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REVIEW

Combination cardiometabolic therapy in type 2 diabetes: optimizing SGLT2 inhibitor and GLP-1 receptor agonist use

Laura R. Porterfield[1] · Saad Nadeem[2] · Dallin Swanson[3] · Salim S Hayek[4] · Elizabeth M Vaughan[4,5]

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Abstract

Purpose of review To evaluate the evidence supporting combined sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) in type 2 diabetes, focusing on cardiometabolic outcomes and practical treatment approaches.

Recent findings Cardiovascular outcomes trials and real-world studies indicate that SGLT2is and GLP-1RAs confer complementary, non-redundant cardiovascular, kidney, and metabolic benefits. SGLT2is primarily reduce hospitalization for heart failure and slow kidney disease progression, while GLP-1RAs more effectively reduce atherosclerotic events, particularly stroke; dedicated kidney-outcome and heart-failure trials of GLP-1RAs in chronic kidney disease and obesity-related heart failure with preserved ejection fraction have further broadened their role. Randomized data show that each class retains its benefit irrespective of background use of the other, supporting independent mechanisms; whether this translates into reductions in hard outcomes is being tested prospectively. Emerging evidence supports a phenotype-guided approach that aligns therapy with dominant comorbidities such as atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, and obesity.

Summary Despite advances in pharmacotherapy, substantial cardiometabolic risk remains in type 2 diabetes. Combined SGLT2i and GLP-1RA therapy addresses multiple risk domains through complementary mechanisms and may be most effective within a phenotype-guided framework. This framework prioritizes therapy according to predominant comorbidity and reserves combination treatment for individuals with overlapping high-risk phenotypes.

Keywords Diabetes · Cardiovascular disease · SGLT2 inhibitors · GLP-1 receptor agonists · Combination therapy · Kidney disease

Introduction

Cardiovascular disease (CVD) remains the leading cause of global mortality, accounting for more than 19 million deaths annually and representing a major driver of disability worldwide [1]. CVD prevalence has more than doubled during the last three decades, with the burden of CVD borne disproportionately by individuals with diabetes, who experience a two- to four-fold higher risk of cardiovascular events and mortality [1–3]. While advances in risk

✉ Elizabeth M Vaughan
emvaughan316@gmail.com

Laura R. Porterfield
lauporte@UTMB.EDU

Saad Nadeem
saadnadeem2035@gmail.com

Dallin Swanson
dalswans@utmb.edu

Salim S Hayek
sahayek@UTMB.EDU

[1] Department of Family Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, USA

[2] College of Medicine, Texas A&M. College Station, College Station, TX, USA

[3] School of Medicine, University of Texas Medical Branch, Galveston, TX, USA

[4] Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA

[5] Department of Medicine, Baylor College of Medicine, Houston, TX, USA

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factor management have contributed to substantial declines in deaths from coronary heart disease and cerebrovascular disease, heart failure (HF) has emerged as a persistent and increasingly prominent contributor to morbidity and mortality in this population [4].

Historically, cardiovascular risk reduction in diabetes has focused on control of glycemia and traditional risk factors through pharmacologic and lifestyle interventions. However, over the past decade, landmark cardiovascular outcomes trials of sodium-glucose cotransporter type 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed this paradigm [5–11]. These medications confer cardiovascular, kidney, and metabolic benefits that extend beyond glycemic control, establishing them as foundational and disease-modifying therapies for individuals with type 2 diabetes and at elevated cardiometabolic risk [7–11].

Despite these advances, most individuals do not achieve optimal cardiometabolic outcomes with monotherapy alone [12–14]. A growing body of literature, including randomized clinical trials (RCTs), meta-analyses, and guideline statements, supports the complementary mechanisms and potential benefits of combined SGLT2i and GLP-1RA therapy, yet important questions remain regarding how best to implement this strategy in clinical practice [10, 15–18].

In this review, we review the evidence supporting combined SGLT2i and GLP-1RA therapy in type 2 diabetes with a focus on cardiometabolic outcomes, and we propose a pragmatic framework for clinical use.

Complementary Mechanisms of Action

SGLT2is and GLP-1RAs lower blood glucose levels through distinct yet complementary pathways. SGLT2is reduce glucose reabsorption in the proximal renal tubule, promoting glycosuria independent of insulin. This results in modest reductions in hemoglobin A1c (HbA1c), body weight, and systolic blood pressure, largely mediated through osmotic diuresis and natriuresis [19]. In contrast, GLP-1RAs enhance incretin signaling, increasing glucose-dependent insulin secretion, suppressing glucagon, delaying gastric emptying, and promoting satiety [20]. These effects produce greater reductions in HbA1c and body weight compared with SGLT2is [19, 20].

SGLT2is and GLP-1RAs also provide cardiorenal benefits through distinct mechanisms of action [5, 6, 15, 21]. SGLT2is exert beneficial hemodynamic effects, resulting in reduced preload, afterload, and intraglomerular pressure [6, 21]. Accordingly, SGLT2is significantly reduce the risk of HF hospitalization and slow chronic kidney disease (CKD) progression [6, 21–23]. In contrast, GLP-1RAs exert antiatherogenic and anti-inflammatory effects that promote plaque stabilization and reduce major adverse cardiovascular events (MACE), with the most pronounced effect on ischemic stroke [5, 15, 22, 24]. The two classes diverge with respect to atherothrombotic events: GLP-1RAs modestly reduce myocardial infarction in addition to stroke, whereas the SGLT2i MACE benefit is driven predominantly by reductions in cardiovascular death rather than myocardial infarction [5, 15]. Their complementary mechanisms therefore provide a strong biological rationale for combination therapy in cardiometabolic risk reduction (Table 1, Supplemental Figure).

Table 1 Overview of SGLT2 Inhibitors and GLP-1 Receptor Agonists

Domain	SGLT2 Inhibitors	GLP-1 Receptor Agonists
Mechanism	Block SGLT2 in proximal tubule; insulin-independent glycosuria; natriuresis; reduced preload, afterload, and intraglomerular pressure [6, 21]	Augment incretin signaling; glucose-dependent insulin secretion; suppress glucagon; delay gastric emptying; increase central satiety; anti-inflammatory and anti-atherogenic effects [5, 15, 22]
HbA1c reduction	0.5–0.8% [19]	0.5–1.5% (agent-dependent) [20]
Body weight	↓ 1.0–2.8 kg [19]	↓ 2–5 kg (greater reduction with high-dose semaglutide/tirzepatide*) [20]
Blood pressure	↓ SBP 2–4 mmHg (osmotic diuresis) [19]	↓ SBP 2–6 mmHg [20]
MACE	Modest reduction; class effect ~ 10–11% [23]	Robust ~ 14–21% reduction; strongest effect on stroke [5, 12, 13, 24]
Hospitalization for heart failure	Strong reduction (↓ ~29%) [6, 22, 23]	Modest effect [24]
Kidney outcomes	↓ ~33% in CKD progression; slows eGFR decline; reduces major kidney endpoints [21–23, 30]	↓ albuminuria; ~17–21% reduction in composite kidney outcome (driven by albuminuria) [24]
Common adverse effects	Genital infections; volume depletion; transient eGFR dip [28, 30]	Gastrointestinal intolerance; injection site reactions [15, 28, 29]
Serious adverse effects	Rare euglycemic diabetic ketoacidosis; Fournier gangrene (rare) [28, 30]	Cholelithiasis; pancreatitis (rare); diabetic retinopathy progression (semaglutide); contraindicated in individuals with MTC or MEN2 [15, 28, 29]

CKD, chronic kidney disease, CV cardiovascular, eGFR estimated glomerular filtration rate, GLP-1 glucagon-like peptide-1, HbA1c hemoglobin, A1c HF heart failure, MACE major adverse cardiovascular events, MEN2 multiple endocrine neoplasia type 2, MI myocardial infarction, MTC medullary thyroid carcinoma, SBP systolic blood pressure, SGLT2i sodium-glucose cotransporter 2 inhibitor

* Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist

It is worth noting that the GLP-1RA class is pharmacologically heterogeneous. The cardiovascular benefit is most consistent for the long-acting agents (liraglutide, injectable and oral semaglutide, and dulaglutide), whereas exendin-based and shorter-acting agents (lixisenatide, once-weekly exenatide) were largely neutral on MACE in dedicated outcomes trials [25]. This distinction is relevant when extrapolating metabolic data from combination trials that used agents without an individual cardiovascular outcomes signal.

Safety Profile of Combination Therapy

The safety profile of combined SGLT2i and GLP-1RA therapy is broadly consistent with the known adverse effects of each class, without evidence of novel or synergistic toxicity [11, 26–30]. Current evidence suggests that combination therapy is not associated with an increased risk of adverse events compared with monotherapy [26, 27], although patients remain susceptible to the characteristic drug-specific side effects of each medication class. Gastrointestinal symptoms, including nausea, vomiting, and diarrhea, are more commonly observed with GLP-1RAs, particularly during dose escalation [28, 29]. Similarly, the incidence of genital mycotic infections and volume depletion reflect established effects of SGLT2is [28]. Hypoglycemia risk remains low overall but may be increased when these medications are used in combination with insulin or sulfonylureas [26–29]. Notably, large meta-analyses and collaborative trial datasets have demonstrated no excess risk of severe hypoglycemia, major adverse events, or treatment discontinuation with combination therapy compared with either class alone [11, 28–30], supporting the safety and tolerability of combined use in diverse populations.

Clinicians should remain vigilant for class-specific adverse effects, including rare but serious complications such as euglycemic diabetic ketoacidosis with SGLT2is and gallbladder disease or pancreatitis with GLP-1RAs [11, 15]. Careful patient selection, counseling, and monitoring are essential to optimize tolerability and adherence.

Surrogate Cardiometabolic Endpoints

RCTs consistently demonstrate that combined SGLT2i and GLP-1RA therapy provides benefits in glycemic control, body weight, and blood pressure compared with either medication alone. DURATION-8, the first study to evaluate the effects of combination therapy, showed that co-initiation of exenatide and dapagliflozin resulted in greater reductions in HbA1c, weight, and systolic blood pressure than monotherapy, with benefits sustained over long-term follow-up [26, 27]. Subsequent trials, including AWARD-10 and SUSTAIN-9, further confirmed the efficacy of intensification strategies, demonstrating meaningful improvements in glycemic control and body weight when one class is added to the other [31, 32].

Meta-analyses have reinforced reductions in HbA1c, body weight, and systolic blood pressure with combination therapy, along with a higher likelihood of achieving glycemic targets without an increase in severe hypoglycemia [28, 33, 34]. Although the magnitude of glycemic and weight benefits may attenuate modestly over time, the overall pattern supports complementary and clinically meaningful metabolic effects. A Cochrane network meta-analysis protocol has been registered to formally synthesize these comparisons, although completed pooled estimates are not yet available [35].

Cardiovascular and Kidney Outcomes

No dedicated prospective RCT has yet been powered to compare combined SGLT2i and GLP-1RA therapy versus monotherapy for cardiovascular and kidney endpoints, although the ongoing PRECIDENTD trial is expected to address this gap [36]. Nevertheless, accumulating evidence from subgroup analyses of cardiovascular outcomes trials and large observational studies supports the concept of complementary, and potentially complementary, cardiorenal benefit when both medication classes are used together.

The most rigorous evidence comes from RCT analyses showing that the benefit of each class is preserved irrespective of background use of the other. In the SMART-C consortium meta-analysis, SGLT2i use reduced major cardiovascular and kidney outcomes consistently regardless of baseline GLP-1RA use [30]. Similarly, analyses of GLP-1RA cardiovascular outcomes trials demonstrate preserved reductions in MACE and kidney outcomes irrespective of concomitant SGLT2i therapy [15, 16]. This consistency, together with non-overlapping mechanisms, indicates that the two classes act independently rather than redundantly. Importantly, the absence of statistical interaction establishes that benefit is *retained* in combination; it does not by itself prove that the absolute benefits *sum* on hard outcomes, which remains to be confirmed prospectively.

Real-world evidence is consistent with benefit in routine practice. Observational cohort studies have reported lower risk of MACE, HF hospitalization, and serious kidney outcomes with combination therapy compared with either class alone [37]. Large meta-analyses of observational data similarly suggest substantial reductions in cardiovascular events, mortality, and kidney outcomes with dual therapy [11, 16]. However, the magnitude of some of these observational estimates (for example, relative reductions in cardiovascular or all-cause mortality exceeding 50%) is considerably larger

than would be predicted from the randomized effect sizes of either class and is almost certainly inflated by residual and time-related confounding, including healthy-adherer and prevalent-user biases. These data should therefore be interpreted as hypothesis-generating, with the randomized "no-heterogeneity" findings providing the firmer basis for combining the classes.

Clinical Implications and Remaining Gaps

Modeling studies suggest that the cumulative impact of combination therapy may be substantial, with meaningful gains in cardiovascular and kidney event-free survival when implemented early in high-risk populations [38]. However, these projections rely on assumptions regarding complementary effects and require prospective validation.

Collectively, current evidence from RCT subgroups, observational studies, and mechanistic data supports the biological plausibility and clinical relevance of complementary cardiovascular and kidney benefits with combined SGLT2i and GLP-1RA therapy (Table 2). Contemporary guidelines increasingly reflect this paradigm. For example, the 2026 American Diabetes Association (ADA) Standards of Care note that combination therapy may be considered to achieve complementary cardiovascular and kidney benefits that are largely independent of glycemic control [39].

Table 2 Major studies of SGLT2i and GLP-1RA combination therapy

Study	Design	Population	Main results
Frías, 2016 [26, 27] (DURATION-8)	Phase 3 RCT, 28-, 52-, and 104-wk	695 adults with T2D uncontrolled receiving metformin	Exenatide plus dapagliflozin produced greater reductions in HbA1c (−2.0% vs. −1.6% and −1.4%), weight (−3.4 vs. −2.2 and −1.5 kg), and SBP (−4.6 vs. −1.3 and −1.8 mmHg) than either monotherapy at 28 wk; benefits sustained at 104 wk; well tolerated, no major hypoglycemia
Ludvik, 2018 [31] (AWARD-10)	Phase 3 RCT, 24-wk	424 adults with T2D receiving SGLT2is ± metformin	Dulaglutide added to SGLT2is produced significant additional reductions in HbA1c (−1.34% vs. −0.54% with placebo) and body weight; consistent with sequential addition strategy
Zinman, 2019 [32] (SUSTAIN-9)	Phase 3 RCT, 30-wk	302 adults with T2D inadequately controlled receiving SGLT2is	Semaglutide added to SGLT2is reduced HbA1c by 1.5% (vs. 0.1% placebo) and weight by 4.7 kg (vs. 0.9 kg); confirmed the efficacy of GLP-1RA add-on to SGLT2is
Castellana, 2019 [28]	Meta-analysis (4 RCTs)	1,610 adults with inadequately controlled T2D randomized to SGLT2i vs. SGLT2i + GLP-1RA	GLP-1RAs plus SGLT2i vs. SGLT2i alone: ↓ HbA1c −0.74%, ↓ weight −1.61 kg, ↓ SBP −3.32 mmHg; >2× more achieved HbA1c < 7% (RR 2.15); no excess hypoglycemia
Apperloo, 2024 [30] (SMART-C)	Collaborative meta-analysis (12 RCTs)	73,238 with T2D; 3,065 receiving baseline GLP-1RA	SGLT2is benefits on MACE, HF hospitalization or CV death, CKD progression, and eGFR slope were consistent regardless of baseline GLP-1RA use (all P-heterogeneity > 0.10); supports independent, complementary effects
Neuen, 2024 [15]	Meta-analysis (3 RCTs)	17,072 with T2D; 1,743 receiving baseline SGLT2i	GLP-1RAs reduced MACE by 21% (HR 0.79), hospitalization for HF 27–42% (HR 0.58 with SGLT2is; 0.73 without), composite kidney outcome 21% (RR 0.79); effects consistent with and without SGLT2is (all P-heterogeneity > 0.25)
Simms-Williams, 2024 [37]	Population-based cohort	15,638 matched participants (CPRD, UK)	Combination vs. GLP-1RAs: ↓ MACE 30% (HR 0.70), ↓ serious kidney events 57% (HR 0.43); combination vs. SGLT2is: ↓ MACE 29% (HR 0.71); supports complementary cardiorenal protection in real-world practice
Colombijn, 2025 [11]	Systematic review and meta-analysis (18 cohort studies)	1,164,774 participants	Combination vs. monotherapy: ↓ MACE (RR 0.56), ↓ all-cause mortality (RR 0.50), ↓ CV mortality (RR 0.26), ↓ HHF (RR 0.67), ↓ kidney composite (RR 0.48); no excess severe hypoglycemia, DKA, or genitourinary infections
Shokravi, 2025 [16]	Systematic review and meta-analysis (10 observational studies and 4 RCT analyses)	Multiple cohorts; >1 million combined participants	Combination significantly reduced MACE, MI, stroke, all-cause mortality, and HHF vs. monotherapy in observational data; no significant interaction across CV/kidney endpoints in RCT post hoc analyses, supporting independence of class effects
Wexler, 2026 [36] (PRECIDENTD)	Pragmatic RCT	T2D with ASCVD or high ASCVD risk	The first dedicated randomized comparison of combined SGLT2i plus GLP-1RA therapy vs. monotherapy on hard cardiovascular and kidney endpoints; feasibility data published 2025

ASCVD, atherosclerotic cardiovascular disease CI confidence interval, CKD, chronic kidney disease, CPRD Clinical Practice Research Datalink, CV cardiovascular, DKA diabetic ketoacidosis, eGFR estimated glomerular filtration rate, GLP-1RA glucagon-like peptide-1 receptor agonist, GU genitourinary, HbA1c hemoglobin A1c, HF heart failure, HHF hospitalization for heart failure, HR hazard ratio, MACE major adverse cardiovascular events, MI myocardial infarction, RCT randomized controlled trial, RR relative risk, SBP systolic blood pressure, SGLT2i sodium-glucose cotransporter 2 inhibitor, T2D type 2 diabetes, UK United Kingdom, wk week(s)

A dedicated outcomes RCT is needed to confirm whether these complementary effects translate into complementary and non-redundant reductions in hard endpoints.

Phenotype-Guided Therapy

The emergence of SGLT2is and GLP-1RAs as disease-modifying therapies has shifted treatment paradigms in T2D toward phenotype-guided treatment strategies. Rather than prioritizing glycemic control alone, therapeutic decisions are increasingly guided by dominant cardiometabolic risk, including atherosclerotic cardiovascular disease (ASCVD), HF, CKD, and obesity. Importantly, these phenotypes frequently coexist, so that many high-risk patients qualify for both classes, necessitating integrated and often combination-based treatment strategies (Fig. 1).

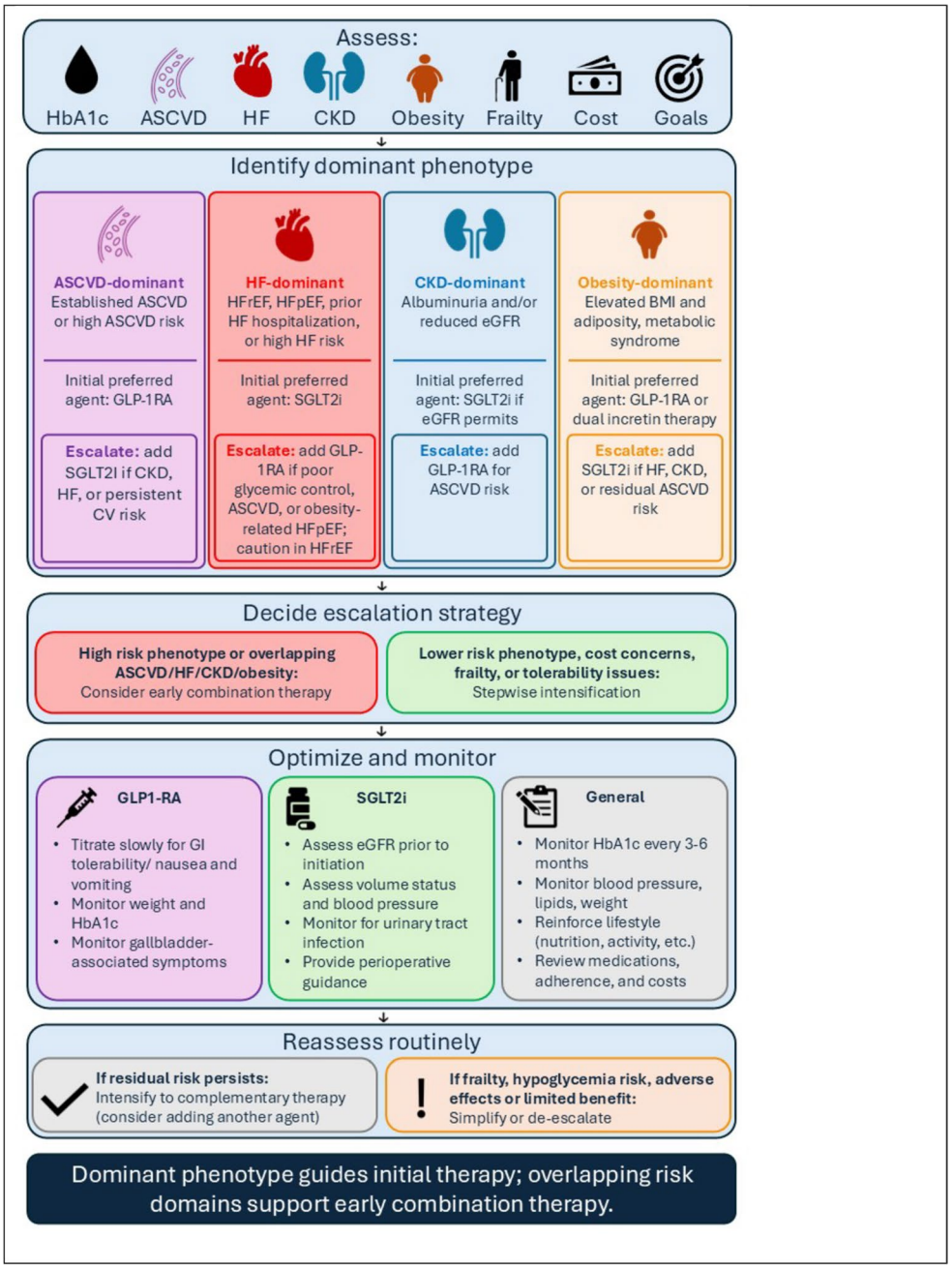

Fig. 1 Phenotype-guided algorithm for initiating and optimizing SGLT2i and GLP-1RA combination therapy in type 2 diabetes

Note. ASCVD atherosclerotic cardiovascular disease, BMI body mass index, CKD chronic kidney disease, CV cardiovascular, eGFR estimated glomerular filtration rate, GLP-1RA, glucagon-like peptide-1 receptor agonists, HbA1c hemoglobin A1c, HF heart failure, HFrEF heart failure with reduced ejection fraction, HFpEF heart failure with preserved ejection fraction, SGLT2i sodium-glucose cotransporter 2 inhibitors

ASCVD-Dominant Phenotype

In individuals with established ASCVD or high atherosclerotic risk, GLP-1RAs are generally prioritized. Cardiovascular outcomes trials and meta-analyses consistently demonstrate reductions in MACE, with particularly robust effects on stroke [5, 12, 13]. Benefits appear consistent across a broad range of subgroups, including those with varying levels of glycemic control and kidney function. The favorable cardiovascular profile of the GLP-1RA class was reinforced by SURPASS-CVOT, in which the dual GIP/GLP-1 receptor agonist tirzepatide was noninferior to dulaglutide, an agent with established cardiovascular benefit, for three-point MACE in patients with type 2 diabetes and ASCVD [40].

Real-world data suggest that GLP-1RAs may confer greater absolute reductions in atherosclerotic events compared with SGLT2is in high-risk populations, supporting preferential use when ASCVD predominates [5, 12, 13]. In individuals with overlapping HF or CKD, combination therapy should be strongly considered [6, 14, 41, 42].

Heart Failure-Dominant Phenotype

SGLT2is are foundational in individuals with HF-dominant disease, regardless of diabetes status or ejection fraction. Across large RCTs and meta-analyses, these medications consistently reduce hospitalization for HF across the ejection fraction spectrum, with reductions in cardiovascular death and all-cause mortality most firmly established in HFrEF (and in chronic kidney disease and atherosclerotic disease) [6, 14, 41, 42]. Benefits are observed across the spectrum of cardiometabolic disease, including individuals with type 2 diabetes, CKD, and ASCVD [6, 14, 41, 42]. These findings establish SGLT2is as first-line therapy in HF-dominant phenotypes.

The role of GLP-1RAs in HF is more nuanced and depends on phenotype. In obesity-related HF with preserved ejection fraction (HFpEF), incretin-based therapy improves symptoms, physical function, and weight: semaglutide improved Kansas City Cardiomyopathy Questionnaire scores and exercise capacity in patients with and without diabetes in the STEP-HFpEF and STEP-HFpEF DM trials [43, 44], and tirzepatide reduced a composite of cardiovascular death or worsening HF, primarily driven by fewer HF events, in SUMMIT [45]. GLP-1RAs are therefore reasonable additions in HFpEF with coexisting obesity, ASCVD, or poor glycemic control. By contrast, GLP-1RAs have not shown benefit in randomized trials of HF with reduced ejection fraction (HFrEF); however, available evidence is limited to liraglutide. In the FIGHT trial of liraglutide in advanced HFrEF, the primary endpoint was neutral, with numerically more heart-failure events observed in the liraglutide group [46]. In the LIVE trial of liraglutide in stable chronic HF, left ventricular function did not improve, heart rate increased, and serious cardiac adverse events were more frequent [47]. GLP-1RAs should therefore be used cautiously for the HFrEF phenotype, with decisions driven primarily by coexisting ASCVD, obesity, or HFpEF rather than by HFrEF itself.

CKD-Dominant Phenotype

In individuals with CKD, SGLT2is provide robust kidney protection, including slowing of eGFR decline and reduction in progression to end-stage kidney disease and other adverse kidney outcomes [41]. These effects extend across a broad range of kidney function and are particularly pronounced in high-risk cardiorenal populations. GLP-1RAs also confer kidney benefits. Once considered to act primarily through reductions in albuminuria, GLP-1RAs now have dedicated hard-endpoint evidence: in the FLOW trial, semaglutide reduced the primary composite kidney outcome (≥ 50% eGFR decline, kidney failure, or kidney or cardiovascular death) by 24% (hazard ratio 0.76, 95% CI 0.66–0.88) in type 2 diabetes and CKD and slowed eGFR decline [48, 49]. A prespecified analysis found the kidney effect to be directionally consistent regardless of baseline SGLT2i use, with no significant treatment-by-subgroup interaction, although only a small minority of participants were taking an SGLT2i at entry, so the combination subgroup was underpowered and does not by itself establish additive benefit. GLP-1RAs are thus valuable for kidney protection and are particularly attractive in CKD with coexisting ASCVD or obesity [7].

Obesity-Dominant Phenotype

GLP-1RAs play a central role in individuals with obesity, producing clinically meaningful and sustained weight loss along with reductions in cardiovascular risk [50]. Recent trial data demonstrate that these benefits extend to individuals without diabetes, underscoring their role as cardiometabolic therapies rather than purely glucose-lowering medications [50, 51]. Dual incretin agonists achieve greater weight reduction than GLP-1RAs alone, and tirzepatide has now demonstrated cardiovascular safety noninferior to a proven GLP-1RA in patients with ASCVD as well as benefit in obesity-related HFpEF [40, 45]. Dedicated placebo-controlled cardiovascular and kidney outcomes data for this class continue to accrue and will further define its place within phenotype-guided strategies [52].

Clinical Implementation

Disease stage further informs clinical decision-making. Earlier initiation of SGLT2is or GLP-1RAs may provide cardiometabolic protection before the development of advanced disease, whereas longer-standing disease often necessitates combination therapy due to progressive β-cell dysfunction and accumulated risk [8]. Notably, substantial residual cardiovascular risk persists despite therapy with either class alone, reinforcing the rationale for combination therapy, particularly in individuals with established ASCVD, HF, CKD, or overlapping risk domains [11, 16, 17, 38].

In clinical practice, optimization of therapy requires balancing early combination strategies with stepwise intensification. Early combination therapy enables faster glycemic control and earlier exposure to cardiovascular and kidney-protective effects, consistent with a disease-modifying approach [8]. Stepwise escalation remains appropriate in lower-risk individuals or when cost and tolerability are limiting factors. These tradeoffs are not merely theoretical: in the pilot phase of the PRECIDENTD pragmatic trial, participants assigned to dual therapy had substantially lower medication fill rates and higher discontinuation than those on monotherapy, driven largely by side effects, cost, and access [36]. Combining two branded agents also roughly doubles drug cost, frequently exceeding USD 1,000 per month in the United States, and the cost-effectiveness of routine dual therapy remains undefined pending outcomes data [53].

Within-class differences further inform selection, as GLP-1RAs are more strongly associated with reductions in atherosclerotic events, while SGLT2is demonstrate greater benefit in HF and kidney outcomes, with modest blood pressure-lowering effects that may contribute to cardiovascular risk reduction [9]. Practical considerations also differ, with GLP-1RAs requiring gradual titration to mitigate gastrointestinal adverse effects, while SGLT2is are typically initiated at therapeutic doses with dose adjustment as needed based on kidney function.

Special Populations and Implementation Gaps

In older or frail individuals, treatment burden, tolerability, and goals of care should be considered, but age or frailty alone should not preclude therapy. Absolute benefit from GLP-1RAs and SGLT2is appears greatest in these populations, with larger reductions in cardiovascular events observed among frail individuals [54]. Available data support the safety and efficacy of both classes even in individuals of very advanced age [54, 55].

Despite strong evidence supporting these therapies, real-world implementation remains limited, particularly among high-risk populations, with only 7–13% of individuals with type 2 diabetes receiving GLP-1RA or SGLT2i therapy [56–58]. Use of GLP-1RAs and SGLT2is is influenced by cost, insurance coverage, access to care, and structural barriers, with lower use observed among socioeconomically disadvantaged individuals and racial and ethnic minority groups [56, 59, 60]. This highlights a critical gap between clinical efficacy and real-world effectiveness. Addressing this gap will require system-level interventions, including improved affordability, formulary access, and care delivery models that support equitable implementation.

Future Directions

Important knowledge gaps remain. Dedicated RCT data evaluating combination therapy on hard cardiovascular and kidney endpoints are limited, and optimal sequencing strategies have not been definitively established; PRECIDENTD is expected to provide the first randomized evidence [36]. In addition, the role of emerging dual incretin therapies in cardiometabolic care requires further investigation, particularly regarding their cardiovascular and kidney benefits and their use alongside SGLT2is. Evidence is also sparse in advanced CKD, distinct HF phenotypes, and adults over 80 years [61–63]. Future research should prioritize pragmatic trials, comparative effectiveness studies, and precision medicine approaches to identify individuals most likely to benefit from specific therapeutic combinations.

Conclusions

Combination therapy with SGLT2is and GLP-1RAs represents a major advance in the management of type 2 diabetes, targeting residual cardiometabolic risk through complementary mechanisms. Together, these medications provide an integrated strategy to address ASCVD, HF, CKD, and obesity. In clinical practice, treatment may be guided by dominant cardiometabolic phenotype, with early combination therapy considered in individuals at high risk or with overlapping disease domains. Stepwise intensification remains appropriate in lower-risk individuals or when cost and tolerability limit use. Successful implementation requires attention to individual preferences, access, and adherence, as well as proactive management of class-specific adverse effects.

Despite strong evidence, important gaps remain. Randomized data on combination therapy for hard cardiovascular and kidney outcomes are still limited, and the extent to which the complementary benefits of the two classes are truly additive on these endpoints awaits prospective confirmation. Moreover, the potential population-level impact of these therapies will remain constrained without addressing

substantial disparities in access. Equitable access remains a critical challenge. Use of these therapies is lower among socioeconomically disadvantaged and minoritized populations, largely due to cost and structural barriers. Addressing these disparities through improved affordability, access, and care delivery models will be essential to realize their full population-level benefit. Improving affordability, expanding equitable access, and developing care delivery models that support appropriate implementation will be essential to ensure that advances in cardiometabolic therapy translate into meaningful reductions in population-level disease burden rather than primarily benefiting those with greater resources.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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