. *J Investig Med* 1997; 45: 50–56

61. Cherney DZ, Perkins BA, Soleymanlou N *et al*. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014; 129: 587–597

62. Jordan J, Tank J, Heusser K *et al*. The effect of empagliflozin on muscle sympathetic nerve activity in patients with type II diabetes mellitus. *J Am Soc Hypertens* 2017; 11: 604–612

63. Lambers Heerspink HJ, de Zeeuw D, Wie L *et al*. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; 15: 853–862

P. Sarafidis *et al*.

64. Inzucchi SE, Zinman B, Fitchett D et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME Trial. Diabetes Care 2018; 41: 356–363

65. Lansang MC, Hollenberg NK. Renal perfusion and the renal hemodynamic response to blocking the renin system in diabetes: are the forces leading to vasodilation and vasoconstriction linked? Diabetes 2002; 51: 2025–2028

66. Bonner C, Kerr-Conte J, Gmyr V et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015; 21: 512–517

67. Burge MR, Hardy KJ, Schade DS. Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. J Clin Endocrinol Metab 1993; 76: 1192–1198

68. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME Trial: a "thrifty substrate" hypothesis. Diabetes Care 2016; 39: 1108–1114

69. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Cell Metab 2017; 25: 262–284

70. Lopaschuk GD, Verma S. Empagliflozin's fuel hypothesis: not so soon. Cell Metab 2016; 24: 200–202

71. Baartscheer A, Schumacher CA, Wust RC et al. Empagliflozin decreases myocardial cytoplasmic Na(+) through inhibition of the cardiac Na(+)/H(+) exchanger in rats and rabbits. Diabetologia 2017; 60: 568–573

72. Uthman L, Baartscheer A, Bleijlevens B et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na(+)/H(+) exchanger, lowering of cytosolic Na(+) and vasodilation. Diabetologia 2018; 61: 722–726

73. Bertero E, Prates Roma L, Ameri P et al. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. Cardiovasc Res 2018; 114: 12–18

74. Cherney DZI, Zinman B, Inzucchi SE et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017; 5: 610–621

75. Sarafidis PA, Stafylas PC, Kanaki AI et al. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. Am J Hypertens 2008; 21: 922–929

76. Parving HH, Brenner BM, McMurray JJ et al. Cardiorenal end points in a trial of Aliskiren for type 2 diabetes. N Engl J Med 2012; 367: 2204–2213

77. Fried LF, Emanuele N, Zhang JH et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013; 369: 1892–1903

78. Sarafidis PA, Alexandrou ME, Ruilope LM. A review of chemical therapies for treating diabetic hypertension. Expert Opin Pharmacother 2017; 18: 909–923

79. de Zeeuw D, Remuzzi G, Parving HH et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004; 65: 2309–2320

80. Atkins RC, Briganti EM, Lewis JB et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 2005; 45: 281–287

81. DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012; 14: 5–14

82. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pflugers Arch 2004; 447: 510–518

83. Vallon V, Muhlbauer B, Osswald H. Adenosine and kidney function. Physiol Rev 2006; 86: 901–940

84. Ferrannini E, Baldi S, Frascerra S et al. Renal handling of ketones in response to sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes. Diabetes Care 2017; 40: 771–776

85. O'Neill J, Fasching A, Pihl L et al. Acute SGLT inhibition normalizes O2 tension in the renal cortex but causes hypoxia in the renal medulla in anaesthetized control and diabetic rats. Am J Physiol Renal Physiol 2015; 309: F227–F234

86. Ojima A, Matsui T, Nishino Y et al. Empagliflozin, an inhibitor of sodium-glucose cotransporter 2 exerts anti-inflammatory and antifibrotic effects on experimental diabetic nephropathy partly by suppressing AGEs-receptor axis. Horm Metab Res 2015; 47: 686–692

87. Panchapakesan U, Pegg K, Gross S et al. Effects of SGLT2 inhibition in human kidney proximal tubular cells–renoprotection in diabetic nephropathy? PLoS One 2013; 8: e54442

88. Salim HM, Fukuda D, Yagi S et al. Glycemic control with ipragliflozin, a novel selective SGLT2 inhibitor, ameliorated endothelial dysfunction in streptozotocin-induced diabetic mouse. Front Cardiovasc Med 2016; 3: 43

89. Rahmoune H, Thompson PW, Ward JM et al. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. Diabetes 2005; 54: 3427–3434

90. Freitas HS, Anhe GF, Melo KF et al. Na(+)-glucose transporter-2 messenger ribonucleic acid expression in kidney of diabetic rats correlates with glycemic levels: involvement of hepatocyte nuclear factor-1alpha expression and activity. Endocrinology 2008; 149: 717–724

91. Vlotides G, Mertens PR. Sodium-glucose cotransport inhibitors: mechanisms, metabolic effects and implications for the treatment of diabetic patients with chronic kidney disease. Nephrol Dial Transplant 2015; 30: 1272–1276

92. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? Kidney Int 2014; 86: 693–700

93. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med 1982; 72: 375–380

94. Jerums G, Premaratne E, Panagiotopoulos S et al. The clinical significance of hyperfiltration in diabetes. Diabetologia 2010; 53: 2093–2104

95. Terami N, Ogawa D, Tachibana H et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One 2014; 9: e100777

96. Skrtic M, Yang GK, Perkins BA et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. Diabetologia 2014; 57: 2599–2602

97. Heerspink HJ, Desai M, Jardine M et al. Canagliflozin slows progression of renal function decline independently of glycemic effects. J Am Soc Nephrol 2017; 28: 368–375

98. Piperidou A, Sarafidis PA, Boutou A et al. The effect of SGLT-2 inhibitors on albuminuria and proteinuria in diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. J Hypertension 2019 (e pub ahead of print)

99. Kohan DE, Fioretto P, Tang W et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014; 85: 962–971

100. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160: 685–693

101. Tsimihodimos V, Filippas-Ntekouan S, Elisaf M. SGLT1 inhibition: Pros and cons. Eur J Pharmacol 2018; 838: 153–156

102. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. Diabetologia 2018; 61: 2118–2125

103. Garg SK, Henry RR, Banks P et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med 2017; 377: 2337–2348

104. Nadkarni GN, Ferrandino R, Chang A et al. Acute kidney injury in patients on SGLT2 inhibitors: a propensity-matched analysis. Diabetes Care 2017; 40: 1479–1485

105. Tang H, Dai Q, Shi W et al. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia 2017; 60: 1862–1872

106. Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. N Engl J Med 2017; 376: 2300–2302

107. Inzucchi SE, Iliev H, Pfarr E et al. Empagliflozin and assessment of lower-limb amputations in the EMPA-REG OUTCOME Trial. Diabetes Care 2018; 41: e4–e5

108. Buse JB, Garg SK, Rosenstock J et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American in Tandem1 Study. Diabetes Care 2018; 41: 1970–1980

109. Mann JFE, Orsted DD, Brown-Frandsen K et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017; 377: 839–848

110. Holman RR, Bethel MA, Mentz RJ et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017; 377: 1228–1239

111. Bethel MA, Mentz RJ, Merrill P et al. Renal outcomes in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL). Diabetes 2018; 67: 522-P

112. Newman JD, Vani AK, Aleman JO et al. The changing landscape of diabetes therapy for cardiovascular risk reduction: JACC state-of-the-art review. J Am Coll Cardiol 2018; 72: 1856–1869

113. McHugh KR, DeVore AD, Mentz RJ et al. The emerging role of novel anti-hyperglycemic agents in the treatment of heart failure and diabetes: A focus on cardiorenal outcomes. Clin Cardiol 2018; 41: 1259–1267

114. Scheen AJ. Cardiovascular outcome studies in type 2 diabetes: comparison between SGLT2 inhibitors and GLP-1 receptor agonists. Diabetes Res Clin Pract 2018; 143: 88–100

115. Pfeffer MA, Claggett B, Diaz R et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015; 373: 2247–2257

116. Cefalu WT, Kaul S, Gerstein HC et al. Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections from a diabetes care editors' expert forum. Diabetes Care 2018; 41: 14–31

117. Gerstein HC, Colhoun HM, Dagenais GR et al. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. Diabetes Obes Metab 2018; 20: 42–49

118. Trulicity® (dulaglutide) Demonstrates Superiority in Reduction of Cardiovascular Events for Broad Range of People with Type 2 Diabetes. 2018. https://investor.lilly.com/news-releases/news-release-details/trulicityr-dulaglutide-demonstrates-superiority-reduction (6 December 2018, date last accessed)

119. Bain SC, Mosenzon O, Arechavaleta R et al. Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial. Diabetes Obes Metab 2018 (e pub ahead of print)

120. Oral Semaglutide Demonstrates Favourable Cardiovascular Safety Profile and Significant Reduction in Cardiovascular Death and All-cause Mortality in People with Type 2 Diabetes in the PIONEER 6 trial. 2018. https://www.novonordisk.com/media/news-details.2226789.html (6 December 2018, date last accessed)

121. Zheng SL, Roddick AJ, Aghar-Jaffar R et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. JAMA 2018; 319: 1580–1591

122. Ryder RE, Defronzo RA. Diabetes medications with cardiovascular protection in the wake of EXSCEL: is there a class effect for long-acting GLP-1 receptor agonists? Br J Diabetes 2017; 17: 131–133

123. Scheen AJ. GLP-1 receptor agonists and cardiovascular protection: A class effect or not? Diab Metab 2018; 44: 193–196

124. Nauck MA, Meier JJ, Cavender MA et al. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation 2017; 136: 849–870

125. Htike ZZ, Zaccardi F, Papamargaritis D et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab 2017; 19: 524–536

126. Muskiet MHA, Tonneijck L, Smits MM et al. GLP-1 and the kidney: from physiology to pharmacology and outcomes in diabetes. Nat Rev Nephrol 2017; 13: 605–628

127. Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. Nat Rev Endocrinol 2016; 12: 566–592

128. Liu SC, Tu YK, Chien MN et al. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. Diabetes Obes Metab 2012; 14: 810–820

129. Bunck MC, Diamant M, Eliasson B et al. Exenatide affects circulating cardiovascular risk biomarkers independently of changes in body composition. Diabetes Care 2010; 33: 1734–1737

130. Jendle J, Nauck MA, Matthews DR et al. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes Obes Metab 2009; 11: 1163–1172

131. van Can J, Sloth B, Jensen CB et al. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycemic parameters, appetite and energy metabolism in obese, non-diabetic adults. Int J Obes 2014; 38: 784–793

132. Sun F, Wu S, Wang J et al. Effect of glucagon-like peptide-1 receptor agonists on lipid profiles among type 2 diabetes: a systematic review and network meta-analysis. Clin Ther 2015; 37: 225–241 e228

133. Pi-Sunyer X, Astrup A, Fujioka K et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015; 373: 11–22

134. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract 2017; 3: 3–14

135. Sun F, Wu S, Guo S et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Res Clin Pract 2015; 110: 26–37

136. Drucker DJ. The biology of incretin hormones. Cell Metab 2006; 3: 153–165

137. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. Cell Metab 2016; 24: 15–30

138. Gutzwiller JP, Tschopp S, Bock A et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab 2004; 89: 3055–3061

139. Tang-Christensen M, Larsen PJ, Goke R et al. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. Am J Physiol 1996; 271: R848–8R856

140. Crajoinas RO, Oricchio FT, Pessoa TD et al. Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1. Am J Physiol Renal Physiol 2011; 301: F355–F363

141. Muskiet MH, Smits MM, Morsink LM et al. The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol 2014; 10: 88–103

142. Skov J, Dejgaard A, Frøkiær J et al. Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men. J Clin Endocrinol Metab 2013; 98: E664–E671

143. Muskiet MH, Tonneijck L, Smits MM et al. Pleiotropic effects of type 2 diabetes management strategies on renal risk factors. Lancet Diabetes Endocrinol 2015; 3: 367–381

144. Tonneijck L, Smits MM, Muskiet MHA et al. Acute renal effects of the GLP-1 receptor agonist exenatide in overweight type 2 diabetes patients: a randomised, double-blind, placebo-controlled trial. Diabetologia 2016; 59: 1412–1421

145. Yang J, Jose PA, Zeng C. Gastrointestinal-renal axis: role in the regulation of blood pressure. J Am Heart Assoc 2017; 6: e005536

146. von Scholten BJ, Lajer M, Goetze JP et al. Time course and mechanisms of the anti-hypertensive and renal effects of liraglutide treatment. Diabet Med 2015; 32: 343–352

147. Hsieh J, Longuet C, Baker CL et al. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. Diabetologia 2010; 53: 552–561

148. Xiao C, Bandsma RH, Dash S et al. Exenatide, a glucagon-like peptide-1 receptor agonist, acutely inhibits intestinal lipoprotein production in healthy humans. Arterioscler Thromb Vasc Biol 2012; 32: 1513–1519

149. Sancho V, Trigo MV, Martin-Duce A et al. Effect of GLP-1 on D-glucose transport, lipolysis and lipogenesis in adipocytes of obese subjects. Int J Mol Med 2006; 17: 1133–1137

150. El Bekay R, Coin-Araguez L, Fernandez-Garcia D et al. Effects of glucagon-like peptide-1 on the differentiation and metabolism of human adipocytes. Br J Pharmacol 2016; 173: 1820–1834

151. Hirano T, Mori Y. Anti-atherogenic and anti-inflammatory properties of glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide,

P. Sarafidis et al.

and dipeptidyl peptidase-4 inhibitors in experimental animals. *J Diabetes Investig* 2016; 7: 80–86

152. Tashiro Y, Sato K, Watanabe T *et al*. A glucagon-like peptide-1 analog liraglutide suppresses macrophage foam cell formation and atherosclerosis. *Peptides* 2014; 54: 19–26

153. Sudo M, Li Y, Hiro T *et al*. Inhibition of plaque progression and promotion of plaque stability by glucagon-like peptide-1 receptor agonist: Serial in vivo findings from iMap-IVUS in Watanabe heritable hyperlipidemic rabbits. *Atherosclerosis* 2017; 265: 283–291

154. Krasner NM, Ido Y, Ruderman NB *et al*. Glucagon-like peptide-1 (GLP-1) analog liraglutide inhibits endothelial cell inflammation through a calcium and AMPK dependent mechanism. *PLoS One* 2014; 9: e97554

155. Chaudhuri A, Ghanim H, Vora M *et al*. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab* 2012; 97: 198–207

156. Nikolaidis LA, Elahi D, Hentosz T *et al*. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation* 2004; 110: 955–961

157. Margulies KB, Hernandez AF, Redfield MM *et al*. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016; 316: 500–508

158. Sokos GG, Nikolaidis LA, Mankad S *et al*. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. *J Card Fail* 2006; 12: 694–699

159. Nikolaidis LA, Mankad S, Sokos GG *et al*. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 2004; 109: 962–965

160. Inoue T, Inoguchi T, Sonoda N *et al*. GLP-1 analog liraglutide protects against cardiac steatosis, oxidative stress and apoptosis in streptozotocin-induced diabetic rats. *Atherosclerosis* 2015; 240: 250–259

161. Gaspari T, Brdar M, Lee HW *et al*. Molecular and cellular mechanisms of glucagon-like peptide-1 receptor agonist-mediated attenuation of cardiac fibrosis. *Diab Vasc Dis Res* 2016; 13: 56–68

162. von Scholten BJ, Hansen TW, Goetze JP *et al*. Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term effect on kidney function in patients with type 2 diabetes. *J Diabetes Complications* 2015; 29: 670–674

163. von Scholten BJ, Persson F, Rosenlund S *et al*. The effect of liraglutide on renal function: A randomized clinical trial. *Diabetes Obes Metab* 2017; 19: 239–247

164. Davies MJ, Bergenstal R, Bode B *et al*. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: The SCALE Diabetes Randomized Clinical Trial. *JAMA* 2015; 314: 687–699

165. Tuttle KR, Lakshmanan MC, Rayner B *et al*. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; 6: 605–617

166. Luis-Lima S, Porrini E. An overview of errors and flaws of estimated GFR versus True GFR in patients with diabetes mellitus. *Nephron* 2017; 136: 287–291

167. Sorensen CM, Holst JJ. Renoprotective effects of dulaglutide in patients with T2DM and CKD. *Nat Rev Nephrol* 2018; 14: 659–660

168. Tanaka T, Higashijima Y, Wada T *et al*. The potential for renoprotection with incretin-based drugs. *Kidney Int* 2014; 86: 701–711

169. Kodera R, Shikata K, Kataoka HU *et al*. 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* 2011; 54: 965–978

170. Tsimihodimos V, Elisaf M. Effects of incretin-based therapies on renal function. *Eur J Pharmacol* 2018; 818: 103–109

171. Bremholm L, Andersen UB, Hornum M *et al*. Acute effects of glucagon-like peptide-1, GLP-19-36 amide, and exenatide on mesenteric blood flow, cardiovascular parameters, and biomarkers in healthy volunteers. *Physiol Rep* 2017; 5: e13102

172. Gorriz JL, Nieto J, Navarro-Gonzalez JF *et al*. Nephroprotection by hypoglycemic agents: do we have supporting data? *J Clin Med* 2015; 4: 1866–1889

173. Tonneijck L, Smits MM, van Raalte DH *et al*. Incretin-based drugs and renoprotection-is hyperfiltration key? *Kidney Int* 2015; 87: 660–661

174. Dicembrini I, Nreu B, Scatena A *et al*. Microvascular effects of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled trials. *Acta Diabetol* 2017; 54: 933–941

175. Shurter A, Genter P, Ouyang D *et al*. Euglycemic progression: worsening of diabetic retinopathy in poorly controlled type 2 diabetes in minorities. *Diabetes Res Clin Pract* 2013; 100: 362–367

176. Faillie JL, Yu OH, Yin H *et al*. Association of bile duct and gallbladder diseases with the use of incretin-based drugs in patients with type 2 diabetes mellitus. *JAMA Intern Med* 2016; 176: 1474–1481

177. Elashoff M, Matveyenko AV, Gier B *et al*. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141: 150–156

178. Singh S, Chang HY, Richards TM *et al*. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013; 173: 534–539

179. Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? *Diabetes Care* 2013; 36: S245–S252

180. Storgaard H, Cold F, Gluud LL *et al*. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. *Diabetes Obes Metab* 2017; 19: 906–908

181. Bethel MA, Patel RA, Merrill P *et al*. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol* 2018; 6: 105–113

182. Lorenz M, Lawson F, Owens D *et al*. Differential effects of glucagon-like peptide-1 receptor agonists on heart rate. *Cardiovasc Diabetol* 2017; 16: 6

183. Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. *Prog Cardiovasc Dis* 2009; 52: 6–10

184. Cooney MT, Vartiainen E, Laakitainen T *et al*. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J* 2010; 159: 612–619 e613

185. Pyke C, Heller RS, Kirk RK *et al*. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology* 2014; 155: 1280–1290

186. Nakatani Y, Kawabe A, Matsumura M *et al*. Effects of GLP-1 receptor agonists on heart rate and the autonomic nervous system using holter electrocardiography and power spectrum analysis of heart rate variability. *Diabetes Care* 2016; 39: e22–e23

187. Evaluation of the effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE). https://clinicaltrials.gov/ct2/show/NCT02065791 (6 December 2018, date last accessed)

188. Jardine MJ, Mahaffey KW, Neal B *et al*. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study rationale, design, and baseline characteristics. *Am J Nephrol* 2017; 46: 462–472

189. Phase 3 CREDENCE Renal Outcomes Trial of INVOKANA® (canagliflozin) is Being Stopped Early for Positive Efficacy Findings. https://www.jnj.com/phase-3-credence-renal-outcomes-trial-of-invokana-canagliflozin-is-being-stopped-early-for-positive-efficacy-findings (27 September 2018, date last accessed)

190. A study to evaluate the effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with chronic kidney disease (Dapa-CKD). https://clinicaltrials.gov/ct2/show/NCT03036150 (6 December 2018, date last accessed)

191. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin.). https://clinicaltrials.gov/ct2/show/NCT03594110 (6 December 2018, date last accessed)

192. Mafham M, Preiss D. HARMONY or discord in cardiovascular outcome trials of GLP-1 receptor agonists? *Lancet* 2018; 392: 1489–1490

193. Gaede P, Vedel P, Larsen N *et al*. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383–393

194. Gæde P, Lund-Andersen H, Parving H-H *et al*. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; 358: 580–591

195. Davies MJ, D'Alessio DA, Fradkin J. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes

Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41: 2669–2701

196. Inzucchi SE, Bergenstal RM, Buse JB *et al*. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015; 58: 429–442

197. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854–865

198. Guideline Development Group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). *Nephrol Dial Transplant* 2015; 30 (Suppl 2): ii1–ii142

199. Khosla N, Sarafidis PA, Bakris GL. Microalbuminuria. *Clin Lab Med* 2006; 26: 635–653

200. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; 49: 1774–1777

201. Jardiance®. Summary of Product Characteristics. 2014. https://www.ema.europa.eu/documents/product-information/jardiance-epar-product-information_en.pdf (6 December 2018, date last accessed)

202. Invokana®. Summary of Product Characteristics. 2013. https://ec.europa.eu/health/documents/community-register/2017/20170428137649/anx_137649_el.pdf (6 December 2018, date last accessed)

203. Invokana®. Highlights of Prescribing Information. 2013 https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf (6 December 2018, date last accessed)

204. Jardiance®. Highlights of Prescribing Information. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf (6 December 2018, date last accessed)

205. Forxiga®. Summary of Product Characteristics. 2012. https://www.ema.europa.eu/documents/product-information/forxiga-epar-product-information_en.pdf (6 December 2018, date last accessed)

206. Farxiga®. Highlights of Prescribing Information. 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf (6 December 2018, date last accessed)

207. Heerspink HJ, Kropelin TF, Hoekman J *et al*. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. *J Am Soc Nephrol* 2015; 26: 2055–2064