Cardiorenal effects of newer antidiabetic agents

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ABSTRACT

Chronic kidney disease is a major problem of public health and is associated with increased cardiovascular mortality and morbidity. Its treatment includes multifactorial intervention: optimal blood pressure and intensive glycaemic control. There are many studies - clinical and experimental - demonstrating that classic and newer antidiabetic agents delay the progression of diabetic nephropathy. Glucagon-like-peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporters-2 (SGLT-2) inhibitors have renoprotective action. Furthermore, these antidiabetic agents have beneficial effects to the cardiovascular system, including weight loss and blood pressure reduction. Large, randomized, placebo-controlled outcome trials have showed that SGLT-2 inhibitors and GLP-1 receptor agonists are able to reduce cardiovascular events. Therefore, the present review aims to summarize the existing data regarding the effect of newer antidiabetic agents on kidney function and cardiovascular system.

KEY WORDS: *Diabetes mellitus, diabetic nephropathy, cardiovascular disease, glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, heart failure*

INTRODUCTION

According to the World Health Organization in 2014 8,5% of the adults, globally, had diabetes mellitus while this number will be doubled in 2030.[1] It is well established that diabetes is an independent cardiovascular (CV) risk factor; patients with diabetes have 2-fold higher risk for death compared to patients without diabetes and similar risk compared to patients with previous myocardial infarction.[2,3] Furthermore, diabetes is the leading cause of end-stage renal disease (ESRD) while one-third of patients with diabetes will develop chronic kidney disease (CKD) during

their life.[4] CKD is a major risk factor for the development of CV mortality and morbidity.[5] The first manifestation of CKD in patients with diabetes is microalbuminuria. The prevalence of microalbuminuria is 25% after 10 years of the clinical onset of diabetes while the annual rate of

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progression to macroalbuminuria is 3%.[6]

In 2008, the Food and Drug Administration (FDA), required for all novel antidiabetic agents to have proven the non-inferiority of the major CV events before licensing.[7] The first trials with dipeptidyl-peptidase-inhibitors (DDP-4i) proved non-inferiority and the other studies with sodium-glucose transporters 2 inhibitors (SGLT-2i)[8-10] and glucagon-like peptide (GLP-1) receptor agonists[11,12] proven superiority. Secondary analyses proved that these antidiabetic agents have renoprotective action. Empagliflozin in EMPA-REG OUTCOME trial reduced the primary 3-point nonfatal myocardial infarction, nonfatal stroke, and CV death (major adverse cardiac events, MACE) outcome significantly, and also reduced CV death, overall mortality, and hospitalization for heart failure (HF)[7,8]. In the CANVAS trial[9], patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo, a result driven by the reduction of the hospitalization for HF. In the DECLARE TIMI 58 trial[10], treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for HF, a finding that reflects a lower rate of hospitalization for HF. The above-mentioned trials have changed the current guidelines and the philosophy of the management of patients with DM. Therefore, the aim of the present review is to summarize the existing literature data, regarding the renal and CV effects or the novel antidiabetic agents, SGLT-2i and GLP-1 agonists.

SGLT-2I, GLP-1 RECEPTOR AGONISTS AND RENAL EFFECTS

The pathogenesis of the development of diabetic nephropathy (DN) is not completely understood. The major pathophysiological mechanisms are; oxidative stress, inflammatory injury of tubular cells, tubulointerstitial fibrosis, podocytes loss, and endothelial dysfunction.[13] Clinical trials have demonstrated that intensive control of glycaemia and blood pressure delay the progression of DN.[14-17] On the other hand, intensive glycaemic control leads to reduction of the onset as well as the progression of albuminuria in patients with type 1 and type 2 diabetes (T2D).[18-21]

The Diabetes Control and Complications Trial (DCCT), in patients with type 1 diabetes, demonstrated that intensive glycaemic control reduces the progression of DN.[20] More intensive blood glucose control resulted in both a 33% reduction in relative risk of development of microalbuminuria or clinical grade proteinuria at 12 years.[21] Furthermore, in the ADVANCE Study, intensive glycaemic control reduced albuminuria and the need for dialysis[22] and, in accordance, in the ACCORD Study, intensive gly-

caemic control reduced albuminuria.[23] In the ADVANCE Study reduction of blood pressure and intensive glucose control leaded to the reduction of all-cause mortality and major renal events (21% relative risk reduction of new or worsening nephropathy).[22] Despite the above beneficial results, the VADT Study showed that intensive glycaemic control did not improve either nephropathy or retinopathy.[24]

GLP-1 receptor agonists

The favorable effect of GLP-1 receptor agonists on renal function (Table 1), except for glycaemic control, is mediated through the multifactorial management of the blood pressure, dyslipidemia and body weight. Carefully designed studies in people with T2D using inulin and p-aminohippuric acid infusion techniques measured changes in GFR and renal plasma flow failed to demonstrate that GLP-1 receptor agonists reduce glomerular pressure or have other beneficial renal hemodynamic actions.[25,26] Additionally, GLP-1 receptor agonists reduce proteinuria via reduction of the endothelial injury and oxidative stress.[27,28] However, the main renoprotective effect of GLP-1 receptor agonists is their favorable action in distal convoluted tubule and promote natriuresis, via reduction of sodium reabsorbtion, in distal convoluted tubule.[29,30] GLP-1 receptor agonists restore the tubule-glomerular feedback, as a result of vasoconstriction of afferent arteriole, promoting the reduction of intra-glomerular pressure.[29] Von Sholten et al., showed that liraglutide, in 1.8 mg/day, reduced progressively albumin to creatinine ratio, estimated glomerular filtration rate (eGFR) and fractional albumin excretion.[31] Finally, it seems that the main renoprotective action of GLP-1 receptor agonists is mediated by the vasoconstriction of the afferent arteriole and the reduction of intra-glomerular pressure.[32]

In the LEADER trial, liraglutide therapy reduced significantly the composite end point of macroalbuminuria, ESRD, or death from renal disease versus placebo [Hazard ratio (HR):0.78, 95% confidence interval (CI): 0.67-0.92].[33] The above result is mainly due to the reduction of new-onset macroalbuminuria, and not from the reduction of the others components (HR:0.74, 95% CI: 0.60-0.91). It is noteworthy that the reduction of the composite end point was similar in the sub-group of patients with eGFR<60 ml/min/1.73m². The urine albumin to creatinine ratio (UACR) was reduced by 17% in the liraglutide group independently of eGFR. The incidence of microalbuminuria was lower significantly in liraglutide group (HR:0,87, 95% CI: 0,83-0,93), while there were no differences in renal adverse events among the two study groups.[31] In smaller studies, liraglutide reduced albuminuria about 30% independently

TABLE 1. Cardiovascular and renal outcomes of GLP-1 receptor agonists

	ELIXA	LEADER	EXSCEL	SUSTAIN 6	REWIND	HARMONY
Patients with established cv disease	100%	81%	73%	83%	31.5%	100%
CV outcomes						
MACE-3	-	0.87 (0.78 – 0.97)	0.91 (0.83 - 1.00)	0.74 (0.58 – 0.95)	0.88 (0.79-0.99)	0.78 (0.68–0.90)
CV death	0.98 (0.78 – 1.22)	0.78 (0.66 – 0.93)	0.88 (0.76 – 1.02)	0.98 (0.65 – 1.48)	0.91 (0.78-1.06)	0.93 (0.73–1.19)
Non-fatal MI	-	0.88 (0.75 – 1.03)	0.97 (0.8 – 1.10)	0.74 (0.51-1.08)	0.96 (0.79–1.16)	0.75 (0.61–0.90)
Non-fatal stroke	-	0.89 (0.72 – 1.11)	0.85 (0.70 – 1.03)	0.61 (0.38 – 0.99)	0.76 (0.61–0.95)	0.86 (0.66–1.14)
Mortality	0.94 (0.78 – 1.13)	0.85 (0.74 – 0.97)	0.86 (0.77 – 0.97)	1.05 (0.74 – 1.50)	0.90 (0.80–1.01)	0.95 (0.79–1.16)
HF hospitalization	0.96 (0.75 – 1.23)	0.87 (0.73 – 1.05)	0.94 (0.78 – 1.13)	1.11 (0.77 – 1.61)	0.93 (0.77–1.12)	-
Renal outcomes						
Composite renal outcome	-	0.78 (0.67 – 0.92)	0.88 (0.74 - 1.05)	0.64 (0.46 – 0.88)	0.85 (0.77–0.93)	-

*Data are presented as hazard ratio, 95% confidence intervals
Abbreviations: CV: cardiovascular, MACE: major adverse cardiovascular events, MI: myocardial infraction, HF: heart failure

of eGFR.[34,35] In the SCALE Study, liraglutide 3 mg/day (dose for pharmaceutical treatment for obesity) showed an 18% reduction of albuminuria.[36]

The SUSTAIN-6 trial evaluated the efficacy of semaglutide on kidney function with a secondary renal composite end point the onset of microalbuminuria, doubling of serum creatinine, creatinine clearance >45 ml/min or need for haemodialysis. This point was significantly lower in semaglutide group than placebo (HR:0.64, 95% CI: 0.46-0.88), driven mostly from the reduction of new-onset macroalbuminuria (2.5 % vs 4.9%).[12]

In the ELIXA trial, lixisenatide was associated with a lower increase in UACR compared the placebo (24% vs. 34%, p=0.004).[28] In EXSCEL trial, exenatide LAR was associated with a reduction of the renal composite point (40% reduction in eGFR, need for renal replacement therapy, renal death and new-onset macroalbuminuria) compared with placebo (HR:0.85, 95% CI: 0.73-0.98). This significant reduction of the composite point came from the reduction of new-onset macroalbuminuria.[37] The only finding that we have from the HARMONY trial, with albiglutide, is that there was nodifference in eGFR levels between the two study groups since the trial was early terminated and no further analysis has been published regarding renal outcomes.[38] In accordance, in larger clinical trials no clinically relevant effects on eGFR deterioration or slopes

were observed over the long term, except for a modest eGFR preservation effect in the 30 to 60 mL/min/1.73 m2 subgroup in LEADER and a 1 and 2 mL/min/y preservation of eGFR in AWARD-7 at 52 weeks.[35,39,40]

Finally, in the REWIND trial, dulaglutide was associated with a significant reduction of renal composite of microvascular outcome (new-onset macroalbuminuria, sustained decline in eGFR of 30% or more from baseline, chronic renal replacement therapy) compared with placebo (HR:0.85, 95% CI: 0.77-0.93, p=0.0004). The above reduction was driven by the reduction of new-onset macroalbuminuria (HR:0.77, 95% CI: 0.68-0.87, p<0.0001).[41]

The above findings of landmark CV trials clearly demonstrate that GLP-1 receptor agonists have renoprotective action clinical reflecting to the preservation of eGFR.

SGLT-2i

DN is characterized from hyperfiltration and increased intraglomerular pressure promoting thus the excretion of albumin. In patients with T2D, as a result of increased reabsorption of sodium and chloride in the proximal tubule, delivery to the macula densa is decreased, leadingto lower solute reabsorption. This is the main action of the nephroprotection caused by SGLT-2i.[42-45] SGLT-2i inhibit the reabsorbtion of sodium and glucose in proximal convoluted tubule, as a result of the sodium senses the

macula densa, decreasing the tubule-glomerular feedback promoting the vasoconstriction of afferent arteriole and, therefore, the intraglomerular pressure is reduced.[46,47] There are several other possible pathogenetic mechanisms explaining the nephroprotective action of SGLT-2i, including their effect on blood pressure, fat mass, and uric acid, the reduction of kidney hypoxia , and thus the reduction of energy requirements.[48] finally, experimental data suggest that SGLT-2i have anti-fibrotic, anti-inflammatory and antioxidant actions.[49-51] An animal study showed that SGLT-2i improve histological lesions (interstitial fibrosis, glomerular enlargement, mesangial matrix accumulation), a finding associated with the reduction of progression of diabetic nephropathy.[52] In a human study, empagliflozin reversed the glomerular hyperfiltration by modulating the tone of afferent arteriole. In hyperfiltrating patients, treatment with empagliflozin for 8 weeks resulted in reduction of GFR from 172 ±23 to 139±25 mL/min/1.73 m² (P<0.01). This was associated by a significant increase in renal vascular resistance, suggesting that this was due to decreased afferent arteriole vasodilation.[53]

The EMPAREG-OUTCOME and CANVAS trials have supported the renoprotective action of SGLT-2i expressed in terms of reduction of urine albumin excretion (Table 2).[12,13] In the EMPAREG OUTCOME trial[8], empagliflozin reduced the composite end point of progression of macroalbuminuria, death from renal disease or renal replacement therapy, and doubling of serum creatinine significantly (HR:0.61, 95% CI:

0.73-0.90). The renal analysis of the EMPAREG-OUTCOME trial examined further the effect of empagliflozin on eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. observed A decrease of eGFR compared to placebo was observed with empagliflozin 10 and 25 mg during the firtst month of the trial, while . From week 4 to the end of the study, eGFR was stabilized in both groups, while after the cessation of the study, eGFR increased in both empagliflozin groups compared to placebo (p<0.001). In a post-hoc analysis, empagliflozin reduced the composite point of renal replacement therapy or renal death and doubling serum creatinine significantly (HR:0.54, 95% CI: 0.40-0.75). Furthermore, empagliflozin reduced the progression of macroalbuminuria (HR:0.62, 95% CI: 0.54-0.72), doubling of serum creatinine (HR:0.56, 95% CI: 0.39-0.79) and initiation of renal replacement therapy (HR:0.45, 95% CI: 0.21-0.97). Finally, it must be mentioned that the EMPAREG OUTCOME trial did not enrolled patients with overt diabetic nephropathy. The study enrolled 5,201 patients with an eGFR>60 mL/min/1.73 m² of which 64% had no albuminuria, 27% had microalbuminuria and 8.5% had macroalbuminuria. Only 1,819 patients with eGFR<60 mL/min/1.73 m² (of which 47% had no albuminuria, 34% had microalbuminuria and 19% macroalbuminuria) were enrolled into the study.[8] This was the main limitation of this study regarding the results of renal composite point.

Similar results were observed in the CANVAS trial.[9] In the CANVAS trial, whereas 20.1% of patients had eGFR

TABLE 2. Cardiovascular and renal outcomes of SGLT-2 inhibitors

	EMPA-REG	CANVAS	DECLARE
Patients with established cv disease	99%	65.6%	40.6%
CV outcomes			
MACE-3	0.86 (0.74 – 0.99)	0.86 (0.75-0.97)	0.93 (0.84 – 1.03)
CV death	0.62 (0.49 – 0.77)	0.87 (0.72-1.06)	0.98 (0.82 – 1.17)
Non-fatal MI	0.87 (0.70 – 1.09)	0.85 (0.69-1.05)	0.89 (0.77 – 1.01)
Non-fatal stroke	1.24 (0.92 – 1.67)	0.90 (0.71-1.15)	1.01 (0.84 – 1.21)
Mortality	0.68 (0.57 – 0.82)	0.87 (0.74-1.11)	0.93 (0.82 – 1.04)
HF hospitalization	0.65 (0.50 – 0.85)	0.67 (0.47-0.77)	0.73 (0.61 – 0.88)
Renal outcomes			
Composite renal outcome	0.61 (0.53 – 0.70)	0.64 (0.46 – 0.88)	0.53 (0.43 – 0.66)
Progression of albuminuria	-	0.73 (0.67–0.79)	
40% reduction in eGFR, renal-replacement therapy, or renal death	-	0.60 (0.47–0.77)	0.53 (0.43–0.66)

*Data are presented as hazard ratio, 95% confidence intervals
Abbreviations: CV: cardiovascular, MACE: major adverse cardiovascular events, MI: myocardial infraction, HF: heart failure

<60 ml/min/1.73m^2, canagliflozin significantly reduced the renal composite end point of 40% decline of eGFR, death of renal causes or need for renal replacement therapy (HR:0.60, 95% CI: 0.47-0.77).[9] The reduction of renal composite end point was similar in patients with and without CKD among the 4 study groups (eGFR >90 ml/min/1.73 m^2, 60-90, 45-60, <45, p-heterogeneity=0.28 and >0.5 respectively).[54] Doubling of serum creatinine was significantly reduced (HR: 0.50, 95% CI: 0.30–0.84), but ESRD was not (HR: 0.77, 95% CI: 0.30–1.97).[55] Finally, 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.

In the DECLARE-TIMI 58 trial, dapagliflozin reduced significantly the secondary composite point of death from renal or CV causes, ESRD, >40% decline of eGFR to eGFR <60 ml/min/1.73m^2 (HR:0.76, 95% CI: 0.67-0.87). However, subgroup analyses of albuminuria and composite renal point was not performed in DECLARE-TIMI 58 trial.[10]

In a recent meta-analysis of these 3 trials (EMPAREG-OUTCOME, CANVAS, DECLARE TIMI 58), SGLT-2i reduced the composite point of renal death, ESRD and worsening of renal function by 45% (HR:0.55, 95% CI: 0.48-0.64) in patients with and not established CV disease.[56] It is important to mention that the combination of renin-angiotensin blockade (RAS) with SGLT-2i have renoprotective action due to the greater reduction of intraglomerular pressure from this combination; RAS blockade leads to vasodilation of the efferent arteriole while SGLT-2 inhibition leads to vasoconstriction of the afferent arteriole, resulting to the reduction of intraglomerular pressure and hyperfiltration, and thus to reduction of albuminuria.[57,58]

A recent study supporting the above evidence is the CREDENCE trial.[59] In this trial, all participants had CKD with eGFR 30-90 ml/min/1.73m^2, ACR 300-5000 mg/g and were treated with RAS blockade. Canagliflozin reduced significantly the primary outcome of composite point of ESKD (dialysis, transplantation, sustained eGFR <15 ml/min/1.73m^2), doubling serum creatinine, and death from renal or CV disease, compared to placebo (HR:0.70, 95% CI 0.59-0.82, p=0.00001). Furthermore, canagliflozin reduced significantly the renal-specific composite point of ESKD, doubling serum creatinine, and death from renal causes (HR:0.66, 95% CI: 0.53-0.81, p<0.001) and ESKD (HR:0.68, 95% CI: 0.54-0.86, p=0.002).

Recently, the early termination of Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial was announced based on the observed efficacy of dapagliflozin. DAPA-CKD is an international, multi-center, randomized, double-blinded trial in 4,245 patients designed to evaluate the efficacy of dapagliflozin 10mg, compared with placebo, in patients with CKD stages 2–4 and elevated urinary albumin excretion, with and without T2D. The primary endpoint of DAPA-CKD trial was a composite of worsening of renal function or death (defined as a composite endpoint of ≥50% sustained decline in eGFR, onset of end-stage kidney disease or CV or renal death) in patients with CKD irrespective of the presence of T2D.[60]

SGLT-2I, GLP-1 RECEPTORS AGONISTS AND CV EFFECTS

GLP-1 receptor agonists

It is well established that the CV benefits of GLP-1 receptors agonists, as it has been showed by their major CV trials, is independent of the observed reduction of HbA1c (HbA1c difference 0.4% in LEADER trial[11], 0.8% in SUSTAIN-6 trial[12], 0.6% in HARMONY OUTCOMES trial38 compared to placebo) (Table 1). Many pathogenetic mechanisms have been proposed in order to explain the observed cardioprotection of the GLP-1 receptor agonists. It is well documented that GLP-1 receptor agonists improve renal function, and established CV risk factors like weight and lipid profile.[61,62] They reduce body weight and waist circumference as a result of reducing total fat rather than lean tissue mass.[63,64] Their favorable effect of GLP-1 receptors agonists on weight is mediated by the reduction satiety, the appetite suppression and delaying gastric emptying.[65-67]

Some, but not all, GLP-1 receptor agonists have anti-hypertensive action; according to a recent meta-analysis liraglutide and albiglutide have antihypertensive action but not dulaglutide and exenatide.68 The proposed mechanism for the favorable effect of GLP-1 receptor agonists on blood pressure is mediated by the release of atrial natriuretic peptide leading to natriuresis, vasodilation and improved endothelial function.[69-71] In addition, GLP-1 receptor agonist have direct action to the proximal renal tubule.[72-74] Another pleiotropic effect of GLP-1 receptor agonists is their beneficial effect on lipid profile; the underlying mechanisms include reductions in post-prandial chylomicron synthesis and reduced triglyceride absorption, as well as increased postprandial insulin production and reduction in glucagon release leading to inhibition of adipose tissue lipolysis.[68,75-78]

It must be mentioned that, in contrast to SGLT-2i trials, hospitalization for HF was not improved with GLP-1 receptor agonists; liraglutide did not improve hospitalization for HF or functional status in patients with reduced left ventricular function.[79] However, in a trial with GLP-1 receptor agonist, left ventricular function, functional status and quality of life in patients with severe HF was improved, a finding in both diabetic and non-diabetic patients.[80] In

patients with acute myocardial infarction (MI) and systolic dysfunction, GLP-1 receptor agonist therapy improved left ventricular function after primary angioplasty.[81] The pathogenetic mechanisms for the beneficial action of GLP-1 receptor agonists include their effect on apoptosis of cardiomyocytes and cardiac fibrosis.[82,83]

The first study to examine the CV effects of GLP-1 receptor agonists was the ELIXA trial. In the ELIXA trial, 6,068 patients with T2D with either a MI or hospitalized for unstable angina in the preceding 180 days, were randomized to receive either lixisenatide 10–20 gr or placebo.[30] The primary endpoint was a composite of CV death, MI, stroke or hospitalization for HF. After a median follow-up of 25 months, 13.4% patients receiving lixisenatide and 13.2% receiving placebo reached the primary endpoint (HR: 1.02, 95% CI: 0.89–1.17). The trial showed the non-inferiority of lixisenatide to placebo (p<0.001) but failed to show superiority (p=0.81). There was no difference between groups in any of the CV outcomes when considered individually, or in all-cause mortality. No significant interactions were observed for the primary endpoint and renal function and there were no differences to the risk of hospitalization for HF between the two groups.

In the LEADER trial, with liraglutide, 9,380 patients with T2D and high CV risk were randomized to receive either liraglutide or placebo.[11] The primary endpoint was a composite of CV death, MI or stroke. After a median follow-up of 3.8 years, 13.0% patients on liraglutide and 14.9% patients on 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 CV 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 HF were non-significantly lower in the liraglutide group. Patients with CKD (eGFR<60 mL/min/1.73 m2) showed to have greater benefit (HR: 0.69, 95% CI: 0.57–0.85) than patients with eGFR >60 mL/min/1.73 m2 (HR: 0.94, 95% CI: 0.83–1.07) in the liraglutide arm.

In the SUSTAIN-6 trial, with the once-weekly GLP-1 receptor agonist semaglutide, 3,297 patients with T2D and established CV disease were randomized to once-weekly semaglutide (0.5 or 1.0 mg) or placebo for 104 weeks.[12] The primary composite outcome included CV death, non-fatal MI or non-fatal stroke. The primary outcome occurred in 6.6% patients receiving semaglutide and 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 EXSCEL trial, with exenatide, 14,752 patients with T2D with and without pre-existing CV disease were randomized to once-weekly 2 mg extended-release exenatide or placebo.[84] The primary outcome was a composite of CV death, MI or stroke. After a median follow-up of 3.2 years, the primary outcome occurred in 11.4% patients receiving exenatide and 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 CV outcomes and hospitalization for HF did not differ between groups. All-cause mortality was significantly lower with exenatide (HR: 0.86, 95% CI: 0.77–0.97).

In the HARMONY OUTCOMES trial, with albiglutide, 9,463 patients with T2D and CV disease were randomized to weekly albiglutide (30–50 mg) or placebo.[38] The primary outcome was a composite of CV death, MI or stroke. After a median follow-up of 1.6 years, the primary outcome occurred in 7% patients receiving albiglutide and 9% patients receiving placebo (HR: 0.78, 95% CI: 0.68–0.90). The trial 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, CV death or all-cause mortality.

Finally, the REWIND trial, with dulaglutide, evaluated major CV outcomes with weekly dulaglutide in 9,901 patients with T2D, 69% of whom did not have prior CV disease.[41] The study had a median follow-up of more than 5 years, which is longer than other GLP-1 receptor agonist trials. Dulaglutide significantly reduced the composite endpoint of CV death, non-fatal MI or non-fatal stroke compared with placebo (HR: 0.88, 95% CI: 0.79-0.99; p=0.026 for superiority). There was no reduction in CV death (dulaglutide vs. placebo: 6.4% vs. 7.0%, p=0.21) and non-fatal MI (dulaglutide vs. placebo: 4.1% vs. 4.3%, p=0.65), while there was a significant reduction in non-fatal stroke (dulaglutide vs. placebo: 2.7% vs. 3.5%, p=0.017). Furthermore, dulaglutide did not reduce the hospitalization for HF compared to placebo (4.3% vs. 4.6%, p=0.46).

SGLT-2i

Many hypotheses have been suggested in order to explain the beneficial effect of SGLT-2i on CV disease and mortality, especially HF (Table 2).[85-88] It is known that SGLT-2i reduce the levels of uric acid and, therefore, their uricosuric action has been proposed for their cardioprotective action. However, a recent trials showed that lowering uric acid with febuxostat might increase mortality rates.[89] Furthermore, due to their diuretic action, SGLT-2i cause a small but significant reduction of blood pressure (3-5/1-3 mmHg).[90] In the EMPA-REG OUTCOME mean blood

pressure decreased from 135.3/76.6 mmHg at baseline to 131.3/75.1 mmHg at end of the study, while in CANVAS and DECLARE-TIMI 58 studies, mean blood pressure decreased from 136.4/77.6 to 132.5/76.2 and from 135.1/77.6 to 132.3/75.8 mmHg, respectively.[91,92] It must be mentioned that in the above trials the reduction of blood pressure was not associated with reduction of stroke and MI.[92] A recent study, in 42 healthy subjects randomized to dapagliflozin or bumetanide, 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.[93] The authors suggest that the CV benefit of the SGLT-2i is partly explained by their diuretic action. SGLT-2i decrease the fluid in the interstitial space and not the whole-intravascular volume, as result of not arterial underfilling. Finally, SGLT-2i therapy is accompanied by calorie loss due to osmotic diuresis, reducing the whole fat mass.[94]

The SGLT-2 inhibition in pancreatic alpha-cells induce glucagon secretion, affecting hepatic ketogenesis and circulating ketone levels. Increased circulating ketone levels are thought to be an efficient source of adenosine triphospate (ATP) for the heart. The heart is the organ with the highest energy expenditure and 70% originates from fatty acid oxidation. When heart's oxidize ketone bodies are used as energy source at the expense of fatty acid and glucose oxidation, which are less energetically efficient, less ATP synthesis per molecule of oxygen is needed. 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.[94-98] In addition, SGLT-2i have direct action on cardiomyocytes: they inhibit the sodium–hydrogen exchanger-1, lower cytosolic Na and shift intracellular calcium from the cytosol to the mitochondria.[92,99-101]

The EMPAREG OUTCOME trial, with empagliflozin, randomized 7,028 patients with established CV disease to placebo, empagliflozin 10 mg or empagliflozin 25 mg for 3.1 years. The primary endpoint was the 3-point MACE including CV mortality, non-fatal MI and non-fatal stroke.[8] Patients randomized to empagliflozin group showed a significant reduction in the primary endpoint (HR: 0.86, 95% CI: 0.74–0.99; p=0.04 for superiority; absolute risk reduction 1.6%). This was driven predominantly by a substantial reduction in CV death (HR: 0.62, 95% CI: 0.49–0.77), whereas MI and stroke were not significantly different. In addition, patients treated with empagliflozin had a 35% reduction in hospitalization for HF compared with placebo (HR: 0.65,95% CI: 0.50–0.85) and 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). The participants that have self-reported history of coronary artery bypass surgery treated with empagliflozin had reductions in CV events and all-cause mortality, HF hospitalization and in the worsening of nephropathy[102], while there were no differences regarding the above outcomes between the two sexes.[103] In another analysis of EMPAREG OUTCOME trial, including patients with CKD at baseline [eGFR <60 mL/min/1.73m^2 and/or UACR >300 mg/g], empagliflozin reduced CV death by 29% (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 HF 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) compared to placebo.[104]

In the CANVAS Programme, CANVAS and CANVAS-renal (CANVAS-R) studies, 10,142 participants with T2D and high CV risk were followed for a mean of 188.2 weeks.[9] The primary outcome in both trials was a composite of CV death, non-fatal MI or non-fatal stroke. Canagliflozin was associated with a significant reduction in the risk of MACE (HR: 0.86, 95% CI: 0.75–0.97, p =0.02 for superiority), hospitalization for HF (HR: 0.67, 95% CI: 0.52–0.87) and 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). Another analysis of CANVAS trial in 4 subgroups (eGFR <45, 45 to <60, 60 to <90 and >90 mL/min/1.73 m^2) showed that the reduction in the primary outcome for the overall trial population was similar among the 4 subgroups and for patients with and without CKD (p for heterogeneity=0.33 and 0.08, respectively).[9] Finally, another analysis of CANVAS trial confirmed the observed benefit in the reduction of the risk of hospitalization for HF, in patients having history of HF at baseline.[105]

In the DECLARE TIMI-58 trial, with dapagliflozin, whereas participated mainly patients in primary prevention, 17,160 patients with T2D were followed over a period of 4.2 years.[10] Participants either had established CV disease or were at risk for CV disease. The primary safety outcome was a composite of CV death, MI or ischaemic stroke. The primary efficacy outcomes were MACE and a composite of CV death or hospitalization for HF. 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 CV death or hospitalization for HF (4.9% versus 5.8%, HR: 0.83, 95% CI: 0.73–0.95). Dapagliflozin decreased the risk of hospitalization for HF (HR: 0.73, 95%

CI: 0.61–0.88), while CV death events were similar in the 2 groups (HR 0.98, 95% CI 0.82–1.17). Furthermore, dapagliflozin was not associated with a significant reduction in MI (HR: 0.89, 95% CI: 0.77–1.01), ischemic stroke (HR: 1.01, 95% CI: 0.84–1.21) and all-cause mortality (HR: 0.98, 95% CI: 0.82–1.17).

Recently the results of DAPA-HF trial were published showing a positive effect of dapagliflozin in patients with HF and reduced ejection fraction.[106] In the DAPA-HF trial 4,744 patients (with and without diabetes) with New York Heart Association class II, III, or IV HF and an ejection fraction of 40% or less assigned randomly to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death. The participants were followed over 18.2 months. Dapagliflozin reduced significantly the primary outcome compared to placebo (16.3% vs 21.2%, HR: 0.74; 95% CI: 0.65 - 0.85, p<0.001), the first worsening HF event (10% vs 13.7%, HR: 0.70; 95% CI: 0.59 - 0.83), CV death (9.6% vs 11.5%, HR: 0.70; 95% CI: 0.59 - 0.83), and all-cause mortality (11.6% vs 13.%, HR: 0.83; 95% CI: 0.71 - 0.97). These findings were similar between participants with and no history of diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups. Thus, dapagliflozin demonstrated the beneficial action in patients with HF with reduced ejection fraction regardless of the presence of diabetes.

CONCLUSION

It is well established that in order to slow the progression of CKD and to prevent Cv, a multifactorial approach of patients with T2D, including glycaemic control, blood pressure, lipid profile and lifestyle interventions, is needed.[10,107] According to recent guidelines of the American Diabetes Association[108] metformin remains the first choice of antidiabetic therapy in combination with lifestyle modification (including weight management and physical activity). If a second antidiabetic agent is needed for glycaemic control, then the presence of established atherosclerotic cardiovascular disease (ASCVD) is mandatory for the next step in antidiabetic therapy. If there is established ASCVD or indicators of high-risk ASCVD risk (age ≥55 years with coronary or carotid or lower extremity artery stenosis >50%, left ventricular hypertrophy), GLP-1 receptor agonists with proven CV benefit (liraglutide, semaglutide, dulaglutide) are preferred. Alternatively, SGLT-2i with proven CV benefit (empagliflozin, canagliflozin, dapagliflozin) are preferred if eGFR is adequate. If HF (with reduced ejection fraction, particularly with left ventricular ejection fraction <45%) or CKD predominates (defined as the presence of eGFR 30-60 ml/min/1.73m² or UACR >30 mg/g, particularly >300 mg/g), the use of SGLT-2i with evidence of reducing HF or/and CKD progression are preferred if eGFR adequate. If eGFR is not adequate, then GLP-1 receptor agonists with proven CV benefit are preferred. Consequently, the proven cardioprotective and renoprotective action of SGLT-2i and GLP-1 receptor agonists dictates the use of these in the management of T2D in general practice.

ΠΕΡΙΛΗΨΗ

Καρδιονεφρικές επιδράσεις των νεότερων αντιδιαβητικών παραγόντων

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Η διαβητική νεφροπάθεια αποτελεί μείζον πρόβλημα δημόσιας υγείας και συνδέεται με αυξημένη καρδιαγγειακή θνησιμότητα και νοσηρότητα. Η τρέχουσα θεραπευτική διαχείριση της περιλαμβάνει τη ρύθμιση της αρτηριακής πίεσης και τον εντατικό γλυκαιμικό έλεγχο. Ωστόσο, υπάρχουν μελέτες - κλινικές και πειραματικές - που δείχνουν ότι πολλοί, και κυρίως οι νεότεροι, αντιδιαβητικοί παράγοντες καθυστερούν την εξέλιξη της. Οι αγωνιστές του υποδοχέα του παρόμοιου με τη γλυκαγόνη πεπτιδίου-1 και οι αναστολείς του συν-μεταφορέα νατρίου-γλυκόζης-2 έχουν ευνοϊκή δράση στη νεφρική λειτουργία. Επιπλέον, οι αντιδιαβητικοί αυτοί παράγοντες έχουν ευεργετικές επιδράσεις στο καρδιαγγειακό σύστημα, συμπεριλαμβανομένης της απώλειας βάρους και της μείωσης της αρτηριακής πίεσης. Μεγάλες, τυχαιοποιημένες, ελεγχόμενες με εικονικό φάρμακο κλινικές μελέτες έδειξαν ότι τόσο οι αναστολείς του συν-μεταφορέα νατρίου-γλυκόζης-2 όσο και οι αγωνιστές του υποδοχέα του παρόμοιου με τη γλυκαγόνη πεπτιδίου-1 μειώνουν τα καρδιαγγειακά συμβάματα.

Σκοπός, συνεπώς, της παρούσας ανασκόπησης είναι να συνοψίσει τα υπάρχοντα δεδομένα σχετικά με την επίδραση των νεότερων αντιδιαβητικών παραγόντων στη νεφρική και καρδιακή λειτουργία.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Σακχαρώδης διαβήτης, διαβητική νεφροπάθεια, καρδιαγγειακή νόσος, αγωνιστές του υποδοχέα του παρόμοιου με τη γλυκαγόνη πεπτιδίου-1, αναστολείς του συν-μεταφορέα νατρίου-γλυκόζης-2, καρδιακή ανεπάρκεια*

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