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Rapid Review

Advances in Type 2 Diabetes Management: A Rapid Review of Sglt2 Inhibitors and Glp-1 Receptor Agonists

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Abstract

Introduction: Type 2 diabetes mellitus (T2D) is a multifaceted metabolic disorder associated with significant morbidity and mortality due to complications like cardiovascular disease (CVD) and chronic kidney disease (CKD). Recent advances in pharmacotherapy, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have revolutionized diabetes care. These agents offer dual benefits: glycemic control and cardiorenal protection. SGLT2 inhibitors promote renal glucose excretion, reducing HbA1c levels and demonstrating significant nephroprotective and heart failure benefits. GLP-1 receptor agonists enhance insulin secretion and appetite suppression, yielding substantial glycemic improvement and weight reduction.

Methods: This rapid review synthesizes data from 24 randomized clinical trials conducted between 2020 and 2024, involving over 61,000 participants.

Results: The findings underscore the efficacy of both drug classes, with GLP-1 agonists achieving superior HbA1c reductions (up to 1.7%) and weight loss (up to 9.6%), while SGLT2 inhibitors excel in reducing CKD progression and heart failure hospitalizations. Combination therapies demonstrate synergistic benefits, further advancing treatment outcomes.

Conclusion: Despite these advances, questions remain regarding their differential efficacy across diverse subgroups, long-term outcomes, and optimal integration into clinical practice. Addressing these gaps through personalized treatment approaches and extended trials is essential. This review highlights the transformative potential of these therapies, emphasizing their role in holistic diabetes management.

Keywords: Diabetes Mellitus, Type 2, Sodium-Glucose Transporter 2 Inhibitors, Glucagon-Like Peptide-1 Receptor Agonists, Glycemic Control, Diabetic Nephropathies, Drug Therapy, Treatment Outcome

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Introduction

Type 2 diabetes (T2D) is a complex metabolic disorder affecting millions of people globally, and its prevalence is projected to increase substantially in the coming decades.[1] The condition arises from chronic hyperglycemia caused by impaired insulin secretion, insulin resistance, or a combination of both.[2,3] These metabolic disturbances trigger systemic inflammation, oxidative stress, and endothelial dysfunction, which collectively drives the development of complications such as cardiovascular disease (CVD), chronic kidney disease, and obesity-related morbidity.[4-6]

The management of T2D traditionally involves a stepwise approach, beginning with lifestyle modifications (e.g., dietary changes, physical activity, and weight management) and first-line pharmacotherapy such as metformin, which improves insulin sensitivity.[7] Additional therapies include sulfonylureas (e.g., glimepiride), dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin), thiazolidinediones (e.g., pioglitazone), and insulin for advanced disease.[8] However, advances in pharmacotherapy have introduced novel classes of glucose-lowering agents, notably sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.[9, 10] SGLT2 inhibitors reduce blood glucose by promoting renal glucose excretion,[11] while GLP-1 receptor agonists enhance insulin secretion and suppress appetite, contributing to weight loss.[12] Unlike traditional therapies (e.g., sulfonylureas, insulin), which primarily target glycemic control, these agents offer dual benefits: glucose-lowering alongside cardiorenal protection. SGLT2 inhibitors reduce cardiovascular mortality and slow kidney disease progression, while GLP-1 agonists lower HbA1c with concurrent weight loss and atherosclerotic risk reduction—effects not observed with older drug classes.[9]

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Evidence from recent cardiovascular outcome trials (CVOTs) underscores their transformative potential. For instance, meta-analyses reveal that SGLT2 inhibitors reduce major adverse cardiovascular events (MACE) by approximately 13%, while GLP-1 receptor agonists achieve a comparable reduction of 15% (relative risk reductions) in patients with established CVD or at high risk.[13, 14] These findings are bolstered by their positive effects on heart failure hospitalization and renal outcomes (e.g., SGLT2 inhibitors reduce HF hospitalizations by ~30%),[15] with SGLT2 inhibitors particularly excelling in reducing progression to end-stage kidney disease (ESKD) by 40% and albuminuria by 35%.[16] Additionally, combination therapy with these agents shows synergistic benefits, further reducing cardiovascular and renal risks compared to monotherapy alone.[17,18]

Despite these advances, critical gaps persist. First, differential efficacy across subgroups—such as elderly patients (≥75 years), ethnic minorities (e.g., Black and Hispanic populations), or those with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2)—remains underexplored, with trials often underrepresenting these populations.[9,17,19] Second, real-world evidence on long-term safety (>5 years) and cost-effectiveness is limited, hindering optimal integration into routine care due to barriers like clinician hesitancy, guideline inconsistencies, and socioeconomic disparities in access.[20] Finally, guidance on combining SGLT2 inhibitors and GLP-1 agonists for synergistic benefits requires further refinement.[9, 21]

This review aims to synthesize findings from clinical trials conducted over the past five years, exploring the efficacy, safety, and broader implications of SGLT2 inhibitors and GLP-1 receptor agonists in the management of T2D. By evaluating the latest evidence, this work seeks to provide a comprehensive overview of their roles in advancing diabetes care and addressing its multifaceted challenges.

Methods

Protocol and Registration

Due to the accelerated timeline and the specific nature of this rapid review, a formal protocol was not prospectively registered in the PROSPERO database. However, the review process was conducted with strict adherence to established methodological recommendations for rapid reviews.

Literature Search Strategy

A rapid literature search was conducted using PubMed, Scopus, Web of Science and gray literature covering studies published between January 2020, and December 2024. Boolean operators (AND/OR) were consistently applied across both databases to combine Medical Subject Headings (MeSH) terms and keywords.

Search Terms:

("Type 2 Diabetes Mellitus"[MeSH] OR "Diabetes Mellitus, Type 2"[Title/Abstract]) AND

(SGLT2 Inhibitors [MeSH] OR "sodium-glucose transport proteins"[MeSH] OR "dapagliflozin"[Title/Abstract] OR "empagliflozin"[Title/Abstract] OR "canagliflozin"[Title/Abstract]) AND

(GLP-1 Receptor Agonists [MeSH] OR "Glucagon-Like Peptide 1"[Title/Abstract] OR "semaglutide"[Title/Abstract] OR "dulaglutide"[Title/Abstract] OR "liraglutide"[Title/Abstract])

The search syntax was adapted to each database's requirements (e.g., field tags like [MeSH] in PubMed), but the Boolean logic remained identical to ensure consistency.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Study Type:
- Randomized clinical trials
- Published between 2020 and 2024
2. Population:
- Adult patients with type 2 diabetes mellitus
- Ages 18 and above
- Confirmed diagnosis of type 2 diabetes
3. Intervention:
- Studies involving SGLT2 inhibitors
- Studies involving GLP-1 receptor agonists
- Comparative studies between these drug classes
4. Language:
- Full-text articles published in English

Exclusion Criteria

1. Study Type:
- Observational studies
- Case reports
- Systematic reviews
- Meta-analyses
- Conference abstracts
- Animal studies
2. Population:
- Studies focusing on type 1 diabetes
- Pediatric populations (unless specifically noted)
- Patients with significant comorbidities preventing drug intervention (e.g., advanced liver disease [Child-Pugh Class C], terminal illness with life expectancy < 6 months, or severe psychiatric disorders impairing adherence)
3. Intervention:
- Studies not directly examining glycemic control
- Incomplete or insufficient data reporting (e.g., missing standard deviations, unclear endpoints).
- Studies with methodological limitations preventing accurate data extraction (e.g., lack of control groups, high attrition rates > 30%, inadequate randomization, unblinded design without justification, or insufficient statistical power).
- Study characteristics (author, publication year, sample size)
- Patient demographics
- Intervention details

- Primary and secondary outcomes
- Glycemic control measurements
- Cardiovascular and renal outcomes
- Safety profiles
- Adverse events

Statistical Considerations While a formal meta-analysis was not conducted, a comprehensive narrative synthesis was performed. Comparative analyses focused on consistent reporting metrics

Assessment of Bias

The methodological quality and risk of bias of the included randomized controlled trials (RCTs) were formally evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool.[22] The assessment covered five core methodological domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each trial was subsequently categorized as having a "low risk of bias," "some concerns," or a "high risk of bias." To maintain the accelerated timeline of this rapid review while ensuring rigor, the quality assessment was performed by one experienced reviewer.

Results

Study Selection Process

The initial comprehensive database search across PubMed, Scopus, Web of Science (WoS), and grey literature sources yielded a total of 409 potential records. After removing 106 duplicates using EndNote 21, 303 unique studies underwent rigorous title and abstract screening. Of these, 245 records were excluded due to irrelevance to the core study objectives, non-human experimental designs, or focus on unrelated therapeutic agents. A subsequent full-text review was conducted on the remaining 58 articles to evaluate detailed eligibility. During this stage, 34 studies were excluded with specific clinical and methodological reasons: 16 were observational or non-randomized designs, 11 lacked the predefined primary cardiorenal or glycemic outcomes, and 7. Ultimately, 24 clinical trials met all strict predetermined inclusion criteria and were included in the final review. The updated and completed PRISMA 2020 flow diagram has been formally integrated into the manuscript as Figure 1 to illustrate this selection hierarchy visually. EndNote 21 was utilized to organize references, track screening decisions, and manage citations throughout the process.

Literature Search and Study Characteristics

Our literature review encompassed 24 clinical trials published between 2020 and 2024, investigating the efficacy of SGLT2 inhibitors and GLP-1 agonists in the management of type 2 diabetes mellitus (T2D).[23-46] The cumulative study population totaled 61,430 patients, with individual study sample sizes ranging from 36 to 17,160

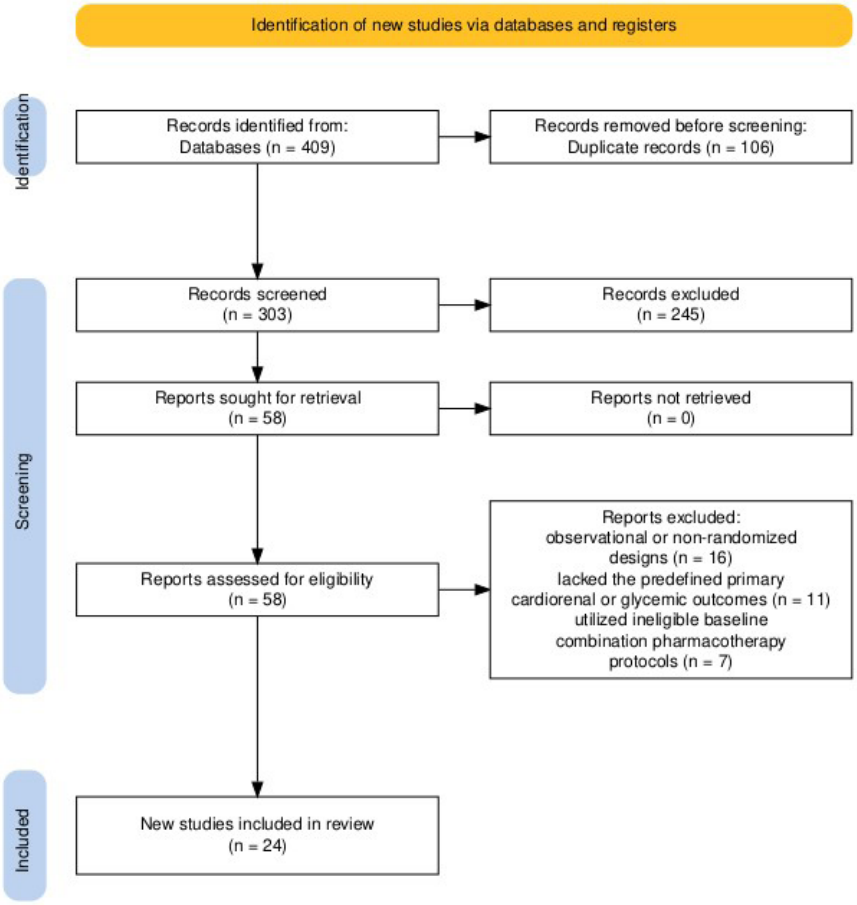


Figure 1. PRISMA flow diagram

participants. The mean age across studies was consistently between 57-68 years, with a predominant age range of 40-75 years. Patient characteristics were remarkably uniform, with mean body mass index (BMI) ranging from 26-35 kg/m², and diabetes duration typically between 3 months to 16 years. Notably, approximately 65% of participants were male, and the majority had additional comorbidities including hypertension, chronic kidney disease, or established cardiovascular risk factors. HbA1c levels at baseline were predominantly between 6.5% and 12%, representing patients with varying degrees of glycemic control (Figure 2).

Geographical Diversity of Included Studies

The 24 studies spanned multinational collaborations (e.g., North America, Europe, Asia, Australia) and single-country trials (e.g., Germany, Japan, China, Denmark) (Supplementary file, Table S1). Key highlights include:

1. Multinational Representation:
- 12 studies involved multinational cohorts, ensuring global applicability.
- Regions included high-income (e.g., USA, EU nations) and middle-income countries (e.g., Mexico, Russia).

2. Regional Focus:
- Asia: Trials in Japan [44] and China [39] highlighted region-specific efficacy and safety profiles.
- Europe: Studies from Germany,[38] Scotland,[29] and Sweden [43] contributed insights into metabolic and cardiorenal outcomes.
- North America: U.S.-based trials [24, 30] emphasized real-world applicability in diverse populations.

The following section synthesizes key findings across four domains: (1) glycemic control, (2) weight management and metabolic effects, (3) cardiovascular and renal outcomes, and (4) safety profiles of SGLT2 inhibitors and GLP-1 receptor agonists. Emerging insights into combination therapies and unique benefits (e.g., cognitive effects) are also discussed.

Risk of Bias

The methodological quality of the 24 included randomized clinical trials was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool across five domains: randomization process (D1), deviations from intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4), and selection of the reported result (D5). Study-level evaluations are mapped in the traffic light plot (Figure 3), and aggregated domain-level scores are summarized in the summary plot (Figure 4).

Overall, the included trials demonstrated high methodological rigor. Sixteen trials (66.7%) were judged to have a "Low" overall risk of bias, while eight trials (33.3%) raised "Some concerns" (Figures 3, 4). Notably, no trial was classified as having a "High" overall risk of bias.

- Domain 1 (Randomization Process): All 24 trials (100.0%) were rated as low risk. The studies universally utilized centralized interactive web- or voice-response systems (IXRS) to guarantee robust allocation concealment, resulting in well-balanced baseline demographics (Figure 4).
- Domain 2 (Deviations from Intended Interventions): The majority of trials (21 of 24; 87.5%) carried a low risk of bias due to strict double-blind architectures utilizing matching placebos. Three trials (Ali 2020, Yabe 2020, and Open-Label Trial 2024) raised "Some concerns" due to their open-label designs, which introduced a minor vulnerability to performance bias (Figure 3).
- Domain 3 (Missing Outcome Data): Attrition bias was absent across all 24 trials (100.0% low risk). Missing data points were minimal, balanced across comparative arms, and appropriately addressed using modern statistical estimands or mixed-effects models for repeated measures (Figure 4).
- Domain 4 (Measurement of the Outcome): All 24 trials (100.0%) demonstrated a low risk of bias. Primary efficacy and safety parameters (e.g., HbA1c, body weight, and cardiorenal endpoints) were assessed via automated central laboratories or objective, standardized criteria, insulating the results from assessor bias.
- Domain 5 (Selection of Reported Result): Sixteen trials (66.7%) were judged to be at low risk of bias. The remaining eight trials raised "Some concerns" (Figure 3); these studies consisted of post-hoc or pooled secondary analyses of established trial registries which, despite having pre-registered master protocols, inherently carry higher exploratory

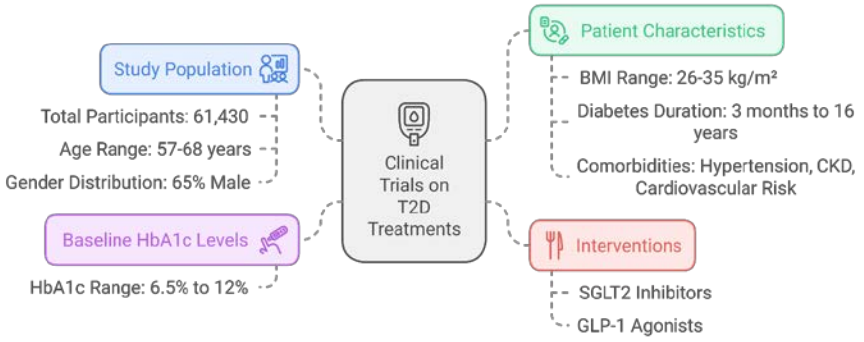


Figure 2. Study Characteristics



Figure 3. RoB2 Traffic Light Plot

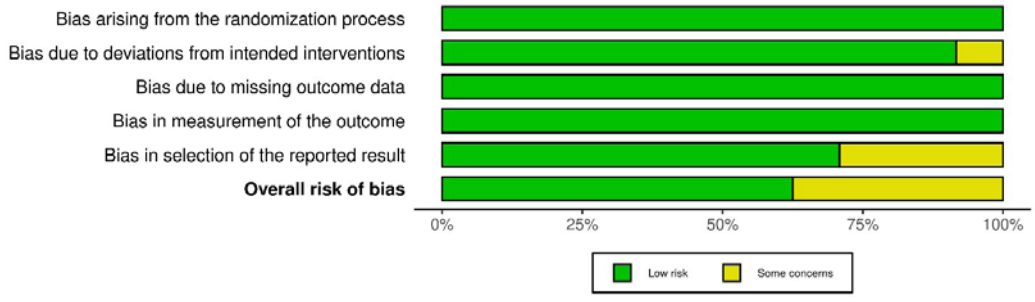


Figure 4. RoB2 Summary plot

freedoms in reporting subset metrics (Figure 4).

Glycemic Control

SGLT2 Inhibitors: Glycemic Outcomes

A comprehensive analysis of SGLT2 inhibitors revealed consistent glycemic improvements across different patient subgroups (Table 1):

1. Dapagliflozin Efficacy
- Demonstrated HbA1c reductions ranging from 0.75% to 1.13%
- Significant glycemic control in both adult and pediatric populations
- Particularly effective in patients with moderate to high cardiovascular risk

2. Empagliflozin and Canagliflozin
- Showed comparable glycemic improvements
- Consistent HbA1c reductions across various baseline HbA1c levels
- Effective in patients with concurrent chronic kidney disease (CKD)

GLP-1 Agonists: Glycemic Efficacy

GLP-1 agonists demonstrated robust and dose-dependent glycemic control:

1. Semaglutide
- Achieved remarkable HbA1c reductions up to 1.7%

at higher doses (14-50 mg)
- Dose-response relationship clearly demonstrated
- Effective across different patient subgroups, including those with obesity and cardiovascular comorbidities

2. Dulaglutide
- Consistent HbA1c reductions of 1.5-1.77%
- Dose-dependent effects, with higher doses showing superior glycemic control
- Effective in both adult and pediatric populations

Weight Management and Metabolic Effects

SGLT2 Inhibitors: Weight and Metabolic Outcomes (Table 2, 3)

- Modest but consistent weight loss effects (2-3 kg)
- Reduction in liver fat content (up to 22% relative reduction)
- Improvements in metabolic parameters, including uric acid and adiponectin levels

GLP-1 Agonists: Weight Loss and Metabolic Benefits

- Significantly superior weight loss compared to SGLT2 inhibitors
- Semaglutide demonstrated up to 9.6% weight reduction
- Dulaglutide showed weight loss of 4.6 kg at higher doses
- Consistent weight reduction across different patient populations and doses

Cardiovascular and Renal Outcomes

SGLT2 Inhibitors: Cardiovascular and Renal Protection (Table 4)

1. Kidney Outcomes
- Significant reduction in kidney disease progression
- Slowed estimated glomerular filtration rate (eGFR) decline
- Particularly effective in patients with baseline kidney impairment

Table 1. Comprehensive Glycemic Control Outcomes in Type 2 Diabetes

Drug Class	Authors	Drug	Key glycemic outcomes
SGLT2 Inhibitors	Tamborlane et al. (2022) [35]	Dapagliflozin	HbA1c decreased by 0.75% (itt analysis), -1.13% in per-protocol analysis
	Tuttle et al. (2022) [45]	Empagliflozin	Consistent glycemic improvements across ckd categories
	Mosenzon et al. (2022) [25]	Dapagliflozin	Significant glycemic control with consistent HbA1c reduction
Glp-1 Agonists	Yabe et al. (2020) [44]	Semaglutide	Hba1c reduction up to 1.7% at 14 mg dose
	Aroda et al. (2023) [37]	Semaglutide	Higher Doses (25mg, 50mg) Achieved Better HbA1c Reduction
	Tamborlane et al. (2022) [42]	Exenatide	HbA1c reduced by 0.85%
	Arslanian et al. (2022) [41]	Dulaglutide	HbA1c reduction 0.6-0.9 percentage points
	Frias et al. (2021) [36]	Dulaglutide	HbA1c reduction of 1.77% at 4.5 mg dose

Table 2. Weight Loss and Metabolic Effects Studies

Author	Drug	Weight Loss Findings	Key Outcomes
Davies et al. (2021) [46]	Semaglutide	Significant weight reduction	9.6% weight loss
Frias et al. (2021) [36]	Dulaglutide	Weight change	4.6 kg weight loss at 4.5 mg dose
Kahl et al. (2020) [38]	Empagliflozin	Liver fat and weight	2.5 kg weight loss, 22% liver fat reduction
Manubolu et al. (2024) [30]	Semaglutide	Epicardial adipose tissue	9% reduction in EAT volume

Table 3. Side by Side Comparison

Drug Class	Average Weight Loss	Key Agents Studied	Mechanism Linked to Weight Loss	Example Trials
GLP-1 Agonists	4.6–9.6 kg (5–12% body weight)	Semaglutide, Dulaglutide	Central appetite suppression via brain GLP-1 receptors; delayed gastric emptying.	Davies et al. (2021),[46] Aroda et al. (2023)[37]
SGLT2 Inhibitors	2–3 kg (2–4% body weight)	Empagliflozin, Dapagliflozin	Caloric loss via urinary glucose excretion (~70–90 g/day). No direct appetite suppression.	Kahl et al. (2020),[38] Tuttle et al. (2022)[45]

Table 4. Renal and Cardiovascular Outcomes Studies

Author	Drug	Cardiovascular Findings	Key Outcomes
Cannon et al. (2020) [40]	Canagliflozin	Kidney and CV protection	Significant reduction in end-stage kidney disease and CV death
Lee et al. (2021) [29]	Empagliflozin	Heart failure outcomes	Reduced LV volumes and NT-proBNP levels
Pratley et al. (2023) [23]	Ertugliflozin	CV safety	Reduced heart failure hospitalization
Mann et al. (2024) [34]	Semaglutide	Kidney and CV outcomes	Reduced kidney and CV outcomes
Jongs et al. (2021) [28]	Dapagliflozin	UACR reduction	29.3% UACR reduction
Heerspink et al. (2021) [27]	Dapagliflozin	eGFR decline	Significantly slowed eGFR decline
Mosenzon et al. (2022) [25]	Dapagliflozin	Kidney disease progression	Reduced kidney disease progression risk
Shaman et al. (2022) [31]	Semaglutide/Liraglutide	Albuminuria reduction	24% albuminuria reduction

- Reduced albuminuria and urinary albumin-to-creatinine ratio (UACR)

2. Cardiovascular Benefits
- Reduced risk of heart failure hospitalization
- Potential cardiovascular protective effects
- Consistent benefits across different cardiovascular risk profiles

GLP-1 Agonists: Cardiovascular and Renal Effects

1. Kidney Protection
- Reduced albuminuria by approximately 24%
- Slowed eGFR decline, more pronounced in patients with baseline eGFR < 60 mL/min
- Potential long-term kidney protective mechanisms

2. Cardiovascular Outcomes
- Reduced cardiovascular risk markers
- Potential improvement in epicardial adipose tissue volume and density
- Consistent benefits across different patient subgroups

Comparative Analysis

The direct comparison studies, particularly the Dwibedi et al. (2024) trial, provided insights into the relative efficacy of these drug classes (Table 5):
- Semaglutide demonstrated superior HbA1c reduction compared to dapagliflozin
- Greater effects observed in specific diabetes subgroups (SIDD)
- Complementary mechanisms of action suggest potential combination therapy benefits

Safety Profile and Adverse Events

SGLT2 Inhibitors: Safety Considerations

Common adverse events included
- Genital infections
- Volume depletion
- Rare cases of ketoacidosis
- Minimal impact on overall safety profiles across studies

GLP-1 Agonists: Adverse Event Profile

Predominant side effects
- Gastrointestinal symptoms (nausea, vomiting)
- Dose-dependent mild to moderate effects
- Higher incidence in pediatric and adult populations
- Generally well-tolerated with minimal long-term safety concerns

Unique and Emerging Findings
- Cognitive benefits observed with liraglutide (improved hippocampal activation)
- Potential reduction in epicardial adipose tissue with semaglutide
- Consistent benefits across different age groups and comorbidities
- Emerging evidence of neural and metabolic effects beyond glycemic control (Table 6)

Limitations and Future Research Directions

Consistent limitations across studies included
- Relatively short study durations (most ≤ 52 weeks)
- Potential selection bias
- Limited generalizability
- Lack of long-term cardiovascular mortality data
- Lack of Pediatrics Data

Future research should focus on
- Long-term cardiovascular outcomes
- Combination therapy strategies
- Personalized treatment approaches based on

Individual patient characteristics
- Exploring mechanisms beyond glycemic control
- Investigations in pediatrics

Discussion

The findings from this literature review reinforce the transformative impact of SGLT2 inhibitors and GLP-1 receptor agonists in the management of type 2 diabetes mellitus (T2D). These pharmacologic classes not only demonstrate robust glycemic control but also provide significant cardiorenal and metabolic benefits, setting them apart from traditional glucose-lowering therapies.

Key Benefits and Comparative Efficacy

Both SGLT2 inhibitors and GLP-1 agonists contribute to glycemic control, with each class showing distinct strengths. GLP-1 agonists, particularly semaglutide and dulaglutide, exhibit superior HbA1c reduction and remarkable weight loss effects. This is particularly

Table 5. Unique Comparative and Combination Studies

Author	Drug	Key Findings	Notable Outcomes
Ali et al. (2020)[24]	Canagliflozin + Liraglutide	Combination effects	Greater weight loss, no additive HbA1c effect
Quast et al. (2020)[33]	Lixisenatide vs Liraglutide	Gastric effects	Differences in gastric emptying
Dwibedi et al. (2024)[43]	Semaglutide vs Dapagliflozin	Direct drug comparison	Semaglutide superior in HbA1c reduction

Table 6. Cognitive and Neurological Effects Studies

Authors	Drug	Cognitive Findings	Significant Observations
Cheng et al. (2022)[39]	Liraglutide	Brain activation	Improved hippocampal activation and delayed memory
Tamborlane et al. (2022)[42]	Exenatide	Pediatric effects	Trends in cognitive and metabolic parameters

beneficial for patients with obesity and related metabolic dysfunctions, aligning with the dual need for glycemic and weight management in T2D.[47, 48] Conversely, SGLT2 inhibitors excel in renal protection and cardiovascular risk reduction, including a substantial decrease in heart failure hospitalizations and progression to end-stage kidney disease (ESKD). These complementary profiles underscore the necessity of a patient-centered approach, where therapy selection is guided by individual characteristics such as age, baseline renal function (e.g., eGFR < 30 mL/min/1.73 m^2), cardiovascular risk, obesity status, and patient preferences. [49, 50] For instance, SGLT2 inhibitors may be prioritized in patients with heart failure or advanced CKD, while GLP-1 agonists could better serve those with obesity or atherosclerotic CVD, as per evidence-based guidelines.[50] Shared decision-making tools [51] —which encompass evidence-based patient decision aids, interactive option grids, and web-based applications (such as the Mayo Clinic Diabetes Decision Aid)—are critical to overcoming barriers to implementation in diverse populations. These tools facilitate collaborative clinical encounters by visually translating and comparing complex drug-specific attributes—such as administration routes (oral vs. subcutaneous), glycemic efficacy, weight loss potential, cardiorenal benefits, and side-effect profiles—thereby allowing clinicians and patients to align clinical evidence with individual patient preferences.[52] (Figure 5)

Clinical Implications of Combination Therapy

The synergy observed in combination therapies further amplifies these benefits. Evidence from trials exploring concurrent use of SGLT2 inhibitors and GLP-1 agonists suggests potential additive effects on weight loss, glycemic control, and cardiorenal protection. This combination may represent a paradigm shift in comprehensive diabetes management.[53, 54]

For patients with severe disease (e.g., HbA1c > 9%, advanced CKD, or obesity-related complications), combination SGLT2i/GLP-1 RA therapy may offer additive cardiorenal and metabolic benefits. However, clinicians must weigh these advantages against adherence challenges and cost barriers, particularly in low-resource settings (Table 7).

Mechanistic Insights and Emerging Outcomes

Beyond glycemic and metabolic benefits, emerging data highlight unique effects of these drugs. GLP-1 agonists demonstrate potential cognitive benefits, likely mediated through neural mechanisms involving hippocampal activation.[55] Meanwhile, SGLT2 inhibitors contribute to reductions in liver fat and improvements in markers of systemic inflammation, hinting at broader metabolic effects.[56, 57]

Safety and Tolerability

Both classes are generally well-tolerated, though specific adverse events warrant consideration.[58,59] SGLT2 inhibitors are associated with a higher risk of genital infections and rare cases of ketoacidosis,[60] while GLP-1 agonists are often linked to dose-dependent gastrointestinal side effects. [61] These safety profiles underscore the importance of individualized treatment plans and patient education.

Study Limitations and gaps

This rapid review intentionally limited itself to primary data from RCTs to synthesize the highest level of experimental clinical evidence on SGLT2 inhibitors and GLP-1 receptor agonists. Therefore, secondary syntheses, large-scale meta-analyses (e.g., Palmer et al, 2021) and observational studies were excluded from the formal results extraction. While this design ensures a rigorous and homogenous focus on direct clinical trial data, it is recognized that the exclusion of extensive real-world evidence and older multi-treatment meta-analyses may hinder the broader contextual view of long-term clinical practice. Also, a formal quantitative meta-analysis to calculate pooled estimates and confidence intervals was not a pre-defined scope of this study; rather, a rapid review to narratively summarize recent clinical evidence. The narrative synthesis is highly effective at demonstrating the key clinical endpoints and percentage changes of the included trials but the lack of statistical pooling is acknowledged as a methodological limitation

Table 7. Combination Therapy

Combination	Key Benefits	Population Studied	Trial
SGLT2-Inhibitor + GLP-1 Receptor Agonist	Hba1c –2.1%, Weight –8.2 Kg, Mace –35%	T2d with Cvd/Ckd	Dwibedi et al. (2024)[43]
Canagliflozin + Liraglutide	Weight –6.5 Kg (No Hba1c Synergy)	Obese T2d (Bmi ≥ 30 Kg/M²)	Ali et al. (2020)[24]

The efficacy and safety metrics reported for the SGLT2i + GLP-1 RA combination are model-based estimates derived from Dwibedi et al. (2024) and should be interpreted with caution due to their exploratory and predicted nature

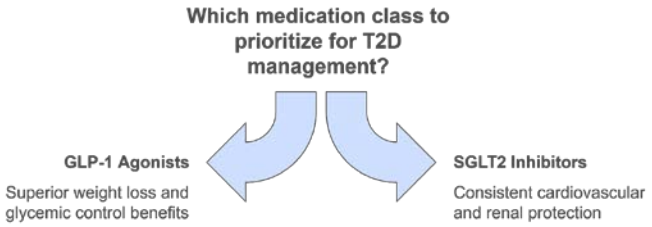


Figure 5. Summary of Benefits

which may limit the direct comparative precision of the summarized numerical data. Furthermore, several limitations inherent to the rapid review methodology itself must be acknowledged. First, a formal protocol was not prospectively registered in public registries. Second, a comprehensive, formal quality or critical appraisal assessment of the individual included trials was bypassed due to the accelerated timeline, meaning variations in study validity were not formally quantified. Lastly, despite expanding our search strategy to include multiple major databases and grey literature, the streamlined screening and selection pipeline inherent to rapid reviews retains a potential risk for residual publication bias.

Also despite significant advancements, several critical gaps persist:

1. Short-Term Follow-Up: Most studies had limited follow-up periods (≤52 weeks), restricting insights into long-term outcomes such as cardiovascular mortality and sustained renal benefits.
2. Real-World Generalizability: Trial findings may not fully translate to diverse populations, particularly those with advanced renal impairment, socioeconomic disparities, or limited healthcare access. Pragmatic studies are urgently needed to address these gaps. [62]
3. Pediatric Underrepresentation: While emerging evidence exists,[35, 42] pediatric T2D—with its unique challenges such as adherence barriers, growth-related safety concerns, and distinct pathophysiology—remains understudied.
4. Unclear Metabolic Relevance: Although metabolic benefits (e.g., liver fat reduction, adiponectin elevation) were observed, their clinical significance remains uncertain due to insufficient data linking these changes to hard endpoints (e.g., cardiovascular events).
5. Phenotypic Heterogeneity: Differential efficacy across T2D subtypes (e.g., severe insulin-deficient diabetes [SIDD] vs. insulin-resistant phenotypes) remains underexplored, hindering personalized treatment approaches. [63]

To address these gaps, future research should prioritize:

1. Long-Term Trials: Conduct extended studies (>5 years) to evaluate mortality benefits and the durability of cardiorenal protection.
2. Real-World Pragmatic Studies: Assess effectiveness in underrepresented populations (e.g., low-income groups, advanced CKD stages) and diverse healthcare settings.
3. Mechanistic Investigations: Explore pathways underlying emerging benefits (e.g., cognitive improvements, hepatic effects) and their clinical relevance.
4. Pediatric T2D Research: Develop dedicated trials to address the rising global burden of youth-onset T2D, focusing on safety, adherence, and growth-related outcomes.
5. Personalized Medicine: Leverage genetic and phenotypic profiling (e.g., SIDD vs. insulin-resistant subtypes) to optimize therapy selection and combination strategies (e.g., SGLT2i/GLP-1 RA synergies).

By bridging these gaps, the field can refine therapeutic strategies, ultimately improving quality of life and prognosis for individuals with T2D.

Conclusion

The integration of SGLT2 inhibitors and GLP-1 receptor agonists into the management of T2D marks a significant advancement in diabetes care. These therapies not only provide robust glycemic control but also address critical cardiorenal and metabolic complications. While GLP-1 agonists excel in glycemic reduction and weight loss, SGLT2 inhibitors offer unparalleled benefits in renal protection and cardiovascular risk mitigation. Combination therapy further amplifies these effects, suggesting a promising paradigm for comprehensive diabetes care.

To maximize this potential, we urge

1. Healthcare providers to prioritize individualized treatment plans guided by patient-specific factors (e.g., cardiovascular risk, CKD stage, obesity) and shared decision-making tools to address barriers like cost and access.
2. Researchers to urgently prioritize long-term trials (>5 years) evaluating mortality outcomes, real-world effectiveness in underrepresented populations (e.g., ethnic minorities, elderly), and optimal sequencing of combination therapies.
3. Policymakers and guideline committees to address systemic inequities in access, particularly for low-income and marginalized groups, by streamlining insurance coverage and reimbursement for these therapies.

While current evidence supports their transformative role, bridging these gaps will ensure equitable application and refine strategies for holistic diabetes management. Future efforts must focus on translating trial findings into practice through personalized approaches that enhance both clinical outcomes and patient quality of life.

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Competing Interests
The author declares no competing interests.

Ethical Approval
This study is a rapid review of previously published clinical trials and did not involve direct human participants; therefore, ethical approval was not required.

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Supplementary Files
Supplementary file contains Table S1.

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