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EDITORIAL

Antidiabetic combination therapy and cardiovascular outcomes: An evidence-based approach

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Abstract

Type 2 diabetes mellitus is associated with a 2-4 times increased risk of cardiovascular (CV) disease. Glucagon-like polypeptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are two important classes of drugs with CV benefits independent of their antihyperglycemic efficacy. The CV outcome trials of both GLP1RA and SGLT2i have demonstrated CV superiority/neutrality concerning major adverse CV events (MACE). While GLP1RAs have exhibited a significant reduction in ischemic stroke and myocardial infarction (MI), SGLT2i have demonstrated a uniformly significant reduction in hospitalization for heart failure (HF) as a class effect. The unique clinical benefits and the distinct but complementary mechanisms of action make the combination of these drugs a mechanistically sound one. Recent meta-analyses suggest an independent and additive benefit of combination therapy of GLP1RA/SGLT2i *vs* monotherapy. Zhu *et al*, in a recent issue of the *World Journal of Diabetes*, demonstrates a numerically lower hazard ratio (HR) for CV outcomes with combination therapy *vs* monotherapy with either agent, with a reduction in MACE compared to GLP1RA alone [HR = 0.51, 95% confidence interval (CI): 0.16-1.65], or SGLT2i alone (HR = 0.48, 95%CI: 0.15-1.54). The CV death rate was also lower with combination therapy compared to GLP1RA alone (HR = 0.58, 95%CI: 0.08-3.39), or SGLT2i alone (HR = 0.55, 95%CI: 0.07-3.25). Fatal and non-fatal MI and fatal and non-fatal stroke were reduced with combination therapy compared to GLP1RA alone (HR = 0.45, 95%CI: 0.10-2.18 and HR = 0.86, 95%CI: 0.12-6.23, respectively), or SGLT2i alone (HR = 0.44, 95%CI: 0.09-2.10 and HR = 0.74, 95%CI: 0.10-5.47,

respectively). Hospitalization for HF was prevented with combination therapy compared to GLP1RA alone (HR = 0.26, 95%CI: 0.03-1.88), or SGLT2i alone (HR = 0.33, 95%CI: 0.04-2.53). They also demonstrated that GLP1RA or SGLT2i monotherapy may not provide significant improvement in CV death and recurrent MI in patients with prior MI or HF, proposing a role for combination therapy in this subgroup. Appropriate patient selection is vital to optimize CV risk reduction as well as the cost-effectiveness of this combination therapy.

Key Words: Glucagon-like polypeptide-1 receptor agonists; Sodium-glucose cotransporter-2 inhibitors; Cardiovascular disease; Type 2 diabetes mellitus; Cardiovascular outcome trials

Core Tip: Glucagon-like polypeptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are important antihyperglycemic medications with cardiovascular (CV) benefits in the form of CV superiority or neutrality, and positive effects on cardiometabolic risk factors. The divergent clinical benefits include significant reductions in hospitalization for heart failure (HF) with SGLT2i, and ischemic stroke and myocardial infarction (MI) with GLP1RA. Zhu *et al*, in a recent issue of the *World Journal of Diabetes,* suggest combination therapy with GLP1RA/SGLT2i *vs* monotherapy with either agent for additional improvement in CV death and recurrent MI, especially in the setting of prior MI or HF.

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INTRODUCTION

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The underlying mechanisms for the added cardiovascular (CV) risk in T2DM extend beyond dysglycemia and include hypertension, dyslipidemia, central obesity, insulin resistance, endothelial dysfunction and several other metabolic perturbations. Hence, optimal CV risk reduction in T2DM has evolved beyond glycemic control and includes the identification and addressing of underlying metabolic disturbances.

Identifying CV safety as a common therapeutic end goal in diabetes management, the United States Food and Drug Administration issued a guidance in 2008, making demonstration of CV safety mandatory for all new antidiabetic medications for T2DM through dedicated CV outcome trials (CVOTs) prior to marketing to the public[1]. Since then, over 13 CVOTs have been completed for antidiabetic medications. Based on these, several new drug molecules with different mechanisms of action have emerged in the past few years with remarkable CV benefits including reduced mortality[2]. Glucagon-like polypeptide-1 receptor agonists (GLP1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are two important classes of such drugs with proven CV safety and mortality benefits which have changed the T2DM treatment landscape in the past couple of decades.

Diabesity (diabetes as a direct consequence of adiposity) is a major issue in most patients with T2DM. GLP1RAs, as a class effect, have demonstrated remarkable efficacy with respect to improvements in glycated hemoglobin (HbA1c) levels and body weight, with newer longer acting agents like injectable semaglutide demonstrating the most efficacy among the mono-agonists[3,4]. The CVD risk reduction conferred by GLP1RA correlated well with the degree of improvement in diabesity as evidenced by the data from a very recent meta-analysis of CVOTs[5].

SGLT2i, on the other hand, are the other class of antidiabetic agents with several CVOTs data underlining their CV benefits, with recent real-world data suggesting more marked improvements in diabesity outcomes compared to those reported in randomized controlled trials (RCTs)[5,6]. As the mechanisms of actions of GLP1RA and SGLT2i are entirely different and complementary, the putative mechanisms for CVD risk reduction and renoprotection are also very different and possibly synergistic. On the one hand, GLP1RA reduces CVD risk through anti-atherogenic, anti-oxidative, and anti-inflammatory effects. The SGLT2i exerts CVD risk reduction mainly through hemodynamic effects and changes in cardiac metabolism[7]. Although GLP1RA and SGLT2i reduce major adverse CV events (MACE) to a similar extent, especially in T2DM patients with atherosclerotic CVD (ASCVD), GLP1RA reduces stroke and SGLT2i reduces heart failure (HF) hospitalization and chronic kidney disease (CKD) progression to a greater extent[7]. Therefore, it is important to appraise the potential benefits of combining these agents to improve composite CVD and renal outcomes. Zhu *et al*[8], in their systematic review in the October issue of the *World Journal of Diabetes*, perform this task to improve our understanding of this important matter. This article examines the pathobiological mechanisms behind CV protection conferred by these new antidiabetic agents and their combinations to generate the best evidence for clinical practice.

GLP1RA AND CV OUTCOMES

The discovery of GLP1RA has changed the landscape of diabesity management. Several robust CVOTs involving GLP1RA have provided evidence of their beneficial effects in reducing MACE, which has prompted seminal changes in the guidelines for the management of diabetes. The recent American Diabetes Association (ADA) guidelines 2024, recognizing cardiorenal risk reduction as a primary goal of therapy in high-risk individuals with T2DM, have positioned GLP1RA with proven CV benefits as first-line agents in T2DM patients for cardiorenal risk reduction irrespective of baseline HbA1c and background use of metformin[9].

T2DM is associated with a 2-4 times increased risk of CVD as compared to non-diabetic individuals, with the risk worsening with impaired glycemic control[10]. T2DM has been associated with a higher coronary artery calcium (CAC) burden, as well as increased progression of CAC scores on longitudinal follow-up[11,12]. Additionally, Burke *et al*[13] demonstrated that obesity was independently associated with a 17% increased risk of higher CAC even after adjustment of traditional CVD risk factors.

GLP1RA, in addition to their robust HbA1c lowering effects, addresses several cardiometabolic risk factors which potentially contribute to CV risk reduction, including significant weight loss, improvement in total cholesterol, low-density lipoprotein cholesterol, triglycerides and modest lowering of systolic blood pressure[14,15]. Additionally, GLP1RAs also favorably alter the development of atherosclerosis, owing to their anti-inflammatory and anti-atherogenic effects. Several preclinical models have demonstrated reduced atherosclerotic lesion development and progression, leading to more stabilized and less vulnerable plaques[16,17].

The evidence from CVOTs has further cemented the cardioprotective role of GLP1RA. A significant CV benefit concerning 3-point MACE outcomes was demonstrable in the CVOTs of liraglutide, dulaglutide and subcutaneous semaglutide. On the other hand, CV neutrality was seen with exenatide, lixisenatide and oral semaglutide. Data from major CVOTs involving GLP1RA with pertinent clinical outcomes are summarized in Table 1[18-24].

In a recent meta-analysis including 24 RCTs by Hosseinpour *et al*[25], patients on GLP1RAs had a lower risk of MACE, CV death, myocardial infarction (MI), stroke, and hospitalization for HF. Subgroup analysis revealed that overweight/obese non-diabetic individuals also had a comparable reduction in adverse CV events as compared to diabetic individuals. The use of GLP1RA was associated with increased odds of regression to normoglycemia and decreased risk of progression to T2DM in overweight/obese individuals with prediabetes as reported in the meta-analysis by Yanto *et al*[26]. GLP1RAs have also demonstrated reduced fat accumulation (visceral and subcutaneous adipose tissue) in addition to decreased body weight, improved glycemic parameters (fasting and postprandial blood glucose, HbA1c), insulin resistance and fibrosis-4 scores in patients with diabetes mellitus and non-alcoholic fatty liver disease or obesity[27]. Hence, GLP1RA provides robust CV protection by targeting multiple pathways that contribute to the risk of adverse CV events. The CV benefits conferred by GLP1RAs and the putative mechanisms are depicted in Figure 1. The putative mechanisms for CV protection associated with the use of glucagon-like insulinotropic peptide-1 receptor agonists are detailed in Figure 1.

SGLT-2I AND CV OUTCOMES

SGLT2i are the other class of modern antihyperglycemic agents which have a cardioprotective role in the management of hyperglycemia. SGLT2i decreases blood glucose levels by inhibiting SGLT2 in the proximal tubule of the kidney, effectively inhibiting glucose reabsorption.

SGLT2i address several of the CV risk factors directly *via* their antihyperglycemic effect (HbA1c reduction of about 0.69% *vs* placebo), antihypertensive effect mediated by osmotic diuresis, natriuresis and inhibition of sympathetic nervous system activity, mild to modest weight loss of 0.9-2.5 kg mediated by negative caloric balance, along with improved waist circumference and visceral obesity[3,28].

SGLT2i also improves myocardial bioenergetics by mobilizing fatty acids from adipose tissue and improving the supply of ketone bodies to the heart[29]. Other mechanisms include inhibition of cardiac SGLT1, Sodium/hydrogen exchanger, increased erythropoietin levels, and reduced oxidative stress. Additionally, SGLT2i ameliorates the inflammatory milieu in diabetes by decreasing the macrophage inflammatory response, and directly targeting the inflammatory pathway by inhibiting the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 inflammasome which mediates the chronic inflammation in HF. This effect is possibly mediated by increased levels of cir-culating β-hydroxybutyrate and occurs independent of glucose-lowering. The anti-inflammatory effect, along with improvement in cardiac remodeling *via* inhibition of the mammalian target of the rapamycin pathway contributes to the improvement in cardiac function[29].

CVOTs with all SGLT2i have uniformly demonstrated a significant (27%-35%) reduction in hospitalization for HF, suggestive of a class effect[29]. SGLT2i activates tubuloglomerular feedback by increasing sodium delivery to the distal tubule, leading to inhibition of the renin-angiotensin system. This, in addition to a preferential contraction of interstitial volume vis-à-vis intravascular volume, explains the salutary effect of SGLT2i in HF[29]. On the other hand, superiority for 3-point MACE outcomes was demonstrable only with empagliflozin and canagliflozin[30,31]. However, dapagliflozin treatment was associated with superior MACE outcomes in those with previous MI [hazard ratio (HR) = 0.84; 95% confidence interval (CI): 0.72 to 0.99; P = 0.039 for superiority][32]. The likely explanation for the failure to achieve superior MACE outcomes with dapagliflozin is due to the study design in which only 41% had ASCVD at baseline. The pertinent characteristics of the CVOTs of SGLT2i are outlined in Table 2[30-35]. McGuire *et al*[36] conducted a meta-analysis of 6 placebo-controlled trials of SGLT2i and reported that SGLT2i were associated with a significant reduction in

Table 1 Data from major cardiovascular outcome trials with glucagon-like polypeptide-1 receptor agonists

Trial name (*n*)	Drug *vs* comparator	Mean difference in HbA1c (%) (95%CI)	Mean difference in body weight in kg (95%CI)	CV outcome HR (95%CI)	Effect on MACE (non-inferior *vs* superior)
EXSCEL (*n* = 14752)[18]	Exenatide once weekly *vs* placebo	-0.53 (-0.57 to -0.50)	-1.27 (-1.4 to -1.13)	3-point MACE: 0.91 (0.83 to 1); *P* < 0.001 for non-inferior and *P* = 0.06 for superior	Non-inferior
ELIXA (*n* = 6068)[19]	Lixisenatide *vs* placebo	-0.27 (-0.31 to -0.22)	-0.70 (-0.9 to -0.5)	4-point MACE: 1.02 (0.89 to 1.17); *P* < 0.001 for non-inferior and *P* = 0.81 for superior	Non-inferior (likely failure to achieve superiority due to suboptimal GLP1 inhibition because of once a day dosing of lixisenatide despite being a short acting GLP1RA, and history of recent acute coronary event in all study participants)
LEADER (*n* = 9340)[20]	Liraglutide *vs* placebo	-0.40 (-0.45 to -0.34)	-2.30 (-2.5 to -2)	3-point MACE: 0.87 (0.78 to 0.97); *P* < 0.001 for non-inferior and *P* = 0.01 for superior	Superior. Reduced CV death
REWIND (*n* = 9901)[21]	Dulaglutide *vs* placebo	-0.61 (-0.65 to -0.58)	-1.46 (-1.67 to -1.25)	3-point MACE: 0.88 (0.79 to 0.99); *P* = 0.026 for superiority	Superior. Reduced non-fatal stroke and microvascular complications
HARMONY OUTCOMES (*n* = 9463)[22]	Albiglutide *vs* placebo	-0.52 (-0.58 to -0.45)	-0.83 (-1.06 to -0.6)	3-point MACE: 0.78 (0.68 to 0.90); *P* < 0 0001 for non-inferior and *P* = 0 0006 for superior	Superior. Reduced non-fatal MI
SUSTAIN-6 (*n* = 3297)[23]	Semaglutide s.c. *vs* placebo	-0.7 (-0.80 to -0.52) for 0.5 mg/week dose -1 (-1.19 to -0.91) for 1 mg/week dose	-2.90 (-3.47 to -2.28) for 0.5 mg/week dose -4.30 (-4.94 to -3.75) for 1 mg/week dose	3-point MACE: 0.74 (0.58 to 0.95); *P* < 0.001 for non-inferior; *P* = 0.02 for superior	Superior (as *per* posthoc analysis). Reduced non-fatal stroke; Worse retinopathy 1.76 (1.11 to 2.78; *P* = 0.02); No worse/new nephropathy
PIONEER-6 (*n* = 3183)[24]	Semaglutide oral *vs* placebo	-0.7 (-0.42 to -1.26)	-3.40 (-4.20 to -2.30)	3-point MACE: 0.79 (0.57 to 1.11); *P* < 0.001 for non-inferior	Non-inferior. Reduced CV death

CVOTs: Cardiovascular outcome trials; GLP1RA: Glucagon-like polypeptide-1 receptor agonists; MACE: Major adverse cardiovascular events; GLP1: Glucagon-like polypeptide-1; CV: Cardiovascular; HR: Hazard ratio; CI: Confidence interval.

MACE and kidney outcomes. Risk reduction for hospitalization due to HF was consistent across all trials, whereas there was significant heterogeneity concerning CV death[36]. In a recent meta-analysis of eleven trials (*n* = 78607), SGLT2i uniformly reduced the risk of MACE across a broad range of patients irrespective of ASCVD, diabetes, kidney function, or other major clinical characteristics at baseline (HR = 0.86, 95%CI: 0.81-0.92, *P*< 0.0001). This reduction was primarily driven by a decrease in CV death (HR = 0.86, 95%CI: 0.81-0.92, *P* < 0.0001), especially HF death (HR = 0.68, 95%CI: 0.46-1.02) and sudden cardiac death (HR = 0.86, 95%CI: 0.78-0.95). On the contrary, there was no significant effect on MI and stroke event rates in SGLT2i-treated patients as compared to placebo[37].

Keeping with the growing evidence in favour of SGLT2i, professional societies have embraced the use of this class of agents vocally in recent years. ADA 2024 guidelines recommend SGLT2i with proven CVD benefit as a first-line agent in patients with ASCVD, or patients at high risk of ASCVD, irrespective of baseline HbA1c and background use of metformin. Additionally, SGLT2i remains the drug of choice in diabetic patients with HF- both HF with reduced ejection fraction and HF with preserved ejection fraction[9]. Potential mechanisms for CV protection conferred by SGLT2i are detailed in Figure 2.

ROLE OF GLP1RA, SGLT2I AND COMBINATION THERAPY IN DIABESITY

The positive effects of GLP1RAs and SGLT2i in CVOTs are particularly impressive considering the study population in these trials received standard-of-care cardioprotective preventive therapies at baseline. Recent ADA guidelines recognize the cardiorenal risk reduction afforded by both GLP1RA and SGLT2i in treatment algorithms, with slight differences in indications where each of these agents is preferred. They give equal weightage to either class of agents (with RCT-proven CV benefits) in diabetic individuals with ASCVD/high risk of ASCVD. On the other hand, SGLT2i remain the preferred class of agents in patients with a prevalent or past history of HF as well as CKD (estimated glomerular filtration rate < 60 mL/minute/1.73 m^2 or albumin creatinine ratio > 30 mg/g)[9].

Table 2 Data from major cardiovascular outcome trials with sodium-glucose co-transporter 2 inhibitor

Trial name (*n*)	Drug *vs* comparator	Baseline CVD or risk factors (%)	Mean difference in HbA1c (%) (95%CI)	Mean difference in body weight in kg (95%CI)	Primary outcome HR (95%CI)	Hospitalization for heart failure HR (95%CI)	Composite CV death or heart failure hospitalization HR (95%CI)
CANVAS (*n* = 10142)[31]	Canagliflozin *vs* placebo	ASCVD (66); CAD (56); Stroke/CVD (19); HF (14.4)	-0.58 (-0.61 to -0.56)	-1.6 (-1.70 to -1.51)	3-point MACE: 0.86 (0.75 to 0.97); *P* < 0.001 for non-inferior; *P* = 0.02 for superior	0.67 (0.52 to 0.87)	0.78 (0.67 to 0.91). Amputation risk at the toe and metatarsal level
DECLARE-TIMI (*n* = 17160)[32,33]	Dapagliflozin *vs* placebo	ASCVD (41); CAD (33); Prior MI (21); Stroke/CVD (7); HF (10)	-0.42 (-0.45 to -0.40)	-1.80 (-2.00 to -1.70)	3-point MACE: 0.93 (0.84-1.03); *P* < 0.001 for-non-inferior and *P* = 0.17 for superior	0.73 (0.61 to 0.88); *P* < 0.005	0.83 (0.73 to 0.95); *P* = 0.005 for superiority
EMPA-REG (*n* = 7020)[30]	Empagliflozin *vs* placebo	ASCVD (99); CAD (76); Prior MI (46); Stroke (23); HF (10)	-0.57 (-0.70 to -0.43) for 10 mg -0.64 (-0.77 to -0.50) for 25 mg	-1.63 (-2.11 to -1.5) for 10 mg -2.01 (-2.49 to -1.53) for 25 mg	3-point MACE: 0.86 (0.74 to 0.99); *P* < 0.001 for non-inferior and 0.04 for superior	0.65 (0.5 to 0.85); *P* = 0.002	0.62 (0.49 to 0.77); *P* < 0.001
VERTIS-CV (*n* = 8246)[34]	Ertugliflozin *vs* placebo	ASCVD (100); CAD (76); Prior MI (48); Stroke/CVD (23); HF (24)	-0.70 (-0.90 to -0.50) for 5 mg -0.90 (-1.00 to -0.70) for 15 mg	-3.00 (-3.30 to -2.70) for 5 mg -2.90 (-3.20 to -2.60) for 15 mg	3-point MACE: 0.97 (0.85 to 1.11); *P* < 0.001 for noninferior	0.7 (0.54 to 0.9)	0.88 (0.75 to 1.03); *P* = 0.11 for superiority
SCORED (*n* = 10584)[35]	Sotaglifozin *vs* placebo	ASCVD (89); Prior MI (19.9); Prior PCI (22.8); HF (31); Stroke (8.9)	-1.16 (-1.26 to -1.06)	-1.16 (-1.26 to -1.06)	Total number of deaths from CV causes, hospitalization for HF, and urgent visits for HF: 0.74 (0.63-0.88); *P* < 0.001	0.67 (0.55 to 0.82); *P* < 0.001	0.77 (0.66 to 0.91)

CVD: Cardiovascular disease; HbA1c: Glycated hemoglobin; CV: Cardiovascular; HR: Hazard ratio; CI: Confidence interval; ASCVD: Atherosclerotic cardiovascular disease; CAD: Coronary artery disease; HF: Heart failure; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

While this dichotomy helps in the selection of patients most likely to benefit from a specific drug class, it is pertinent to note that there often is significant overlap between ASCVD and HF/CKD subgroups in clinical practice. Secondly, it is important to note that the majority of CVOTs were designed as CV safety trials, to accrue more events in a shorter period with a smaller sample size. As a result, most CVOTs majorly enrolled a secondary prevention population, and hence were not powered enough to demonstrate superiority in primary prevention settings. Thirdly, the use of composite CV outcomes as primary endpoints in CVOTs, while resource-efficient, does not distinguish between each of the components of the composite outcome, assumes a uniform directionality and includes only the first event in a traditional time-to-event analysis[38]. Hence, it is important to examine the nuances of CVOTs for appropriate patient selection and explore the potentially additive role of combination therapy in selected patients.

The questions of differential CV benefits and their role in secondary *vs* primary prevention of ASCVD of both these classes of agents have been addressed in a few studies. In a meta-analysis by Zelniker *et al*[39] including 77242 patients (73.1% with established ASCVD), both GLP1 and SGLT2i significantly reduced MACE by a similar degree (12% and 11%, respectively). However, this reduction was confined to patients with preexisting ASCVD (14% reduction), with no significant effect in patients without established ASCVD. Both SGLT2i and GLP1RA significantly reduced the progression of renal disease. Only GLP1RA significantly reduced the risk of ischemic stroke, whereas only SGLT2i had a significant 31% reduction in hospitalization for HF and the composite renal outcome[39]. SGLT2i-mediated natriuresis and tubuloglomerular feedback inhibition are likely the primary mechanisms responsible for the observed reduction in hospitalization for HF and the composite renal outcome.

Similar findings were also seen in another large meta-analysis by Palmer *et al*[40], where both GLP1RAs and SGLT2i were associated with lower all-cause and CV mortality, non-fatal MI and renal failure. However, SGLT2i reduced HF-related hospitalization more than GLP1RA, and only GLP1RA reduced non-fatal stroke significantly. The lack of benefit in the primary prevention of CV events by both GLP1RA and SGLT2i was also noted in the meta-analysis by Mannucci and Silverii[41].

The REWIND trial (dulaglutide *vs* placebo) was the first study to suggest the CV benefits of GLP1RA even in subjects without ASCVD. The important distinction in this trial was that the majority of the patients (69%) did not have a prior history of ASCVD, and the uniquely long median follow-up of 5.4 years (20). Marsico *et al*[42] reported no difference in 3-

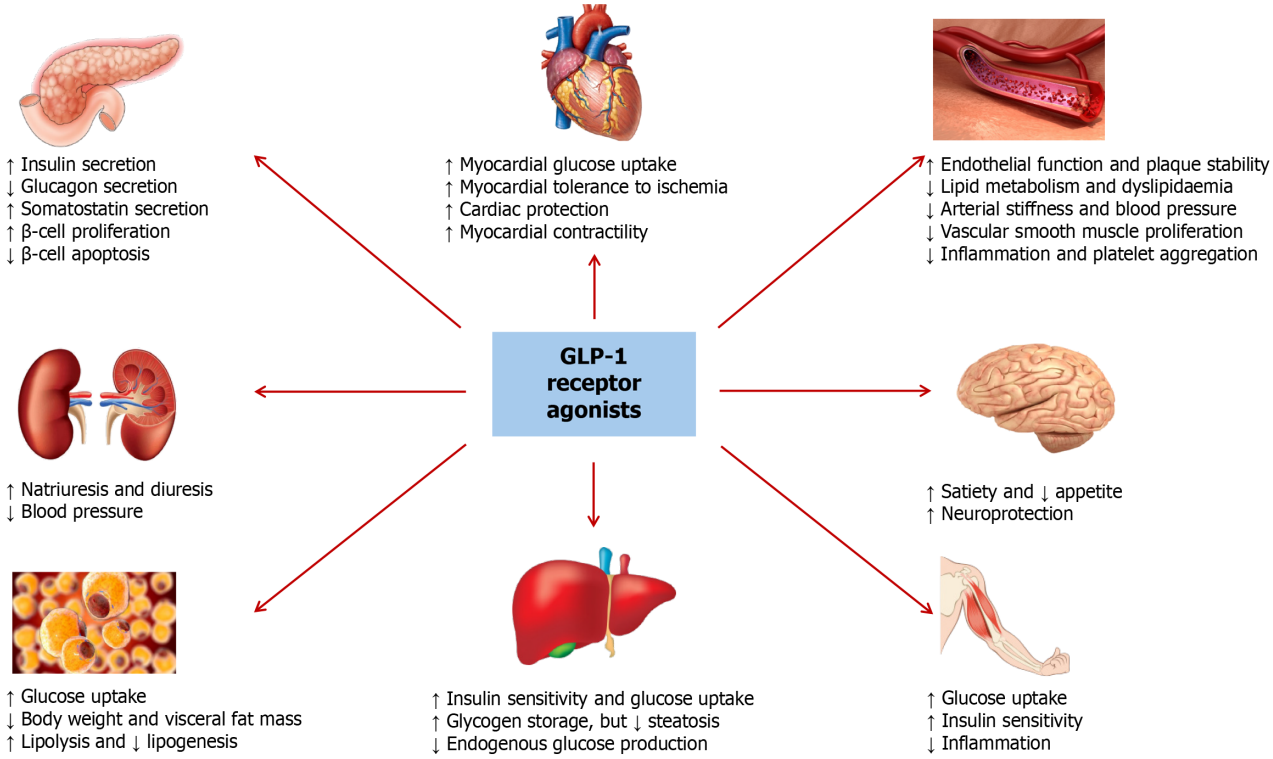

Figure 1 The putative mechanisms for cardiovascular protection associated with the use of glucagon-like insulinotropic peptide-1 receptor agonists. GLP-1: Glucagon-like insulinotropic peptide-1.

point MACE outcomes in GLP1RA-treated individuals with preexisting ASCVD *vs* patients with CV risk factors only[42]. Hence, it is plausible that the CV benefits of GLP1RA extend to patients without established ASCVD but may take a longer time to be evident.

The role of combination therapy for further optimization of CV risk has been recognized as a research gap by the European Society of Cardiology guidelines[43]. The SGLT2i/GLP1RA combination resulted in better control of cardiometabolic risk factors like fasting plasma glucose, HbA1c, and systolic blood pressure without increasing the risk of hypoglycemia as compared to SGLT2i monotherapy, while there was no such benefit when compared to GLP1RA monotherapy[44].

CV outcomes with combination therapy have also been explored in recent studies. A nested case-control study by Wright *et al*[45] revealed that the current use of the SGLT2i/GLP1RA combination was nominally associated with lower odds of MACE than either agent alone in primary prevention settings. In a recent meta-analysis by Neuen *et al*[46], the CV, renal and mortality benefits of GLP1RA were consistent regardless of baseline use of SGLT2i. Surprisingly, GLP1RA also resulted in a significant reduction in hospitalization for HF irrespective of baseline SGLT2i use. Similarly, Apperloo *et al*[47], in their meta-analysis, demonstrated that the beneficial effects of SGLT2i on CV and renal outcomes were consistent irrespective of background use of GLP1RA.

These findings suggest that the cardiorenal benefits of the two drug classes may be independent of each other and potentially additive, including in primary prevention settings, hence opening newer vistas for further CV risk optimization in T2DM.

POTENTIAL MECHANISMS OF DRUG SYNERGISM IN POSITIVE CV OUTCOMES

The distinct and complementary mechanisms of action make the combination of SGLT2i and GLP1RA a mechanistically rational one. Both classes of agents improve cardiometabolic risk factors, including glycemic and lipid parameters, blood pressure and visceral adiposity, with GLP1RA having a higher efficacy concerning HbA1c and body weight reduction. However, mechanisms for the overall protective CV profile likely extend beyond the control of the traditional CV risk factors.

The predominantly antiatherogenic and anti-inflammatory effect of GLP1RA might explain the more prominent reduction in MI and stroke rates as compared to SGLT2i[48]. Hence, GLP1RA might also be better suited for primary prevention in patients without preexisting ASCVD to delay the development of clinical disease. On the other hand, SGLT2i decrease intraglomerular pressure and improve cellular bioenergetics, which might explain the impressive benefits in heart and renal failure[49]. Hence, there is a role for combining GLP1RA and SGLT2i to realize their respective clinical benefits and optimize CV risk reduction (Figure 3).

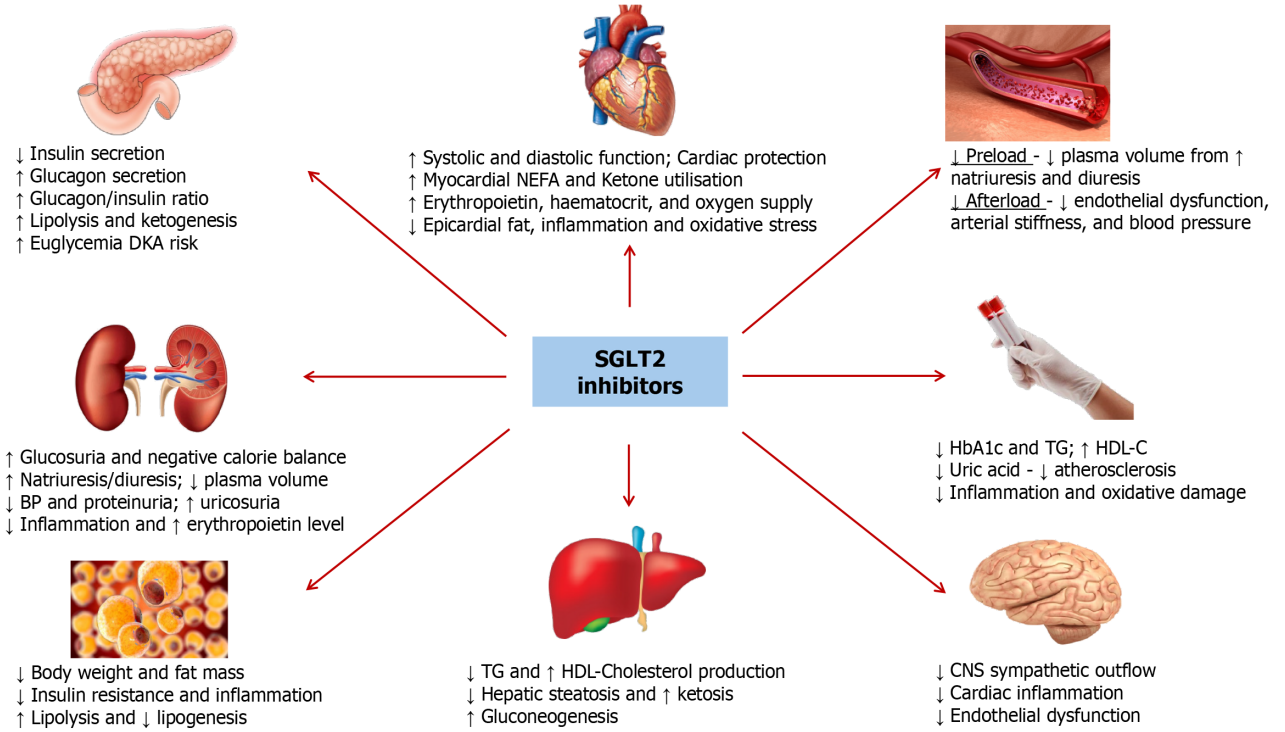

Figure 2 The putative mechanisms for cardiovascular protection associated with the use of sodium-glucose co-transporter 2 inhibitors. DKA: Diabetes ketoacidosis; BP: Blood pressure; NEFA: Non-esterified fatty acids; SGLT2: Sodium-glucose co-transporter 2; HDL: High-density lipoprotein; TG: Triglycerides; CNS: Central nervous system; HbA1c: Glycated hemoglobin.

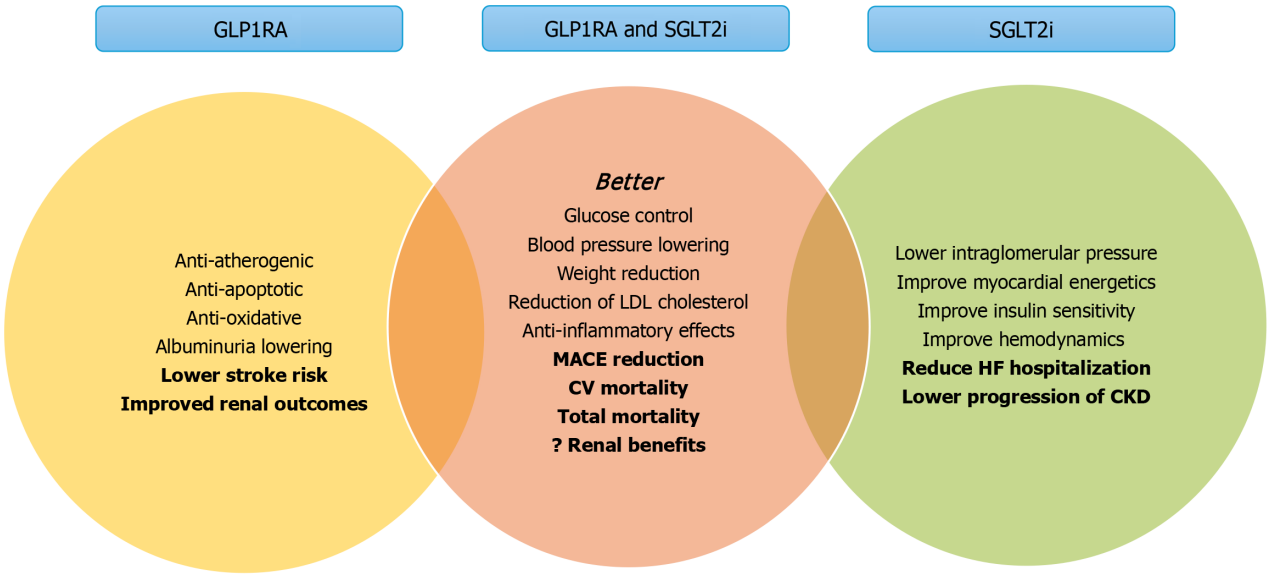

Figure 3 Shows the mechanisms of cardiorenal therapeutic benefits of glucagon-like insulinotropic peptide-1 receptor agonists, sodium-glucose co-transporter 2 inhibitors, and their combination. LDL: Low density lipoprotein cholesterol; CV: Cardiovascular; MACE: Major adverse cardiac event; HF: Heart failure; CKD: Chronic kidney disease; GLP1RA: Glucagon-like insulinotropic peptide-1 receptor agonists; SGLT2i: Sodium-glucose co-transporter 2 inhibitor.

The work by Zhu *et al*[8] in the recent issue of the *World Journal of Diabetes* is an important step in this direction. The study aims to answer two important research questions: The role of combination therapy *vs* monotherapy with SGLT2i or GLP1RA concerning cardiac outcomes, and the effect of preexisting cardiac comorbidities of MI and HF. The use of a set of Bayesian network meta-analyses, lower heterogeneity and the use of meta-regressions to estimate the effect size of combination therapy *vs* monotherapy provides statistical robustness. All CVOTs included in the above meta-analysis were double-blind and randomized placebo-controlled trials. The Cochrane Collaboration's risk-of-bias tool was utilized to assess quality.

One of the major limitations of the study was that the overall credibility using ICEMAN was rated as low to moderate. This resulted from over-specification of the meta-regression model due to a limited number of available CVOTs (only 13), and the generation of β values with a lower statistical power. The overall negative β values (-0.13 to -0.01) and the numerically lower, but statistically insignificant HR with combination therapy *vs* monotherapy are suggestive of its potential role in further reduction in risk of CV outcomes, including MACE, CV death, HF, fatal and non-fatal MI and stroke *vs* monotherapy with either class of drugs.

Additionally, the HR for CV death, and fatal and non-fatal MI in GLP1RA-treated patients was numerically lower in patients with a prior history of MI. Similarly, the risk of hospitalization for HF in SGLT2i-treated patients was further reduced in those with a history of HF. The authors suggest prioritizing combination therapy in patients with these comorbidities. However, the numerical differences are small, and it is difficult to derive conclusions from the data in the absence of statistical significance. This may be attributed to the exclusion of the EMPA-REG trial (due to a lack of data regarding combination therapy), and the relative lack of representation of primary prevention subgroups.

COST-EFFECTIVENESS OF COMBINATION THERAPY

There is evidence to suggest that the combination therapy might result in better CV outcomes as compared to patients on monotherapy, suggestive of an independent and additive effect[37,47]. The study by Zhu *et al*[8] adds further credence to the role of combination therapy. To date, no published studies have evaluated the cost-effectiveness of the GLP-1RA and SGLT2i combination. A recent study by Choi *et al*[50] observed that while SGLT2is and GLP-1RAs are used individually as first-line T2DM therapies, to be considered cost-effective compared to metformin, their costs would need to decrease by at least 70%. The multinational CAPTURE study (n = 9823 adults with T2DM) found that fewer than 25% of patients received a glucose-lowering agent with proven CV benefits (SGLT2i or GLP1RA)[51]. This low number of prescriptions could be related to the high cost of Mediclaim reimbursement models and accessibility challenges, particularly for patients in low-resource settings.

Another multinational DISCOVER study (n = 14576 adults with T2DM) observed that on an average of only 16.1% of patients received a glucose-lowering agent with proven CV benefits with significant variability across countries (0%-62.7%) and specialities, with cardiologists prescribing them more (26.1%), compared to primary care physicians (10.4%)[52]. The DISCOVER study highlights the critical role of healthcare policy and better access to medication usage, emphasizing the need to address structural issues within the healthcare system to empower physicians to provide patients with optimal treatments.

CONCLUSION

The role of the combination of GLP1RA and SGLT2i has rightly garnered attention in recent years. The complementary and independent mechanisms of action make this a rational combination. However, the combination therapy with GLP1RA and SGLT2i has significant cost implications. Head-to-head trials are needed comparing combination therapy with monotherapy to accurately determine the cost-effectiveness of the combination therapy and the patient subgroups who are likely to benefit the most from it. Future studies should explore its role among populations with suboptimal risk reduction with monotherapies, like primary prevention subgroups (patients without established ASCVD), and patients with a history of MI, HF, CKD, cerebrovascular and peripheral vascular disease.

FOOTNOTES

Author contributions: Ganakumar V and Fernandez CJ contributed to the initial drafting of the work by performing the literature search and interpretation of relevant literature and share the first authorship; Fernandez CJ also prepared the figures for the manuscript and contributed substantially in addition to the revision process; Pappachan JM conceptualized the idea and provided overall supervision to the drafting process and figure preparation; All authors contributed to the revision of the article for important intellectual content, and all authors have read and approved the final version of the manuscript.

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