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Cardiovascular Benefits and Pharmacological Mechanisms of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus: A Narrative Review

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ABSTRACT

Type 2 diabetes mellitus (T2DM), caused by hyperglycemia, insulin resistance, inflammation, oxidative stress, and endothelial dysfunction, leads to cardiovascular morbidity and mortality. Sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are classes of therapeutic agents that have shown cardiovascular effects on top of glycemic regulation. In this narrative review, existing evidence on pharmacological mechanisms and cardiovascular outcome data of the two drug classes are synthesized. The main effects of SGLT2 inhibitors are cardioprotective by hemodynamic and natriuretic mechanisms, enhanced myocardial energetics, and renal protection, and strong decreases in heart failure hospitalization and chronic kidney disease progression. Conversely, GLP-1 receptor agonists have anti-atherosclerotic and anti-inflammatory properties, which reduce major adverse cardiovascular events and stroke to a significant degree. Comparative analysis points to complementary processes and phenotype-specific advantages. Incorporation of these agents into modern management of T2DM is a paradigm shift in outcomes-based cardiometabolic care. There are also research gaps and future therapeutic implications.

1. INTRODUCTION

Cardiovascular disease (CVD) is the principal cause of mortality in patients with type 2 diabetes mellitus (T2DM). Globally, 536.6 million individuals were living with diabetes in 2021, expected to rise to 783.2 million by 2045 [1]. Patients with T2DM exhibit markedly increased risks of stroke, heart failure, myocardial infarction, and cardiovascular death, driven by endothelial dysfunction, chronic inflammation, oxidative stress, and metabolic dysregulation [2]. Large trials of intensive glycemic control have failed to consistently determine significant reductions in cardiovascular mortality, indicating that glucose-lowering alone is insufficient to mitigate macrovascular risk [3]. Since 2015, large-scale cardiovascular outcome trials (COVTs) have established sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucose-like peptide-1 receptor agonists (GLP-1s) as disease-altering agents in T2DM. SGLT2i have shown strong reductions in heart failure hospitalization (approximately 25-35%) and progression of chronic kidney disease, largely through hemodynamic modulation and restoration of tubule-glomerular feedback (TGF) [4]. On the other hand, GLP-1s have consistently reduced atherothrombotic events, particularly non-fatal myocardial infarction and stroke, mediated by anti-

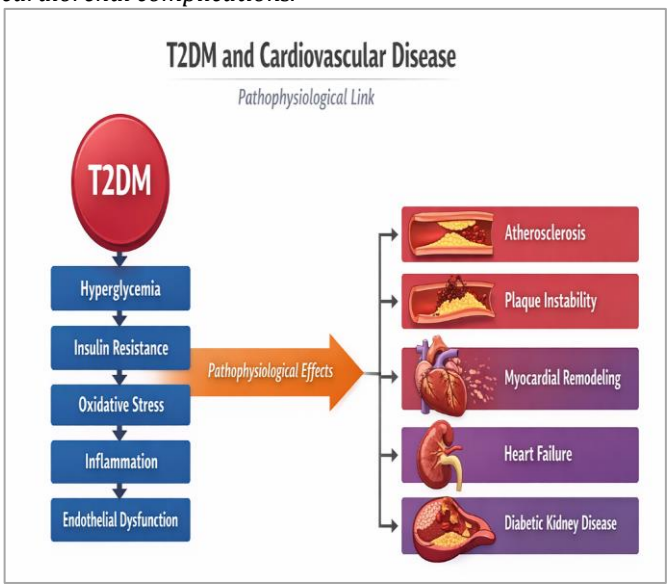
inflammatory, metabolic effects, and atherosclerotic [3]. However, knowledge gaps are still present. First, evidence regarding additive or synergistic effects of combined SGLT2i and GLP-1s therapy remains limited to subgroup analyses and meta-analytic data [5]. Second, the relative contribution of glucose-independent mechanisms such as oxidative stress reduction, mitochondrial modulation, and endothelial protection to cardiovascular benefit is completely defined [2]. This narrative review aims to synthesize mechanistic and clinical evidence regarding GLP-1s and SGLT2i, compare their cardiovascular and cardiorenal effects, and critically evaluate the rationale for combined therapeutic strategies in T2DM.

2 Pathophysiological Link Between Type 2 Diabetes Mellitus and Cardiovascular Disease

T2DM is not only a glucose metabolism disorder but rather a complicated cardiometabolic condition with long-term hyperglycemia, insulin resistance, systemic inflammation, oxidative stress, and dysfunction of the endothelium [6]. The combination of these interrelated abnormalities forms a biological environment that boosts atherogenesis, enhances myocardial remodeling, and increases cardiorenal dysfunction, as shown in **Figure 1**.

Figure 1

Insulin resistance and chronic hyperglycemia in T2DM stimulate oxidative stress, systemic inflammation, and endothelial malfunction. These interactive processes increase the rates of atherogenesis and plaque instability resulting in myocardial remodeling, heart failure, and diabetic kidney disease. The figure represents the gradual shift of metabolic dysregulation to the macrovascular and cardiorenal complications.



2.1 Hyperglycemia, Endothelial Dysfunction, and Atherogenesis

The chronic hyperglycemia has a direct cytotoxic impact on vascular endothelial cells, which are constantly subjected to high glucose levels. Experimental and clinical studies prove that overload with intracellular glucose elevates the mitochondrial generation of reactive oxygen species (ROS), thus causing oxidative stress conditions and reducing the bioavailability of endothelial nitric oxide [7]. Through this redox imbalance, the endothelial activation, which is marked by an increase in vascular permeability and the upregulation of adhesion molecules, is stimulated to promote leukocyte recruitment and transmigration into the vascular intima, the initial critical stages of atherogenesis. Also, the chronic hyperglycemia stimulates the development of advanced glycation end-products (AGEs), which bind to the receptor (RAGE) and induce intracellular inflammatory and pro-atherogenic signaling. Oxidative stress, AGE-RAGE signaling, and endothelial dysfunction all combine to facilitate the development of a plaque and vascular remodeling in T2DM [8].

2.2 Insulin Resistance, Inflammation, and Oxidative Stress

Insulin resistance is a pathophysiological central element that connects T2DM to cardiovascular disease (CVD). Systemic inflammation and oxidative stress that characterize T2DM lead to vascular damage and atherosclerotic overgrowth [9]. The excess of nutrients through obesity triggers the inflammatory pathways, such as the IKK2/NF-kB signaling, which results in the production of pro-inflammatory cytokines that promote the further development of insulin resistance, such as TNF-α and interleukin [10].

Its activation of NLRP3 inflammasome has also been found to contribute to metabolic and vascular pathology, as well as promote the maturation and release of IL-1 mediators of vascular inflammation and plaque instability, such as IL-18 [11]. The continuous inflammatory and oxidative conditions not only lead to coronary atherosclerosis but also myocardial dysfunction. The clinical prognosis of T2DM is a 2.5-fold higher risk of heart failure in diabetic patients than in non-diabetic patients [12].

2.3 Overlapping Cardiometabolic Risk Factors

T2DM often accompanies conventional risk factors of cardiovascular diseases. According to epidemiological data, the prevalence of obesity (32.9%), hypertension (32-80%), and dyslipidemia (39%) is high among T2DM patients [13]. In addition to these more traditional risk factors, nontraditional ones, such as oxidative stress, hypercoagulability, endothelial dysfunction, and autonomic neuropathy, also increase cardiovascular risk. The combination of these factors leads to a multifactorial network, increasing the speed of vascular injury and harming myocardial activity.

2.4 Cardiorenal Interactions in Diabetes

The example of cardiac-renal pathology is diabetic kidney disease (DKD). DKD is common in diabetes (40%) and causes a significant increase in morbidity and mortality in the cardiovascular system. Cardiovascular disease is prevalent in patients with advanced chronic kidney disease, and 40-50% of the deaths are due to cardiovascular causes [14]. Renal dysfunction increases volume overload, neurohormonal activity, systemic inflammation, and cardiac dysfunction, further impairing renal perfusion, resulting in a self-sustaining cardiorenal cycle [15].

2.5 Limitations of Traditional Glucose-Centric Therapies

Traditionally, intensive glycemic control was sought after

as the major approach to minimize the cardiovascular complications in T2DM. Nevertheless, strict glycemic control (HbA1c ≤6.5%) has shown little effect on cardiovascular death and can lead to other risks, such as hypoglycemia and weight gain [16]. Likewise, traditional treatments with classical risk factors, such as renin angiotensin aldosterone system inhibition, can only decrease the renal risk by approximately 20% (relative risk reduction) of the entire cardiorenal risk (kidney failure) remaining [17].

Thus, the conventional antidiabetic solutions have failed to offer adequate solutions to the multifactorial, interlinked pathways between T2DM and cardiovascular disease. This pathophysiological knowledge highlights the importance of therapeutic interventions, which combine hemodynamic, inflammatory, oxidative, and metabolic pathways with glucose-lowering only.

3 Overview of SGLT2 Inhibitors

Sodium glucose cotransporter-2 inhibitors (SGLT2i) were originally designed as glucose-lowering agents but have also turned out to be pleiotropic cardiometabolic agents with extensive cardiovascular and renal effects [18]. Their therapeutic effects are based on the physiology of renal tubules and are not confined to glycemic modulation but to hemodynamic, metabolic, and anti-inflammatory effects.

3.1 Physiological Role of SGLT2 in Renal Glucose Reabsorption

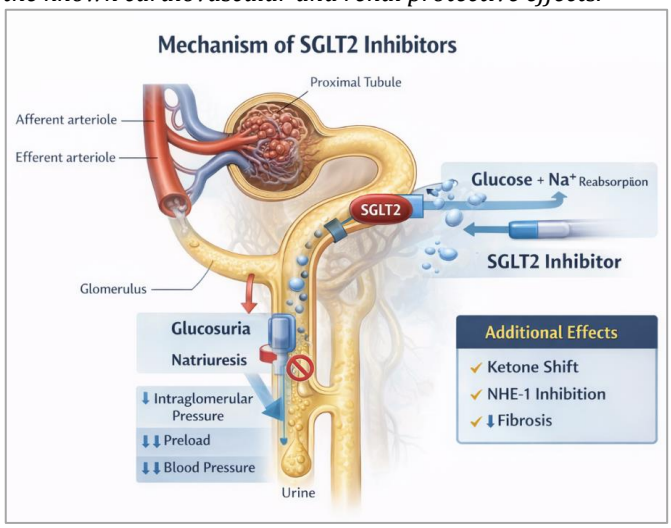
SGLT2 is a low-affinity and high-capacity sodium glucose cotransporter found in the S1 and S2 portions of the proximal renal tubule. It allows the reabsorption of about 90% of the filtered glucose from a glomerular ultrafiltrate [19]. In physiological circumstances, this process helps to suppress glycosuria and energy conservation. But in T2DM, there is an augmented filtered glucose load, which boosts SGLT2-mediated reabsorption, a factor in the perpetuation of hyperglycemia and maladaptive glomerular hyperfiltration [20].

3.2 Effects of SGLT2 Inhibitors on Renal Glucose and Sodium Handling

SGLT2 inhibitors inhibit glucose and sodium reabsorption in the proximal tubule, resulting in the enhancement of urinary glucose excretion and natriuresis. The resultant glucosuria decreases the plasma glucose levels that do not depend on the insulin effects, thus decreasing the risk of hypoglycemia [21]. Notably, improved delivery of sodium to the distal nephron recovers tubule glomerular feedback, lowers intraglomerular pressure, and suppresses hyperfiltration, which is a major pathogenic process involved in diabetic kidney disease development. Osmotic diuresis and natriuresis reduce the plasma volume and ventricular preload hemodynamically, which leads to pressure decreases and hospitalization for heart failure as shown in Figure 2 [22].

Figure 2

Mechanism of action and cardiorenal effects of SGLT2 inhibitors. SGLT2 inhibitors inhibit sodium–glucose cotransporter-2 (SGLT2) in the proximal renal tubule; that is, inhibiting glucose and sodium reabsorption. This leads to glucosuria and natriuresis which restore tubule-glomerular feedback and lowers intraglomerular pressure. Osmotic diuresis reduces plasma volume, ventricular preload, which is hemodynamically contributing to the reduction of blood pressure. Other recommended mechanisms are a transition to the use of ketone bodies, the blockage of myocardial sodium–hydrogen exchanger-1 (NHE-1), and the prevention of cardiac fibrosis. Altogether, these processes contribute to the known cardiovascular and renal protective effects.



3.3 Pharmacokinetic Considerations

Majors of this group, such as empagliflozin and dapagliflozin, are orally taken, once-daily drugs that are highly selective for the SGLT2 over SGLT1 [23]. Although there are minor variations in the pharmacokinetic parameters of various agents (e.g., bioavailability, hepatic metabolism by glucuronidation, renal excretion), there are minor clinically relevant differences. Their extended half-lives allow them to be inhibited from renal glucose transportation for a duration of 24 hours. Their renal mechanism of action is mostly dose adjustments, which are determined by approximated glomerular filtration rate (eGFR) [24].

3.4 Metabolic and Renal Effects Beyond Glucose Lowering

Along with the reduction of HbA1c level (usually 0.5-1.0%), SGLT2 inhibitors trigger the reduction of weight due to the caloric loss in the urine and a light diuretic effect. They also lower systolic blood pressure with natriuretic and depleting effects [25]. The advantages of Cardiorenal are even bigger. SGLT2is have a large effect on hospitalization due to heart failure, as it is reduced by 25–35%, and leads to better renal outcomes, such as delaying the growth of diabetic kidney disease [26]. These benefits, in a mechanistic sense, are not confined to hemodynamic actions but also to enhanced myocardial energetics (shift to ketone use), oxidative stress, inflammation, and mitochondrial function. This set of mechanisms justifies the categorization of them as cardiorenal-protective

agents and not forgetting them as antihyperglycemic drugs.

3.5 Safety and Tolerability

In general, SGLT2 inhibitors are relatively well tolerated, but there are certain adverse effects associated with their pharmacology, which are associated with a specific mechanism. Genital mycotic infections are predisposed by increased glycosuria [27]. Osmotic diuresis can lead to loss of volume and hypotension, especially in old patients or those using diuretics. Clinically rare events, but of clinical importance, are euglycemic diabetic ketoacidosis and acute kidney injury, especially during dehydration or in the case of a serious illness [28].

Despite these risks, recent large cardiovascular outcome trials have shown overall positive safety profiles, which confirms the benefit-to-risk balance of patients with T2DM and high cardiovascular or renal risk. SGLT2 inhibitors are involved in inhibiting renal glucose and sodium reabsorption to generate insulin-independent glycemic regulation and, at the same time, have hemodynamic, metabolic, and anti-inflammatory actions [29]. It is their special mechanism, which lowers the glucose and has a large cardiovascular and renal protective ability.

4 Cardiovascular Benefits of SGLT2 Inhibitors

The results of massive cardiovascular outcome trials (CVOTs) have defined SGLT2 inhibitors (SGLT2i) as cardioprotective agents in T2DM, as they have shown the reduction of events, beyond that of glucose. Empagliflozin was the first agent to benefit cardiovascular outcomes in high-risk T2DM: three-point MACE was lower by 14% and heart-failure (HF) hospitalization by 38%, and all-cause mortality by 32% in EMPA-REG OUTCOME (n=7,020; median follow-up 3.1 years) [30]. Canagliflozin in the CANVAS Program can also cut down on MACE in T2DM patients with high cardiovascular risk, which supports a class impact on atherothrombotic outcomes in more vulnerable groups [31]. Comparatively, DECLARE-TIMI 58 recruited a larger cohort with decreased cardiovascular risk at baseline and failed to show a general decrease in MACE, but showed a 27% HF hospitalization decrease in a subpopulation with a history of myocardial infarction, indicating that the strength and detectability of the benefit vary with enriching the baseline risk and the study endpoint [32].

In the trials, HF event prevention is the most reliable cardiovascular signal. In addition to diabetes-specific CVOTs, the trials conducted in established HF patients (with and without T2DM) demonstrate a rapid and clinically significant outcome reduction in worsening HF and cardiovascular mortality. DAPA-HF (n=4,744; LVEF ≤40) had a 26% relative risk of HF hospitalization/urgent acute HF visits, and cardiovascular death was lower with dapagliflozin (9.6 vs 11.5; this corresponds to 18% relative risk reduction) [33].

Empagliflozin indexed by EMPEROR-Reduced demonstrated a 25% decrease in cardiovascular deaths and HF hospitalization composite, and a reduction in HF hospitalizations by approximately 30% (RR = 0.70) [34]. EMPEROR-Preserved in HFpEF showed a lower cardiovascular death/HF hospitalization (RR 0.79), which was caused in large part, by less HF hospitalization (RR 0.71)[35]. Aggregated evidence supports these effects: one meta-analysis of five placebo-controlled studies (46,969 participants) showed that SGLT2i decreased all-cause mortality, MACE, and HF hospitalization by 14%, 9%, and 31%, respectively, compared with placebo [36]. The summary of major CB+VOT trials are shown in **Figure 3**.

Figure 3

Timeline of major cardiovascular outcome trials (CVOTs) in type 2 diabetes. This timeline highlights key landmark trials evaluating the cardiovascular effects of SGLT2 inhibitors and GLP-1 receptor agonists, including EMPA-REG (2015), LEADER (2016), CANVAS (2017), DECLARE (2019), DAPA-HF (2020), and EMPEROR (2021), which collectively reshaped cardiometabolic treatment strategies in T2DM.

Mechanically, the effects of cardio protection seem to be the result of the hemodynamic-renal-metabolic interactions. These drugs inhibit proximal tubular SGLT2, leading to glucosuria with natriuresis, a reduction in the circulating volume and blood pressure, and an increase in distal sodium delivery, and the restoration of tubule-glomerular feedback, thus decreasing glomerular hyperfiltration and connecting renal hemodynamics with the reduction of HF risk [37]. Some mechanisms suggested to occur in the myocardium are the modulation of sodium-hydrogen exchanger (NHE-1), a decrease in myocardial fibrosis, a change towards ketone-body use, and a possible decrease in reactive oxygen species [38].

The benefit profile differs in relation to patient phenotype: the reductions of MACE are more distinct in cohorts that are enriched with established ASCVD/high-risk (EMPA-REG, CANVAS), but HF and renal-risk phenotype enhance clinical utility. CREDENCE (T2DM + CKD; n=4,401) found that canagliflozin decreased MACE by 20% and HF hospitalization by 30%, which is a significant finding in areas where cardiorenal risk is richly concentrated [39]. These results clinically suggest the prioritization of SGLT2i in patients with T2DM with established CVD, HF (any EF), or CKD, and the largest absolute risk changes are expected in patients with elevated baseline rates of events.

5 Overview Of Glp-1 Receptor Agonists

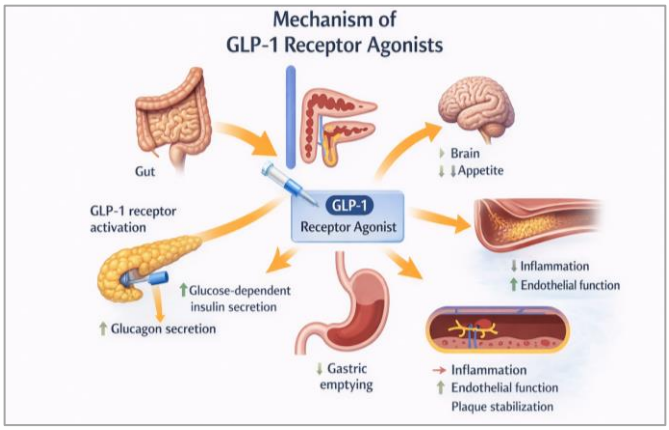
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin-based therapies that reproduce and amplify the physiological actions of endogenous GLP-1, a gut-derived hormone central to glucose homeostasis and energy balance [40].

5.1 Physiological Role of Endogenous GLP-1

The secretion of GLP-1 occurs in intestinal L-cells during the ingestion of nutrients. It interacts with a G-protein-linked receptor, GLP-1 receptor (GLP-1R) present in pancreatic β-cells, the gut, the central nervous system, the kidney, as well as heart tissues [41]. GLP-1, physiologically increases the glucose-dependent insulin secretion, inhibits glucagon release, and slows gastric emptying, which all decrease the postprandial glucose excursions. Nevertheless, native GLP-1 has a very short half-life (minutes) because it is rapidly degraded by the dipeptidyl peptidase-4 (DPP-4) and so has a limited therapeutic potential [42]. The brief mechanism of GLP-1 receptor agonist is shown in **Figure 4**.

Figure 4

GLP-1 receptor agonists stimulate the glucose-dependent insulin secretion, inhibit glucagon secretion, slow down appetite and gastric emptying in addition to improving endothelial functioning and lowering vascular inflammation, leading to greater glycemic regulation and reduced atherosclerotic cardiovascular risk.



5.2 Structural and Pharmacological Diversity

GLP-1 RAs are degradation-resistant synthetic analogs. First-mover agents, e.g., exenatide (exendin-4), are structurally related to human GLP-1, and second-mover agents (liraglutide, semaglutide, dulaglutide) are amino acid analogues or fatty-acid side chain analogues of human GLP-1 with modifications to increase the half-life [43]. The formulations are either twice/once-daily (exenatide, liraglutide) or once-weekly (dulaglutide, semaglutide). An oral semaglutide formulation co-formulated with an absorption enhancer (SNAC) is also present and has increased administration possibilities [44].

5.3 Metabolic Effects

GLP-1 RAs lower HbA1c up to about 0.8-1.5%, depending upon dose and agent. They have a glucose-dependent type of glucose-lowering effect, which gives them a low intrinsic risk of hypoglycemia [45]. In addition to glycemic control, GLP-1 RAs reduce appetite through the stimulation of the hypothalamic GLP-1R, which results in significant weight loss. The effects render them especially useful in patients with obesity-related T2DM [46].

5.4 Currently Approved Agents and Comparative Features

Liraglutide, semaglutide, dulaglutide and albiglutide are major GLP-1 RAs that have cardiovascular outcome data. Although there are variations in molecular structure and dosing schedule, their glucose reduction and cardiometabolic effects seem to be generally similar, and longer-acting agents tend to induce more significant changes in HbA1c and weight loss [47].

5.5 Safety and Contraindications

Gastrointestinal (nausea, vomiting, diarrhea) are the most frequent adverse effects and are dose-dependent and also short-lived. Uncommon issues are pancreatitis and the condition of the gallbladder. GLP-1 RAs should be avoided in individuals with either a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, at least because of the rodent evidence of C-cell hyperplasia [48]. In sum, GLP-1 receptor agonists have glucose-dependent insulinotropic effects and weight-reducing and cardiometabolic effects, which make them a pivotal point in the management of T2DM today.

6 Cardiovascular Benefits of GLP-1 Receptor Agonists

The clinical evidence produced by large cardiovascular outcome trials (CVOTs) demonstrates that a number of GLP-1 receptor agonists (GLP-1 RAs) can minimize atherosclerotic cardiovascular events in individuals with type 2 diabetes (T2D), particularly those with such a history or at risk of atherosclerotic cardiovascular disease [49]. Legal proceedings involve LEADER (liraglutide), SUSTAIN-6 (subcutaneous semaglutide), and REWIND (dulaglutide). Eight key GLP-1 RA CVOTs have been published across the class, with pooled evidence demonstrating a statistically significant change in 3-point MACE (CV death, non-fatal MI, non-fatal stroke)[50]. These eight trials were meta-analyzed and showed a relative risk reduction of 3-point MACE of approximately 14% (HR 0.86) and 15% with low heterogeneity when eliminating ELIXA (lixisenatide), which probably was different because of its short-acting exposure pattern [51].

6.1 Effect on MACE components

The same synthesis postulates that GLP-1 RAs decrease the personal atherothrombotic results (MI, stroke) and CV death, and the general trends indicate ASCVD event decrease as opposed to a key heart failure pathology [50]. GLP-1 RAs are consistently most associated with reduced atherosclerotic events, and event curves in randomized trials can often separate after a time of around 12-18 months in relation to anti-atherosclerotic effects rather than short-term hemodynamic effects.

6.2 Mechanisms that support the CV protection

There are several pathways that are probably involved, which not only act by lowering glucose. GLP-1 RA has modest effects on traditional risk factors that reduce systolic BP, lipids, and weight loss, which, as a rule, do not account for the entire decrease that is seen in MACE [52]. Additional anti-atherogenic and anti-inflammatory effects, such as less aggressive plaque formation/progression and less unstable plaques, are supported by mechanistic evidence that occurs via action on endothelial cells, monocytes/macrophages, and vascular smooth muscle cells, which express GLP-1 receptors [53]. There is also clinical evidence of decreased inflammatory signaling (e.g., decreased production of cytokines) and a decrease in

systemic markers of inflammation (e.g., CRP). These metabolic, vascular, antithrombotic, and anti-inflammatory effects have been demonstrated to be combined, which is why a decrease in atherothrombotic events is likely to be observed.

6.3 Drug and population consistency

The benefits do not apply to all agents and trials. The most powerful label of CV benefit is usually attributed to liraglutide, subcutaneous semaglutide, and dulaglutide (albiglutide/efpeglenatide demonstrates benefits but is not available in all areas)[54]. There was considerable variation in trial populations (ex, REWIND involved more primary-prevention patients), but in general, there seems to be a wide range of ASCVD-risk in which benefits are apparent.

6.4 Comparison between SGLT2 inhibitors

GLP-1 RA and SGLT2 inhibitors minimize CV risk, but the effect varies: GLP-1 RA inhibitors result in greater reductions in MI/stroke/CV death (ASCVD outcomes), whereas SGLT2 inhibitors result in a greater reduction in heart failure hospitalization and cardiorenal outcomes [26]. Practically, most high-risk patients cannot be dichotomized as either atherothrombotic or cardiorenal risk, and therefore, combination therapy may be rational and additive.

7 Comparative Insights: SGLT2 Inhibitors Vs GLP-1 Receptor Agonists

SGLT2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP-1RAs) are associated with lower cardiovascular (CV) risk in T2DM, which follows mechanistically different pathways, leading to a justification of either risk-phenotype selection or combined treatment [55]. Mechanistically, SGLT2i has much greater cardioprotective effects through hemodynamic and cardiorenal (natriuresis/osmotic diuresis reduces preload; blood pressure reduces afterload; myocardial substrate uses shifts toward ketones; inhibits myocardial Na +/H + exchange; fibrosis/necrosis; epicardial/perivascular adipokines; induces erythropoiesis) rather than anti-oxidative, anti-inflammatory, and anti-atherosclerotic [56]. These auxiliary axes promote additivity other than reducing glucose. The overall comparative cardiovascular effects are shown in Figure 5.

Figure 5

This table is a summary of the relative effect of the SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1RA) on key cardiometabolic outcomes. The down arrows (↓) are used to mean risk reduction; strong, moderate and mild are used to show the magnitude of effect seen in cardiovascular outcome trials. SGLT2 inhibitors have especially significant heart failure hospitalization and chronic kidney disease (CKD) progression reductions, but GLP-1 receptor agonists have greater stroke reduction and weight loss. Both classes will prevent major adverse cardiovascular events (MACE), but the benefit profiles will vary based on the leading cardiovascular phenotype. BP: blood pressure; HF: heart failure, CKD: chronic kidney disease.

Comparative Cardiovascular Effects

Outcome	SGLT2i	GLP-1RA
MACE	↓	↓
HF hospitalization	Strong ↓	Mild ↓
Stroke	Mild ↓	Strong ↓
CKD progression	Strong ↓	Moderate ↓
Weight loss	Moderate	Strong
BP reduction	Yes	Mild

In comparison of outcomes made based on meta-analyses of CVOTs, the proportions of reduction in MACE are similar in both classes, with hazard ratios of approximately 0.86 for 0.90 (10-14% relative risk reduction), and the signal is most pronounced in those already with proven ASCVD [50]. Nevertheless, differences in event patterns are clinical; SGLT2i has a greater effect on heart failure hospitalization (e.g., HHF HR 0.69 vs GLP-1RA HR 0.93 in a single pooled analysis), whereas GLP-1RAs have a more pronounced effect on stroke (e.g., stroke HR 0.86 vs SGLT2i HR 0.97) [57].

In line with this logic of phenotype, SGLT2i can be used as a first-line intervention in T2DM in the context of HF and CKD recommendations, although either of the classes may be used to lower MACE in ASCVD (or several ASCVD risk factors) [58]. The selection is also influenced by administration and tolerability: SGLT2is are orally active, whereas GLP-1RAs are orally active by preferential demand subcutaneous injection, but there are also oral GLP-1RA formulations. Combination use could be constrained at the implementation level by reimbursement/cost and polypharmacy, serving as an incentive to make individual decisions that consider patient preferences, toxicity profiles, renal function, glucose-lowering requirements, and weight-loss objectives [59].

The evidence of combination therapy is becoming more complete and increasing. Albiglutide provided equivalent MACE benefit versus no treatment in a post hoc analysis of Harmony Outcomes (P-interaction 0.70), and in a trial-level meta-analysis (Harmony Outcomes + AMPLITUDE-O; n=13,538) [60]. GLP-1RAs provided similar benefits against no intervention with or without baseline SGLT2i use (HR 0.77 vs 0.78; interaction 0.95), indicating the possibility of additive protection and the futility of conducting dedicated combination trials [61].

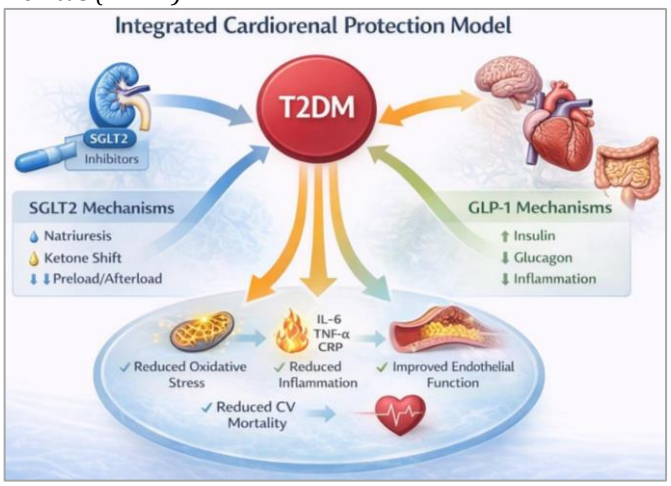
8 Translational and Clinical Implications

The change to making CVOT evidence applicable to real-life practice must be made by matching drug selection to the predominant risk phenotype instead of glycemic indicators alone. In patients with T2DM and heart failure (HF) or chronic kidney disease (CKD), SGLT2 inhibitors should receive the first priority due to their tight relation to hemodynamic and renal responses

(natriuresis/osmotic diuresis and tubule-glomerular feedback restoration). And the guideline pathways have placed SGLT2is first line in HF and CKD to limit the worsening HF and preservation of kidney function [62]. On the other hand, in individuals with proven atherosclerotic CVD or who have multiple risk factors of ASCVD, especially those with co-morbid obesity, GLP-1 receptor agonists are usually sought after due to their ability to produce glucose-reducing and appetite-mediated weight decrease and anti-atherogenic/anti-inflammatory impacts that overlay MACE and stroke-reductions [63]. In cases of residual risk (e.g., persistent albuminuria or lack of adequate metabolic control on one class), the combination therapy is supported by evidence, and subgroup analysis demonstrates GLP-1 RA-associated MACE reduction is sustained regardless of prior SGLT2i use, supporting the use of additive risk reduction in combination with awaiting specific combination trials [64]. The integrated cardiorenal protection model is shown in **Figure 6**.

Figure 6

Integrated cardiorenal protection model in type 2 diabetes mellitus (T2DM).



This diagram shows the supplementary pathways of SGLT2 inhibitors and GLP-1 receptor agonists to provide cardiovascular and renal safety in T2DM. The main effects of SGLT2 inhibitors are natriuresis, hemodynamic effects, and metabolic substrate changes, whereas the main effects of GLP-1 receptor agonists include an increase in insulin secretion, glucagon inhibition, and inflammation. These overlapping pathways lessen oxidative stress and inflammatory products, enhance endothelial activity and eventually lead to less cardiovascular morbidity and mortality.

Uptake in the real world is still low, even where outcome benefits are. The main obstacles are compensation limitations, excessive out-of-pocket expenses, and polypharmacy that may slow down the early introduction or concomitant use. To be implemented, multidisciplinary models are therefore needed; endocrinology, cardiology, nephrology co-management, pharmacist-led titration/education, and structured follow-up to minimize clinical inertia and enhance persistence. The monitoring must be informed by the mechanism [65]. In the case of SGLT2is, monitor volume status and renal function in the early stages (especially in older patients or patients taking diuretics) and offer sick-day management to prevent the risk of dehydration and ketoacidosis. In the case of GLP-1RAs, the gradual increase in dose and symptom-based treatment of gastrointestinal side effects should be applied. In both classes, outcome-based monitoring in the form of monitoring weight, blood pressure, kidney (eGFR/albuminuria), and HF symptoms should be provided, and the adequacy of therapy should be reassessed with changes in comorbidities [66].

9 FUTURE DIRECTIONS AND RESEARCH GAPS

Although the cardiovascular and cardiorenal events decreased steadily, the mechanistic, metabolic, and molecular mechanisms that mediate the benefit that is not related to glycemic control are yet to be fully defined, especially the tissue-specific mechanisms that connect kidney bioenergetics, mitochondrial functionality, the regulation of oxidative stress, and the subsequent cardiovascular events. Clinical implications of such uncertainty are that the existing evidence has no validated predictors of response (biomarkers or clinical characteristics) to define the responders, and direct rational therapy selection is an explicit impediment to the application of precision. It is suggested that further description of subcellular pathways would permit phenotypic sorting and molecular signature of phenotypes with more favorable cardio protection, and that treatment would no longer be a multifunction algorithm [67]. Simultaneously, the emergence of emerging GLP-1-based agents and formulations (with longer-acting and oral approaches) increases the requirement to comprehend how exposure pattern and target engagement are converted into vascular benefit across phenotypes.

These are the key populations that are understated: there is a deficiency of evidence in advanced CKD, dialysis, kidney transplant, and multimorbidity patients, and it is important to include such high-risk populations in trials to quantify the effectiveness and safety. Lastly, durable benefit and optimum combination and integration plans are not determined there is a lack of long-term information on safety, discontinuation consequences, and evidence-based sequencing/combination regimens [68]. Long-term comparative and combination trials are therefore necessary, especially since the present analyses specifically conclude that combination-therapy CV trials are necessary.

10 CONCLUSION

In the last 10 years, the concept of cardiovascular outcome trials has revised the approach to the management of type 2 diabetes mellitus (T2DM), changing the treatment paradigm from a direct glucose-centric approach to a cardiometabolic one based on the evidence of outcomes. Sodium glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have all shown a regular decrease in major adverse cardiovascular events (MACE), cardiovascular mortality, and cardiorenal complications in high-risk groups. Notably, these advantages are not limited to glycemic control, which means their mechanisms can use physiological and molecular pathways that are broader.

One of the initial lessons that can be made based on the evidence is the phenotype-specific potency of each drug class. SGLT2is have significant effects on heart failure hospitalization and renal outcomes by hemodynamic regulation, natriuresis, and re-establishment of tubule-glomerular feedback. GLP-1RA, on the other hand, shows stronger decreases in atherosclerotic events presumably via the anti-inflammatory, anti-oxidative, and anti-atherogenic pathways. A combination of these complementary pathways indicates a unifying framework where the two classes reduce cardiovascular risk by acting on metabolic stress, endothelial dysfunction, inflammation, and maladaptive cardiorenal interactions.

These results radically change the treatment priorities in T2DM. The HbA1c targets are no longer the only factors influencing treatment decisions, but cardiovascular and renal risk profiles must also be considered. Modern guidelines suggest that these agents should preferably be used in individuals who have already developed cardiovascular disease, heart failure, or chronic kidney disease. This is one step in the right direction of integrated cardiometabolic care, but there are still some doubts. It is still not well understood how exactly cardio protection occurs at the molecular level, the best sequencing/combination regimen, and the safety of the process in various populations in the long term. To sum up, SGLT 2 inhibitors and GLP-1 receptor agonists are all pointers of a revolutionary epoch in c care. Their inclusion in the daily practice provides them with a chance not only to manage glucose but to effectively decrease cardiovascular load, which is eventually the defining feature of the prognosis of the T2DM patients.

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