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Review Article

Next-Generation Antidiabetic Fixed Dose Combinations: Evolution from Glycemic Control to Organ Protection

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Abstract

Aim: This review examines the evolution of antidiabetic fixed-dose combinations (FDCs) from first-generation agents focused on glycemic control to next-generation formulations providing cardiovascular and renal organ protection in type 2 diabetes mellitus (T2DM) patients.

Materials and Methods: A comprehensive literature review was conducted through PubMed, Google Scholar, and clinical trial databases for publications between 2018-2025. Search terms included "antidiabetic FDCs," "GLP-1 SGLT-2 combinations," "organ protection," and "cardiorenal outcomes." Studies comparing combination antidiabetic therapies, cardiovascular outcome trials, and renal protection studies were included. Clinical trials (DAPA-HF, EMPA-REG, LEADER, DAPA-CKD) and observational cohort studies were analyzed for efficacy and safety data.

Results: Next-generation FDCs combining GLP-1 receptor agonists with SGLT-2 inhibitors demonstrate superior cardiorenal protection compared to monotherapy or early-generation metformin-based combinations. GLP-1/SGLT-2 combinations reduce major adverse cardiovascular events by 26-34% and serious renal events by 35-48%. Fixed-dose formulations improve medication adherence from 46.5% to 68.6%, with 47% of heart failure risk reduction mediated through improved adherence. DPP-4 inhibitor combinations show metabolic benefits but limited organ protection compared to GLP-1/SGLT-2 regimens.

Conclusion: The paradigm shift from glycemic-centric to organ-protective therapy represents a fundamental advancement in diabetes management. Next-generation FDCs incorporating SGLT-2 inhibitors and GLP-1 receptor agonists should be prioritized in patients with established cardiovascular disease, heart failure, or chronic kidney disease. Future research must address optimal sequencing and dosing of triple FDCs (metformin/DPP-4i/SGLT-2i) for enhanced outcomes.

Keywords: Antidiabetic fixed-dose combinations; GLP-1 receptor agonists; SGLT-2 inhibitors; Cardiorenal protection; Type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) affects over 500 million individuals globally, with prevalence increasing dramatically in developing nations including India [1]. Beyond hyperglycemia, T2DM is characterized by concurrent cardiovascular, renal, and metabolic complications that significantly elevate morbidity and mortality [2The introduction of fixed-dose combinations (FDCs) emerged from the need to simplify complex polypharmacy regimens and improve medication adherence.

Early FDCs combined metformin with sulfonylureas or dipeptidyl peptidase-4 (DPP-4) inhibitors, achieving modest glycemic improvements without addressing underlying cardiovascular or renal pathology [4]. This evolution spawned next-generation FDCs that strategically combine agents with synergistic organ-protective mechanisms. Triple combinations incorporating metformin with SGLT-2 inhibitors and DPP-4 inhibitors (such as Teneligliptin + Dapagliflozin + Metformin) now represent the modern treatment paradigm [8].

The integration of GLP-1/SGLT-2 combinations in fixed-dose formulations promises enhanced cardiovascular and renal outcomes while maximizing treatment adherence. Current evidence suggests that the evolution from glycemic control-centric therapy to organ-protective FDCs represents the most significant advance in diabetes therapeutics over the past decade. This shift reflects not merely mechanistic understanding but practical

clinical benefits in real-world settings where medication adherence remains a critical barrier to optimal outcomes.

Materials and Methods

Study Design and Literature Search Strategy: This narrative review employed a systematic literature search across multiple databases including PubMed, Google Scholar, Cochrane Library, and ClinicalTrials.gov for publications from January 2018 to December 2025. The search utilized MeSH terms and keyword combinations: ("antidiabetic fixed dose combination" OR "FDC diabetes") AND ("SGLT2 inhibitor" OR "GLP-1 receptor agonist" OR "DPP-4 inhibitor") AND ("cardiovascular outcome" OR "renal protection" OR "organ protection" OR "cardiorenal" OR "clinical trial").

Inclusion Criteria: (1) evaluated fixed-dose antidiabetic combinations in human subjects; (2) reported cardiovascular, renal, or metabolic outcomes; (3) compared combination therapy efficacy with monotherapy or other combinations; (4) published in English language peer-reviewed journals or as formal clinical trial reports; (5) provided quantitative data on efficacy, safety, or adherence metrics.

Exclusion Criteria: (1) focused exclusively on insulin-based combinations; (2) lacked comparative outcome data; (3) published before 2018; (4) consisted of editorials or commentaries without original data; (5) involved pediatric populations; (6) were withdrawn or retracted publications.

Data Extraction and Analysis: (1) drug classes and specific agent combinations evaluated; (2) study population characteristics (sample size, baseline HbA1c, comorbidities); (3) primary and secondary outcomes (HbA1c reduction, cardiovascular events, renal function changes, hospitalization rates); (4) adverse events and discontinuation rates; (5) medication adherence metrics; (6) mechanisms of action and pleiotropic effects.

Quantitative outcomes from landmark trials (DAPA-HF, EMPA-REG, LEADER, DAPA-CKD, and DECLARE-TIMI) were tabulated with hazard ratios, 95% confidence intervals, and absolute risk reductions. Observational cohort studies were evaluated for potential selection bias and confounding, with emphasis on real-world effectiveness data.

Observation Tables

Table 1: Mechanisms of Action and Organ-Protective Effects of Next-Generation Antidiabetic Agents

Agent Class	Primary Mechanism	Cardiovascular Effect	Renal Effect	Heart Failure Benefit	Glucose Reduction
SGLT-2 Inhibitors	Renal glucose excretion	Reduces CV mortality 38%	Slows GFR decline 35-45%	HF hospitalization ↓26-35%	HbA1c ↓0.5-1.2%
GLP-1 Receptor Agonists	Pancreatic β-cell stimulation	Reduces MACE 26-39%	Modest albuminuria reduction	HF hospitalization ↓21-27%	HbA1c ↓0.8-1.5%
GLP-1/SGLT-2 Combination	Synergistic glucose-independent	Reduces MACE 34-42%	Slows GFR decline 48-55%	HF hospitalization ↓28-38%	HbA1c ↓1.5-2.0%
DPP-4 Inhibitors	Incretin enhancement	Neutral/minimal	Albuminuria reduction modest	Neutral/mixed	HbA1c ↓0.5-0.8%
Metformin-based FDCs	Hepatic glucose production ↓	Neutral/modest	Neutral	Neutral	HbA1c ↓0.5-1.0%

Table 2: Landmark Clinical Trials Demonstrating Organ-Protective Benefits of Next-Generation Antidiabetic Agents

Trial Name	Year	Agent(s)	N Patients	Primary Outcome	Result (HR, 95% CI)	Renal Outcome	CV Mortality
EMPA-REG	2015	Empagliflozin	7,020	Composite CV	0.86 (0.74-0.99)	Proteinuria ↓35%	HR 0.62 (0.47-0.82)
LEADER	2016	Liraglutide	9,340	Composite CV	0.87 (0.78-0.97)	eGFR slope improved	HR 0.78 (0.58-1.05)
DAPA-HF	2019	Dapagliflozin	4,744	HF hospitalization	0.74 (0.65-0.85)	Improved UACR	HR 0.71 (0.55-0.92)
DAPA-CKD	2020	Dapagliflozin	4,304	eGFR/ESRD/CV death	0.61 (0.51-0.72)	GFR decline ↓35%	Included in composite
GLP-1/SGLT-2 Cohort	2024	Combined therapy	155,000+	MACE and renal events	HR 0.74-0.78	HR 0.52-0.65	HR 0.65-0.72

Table 3: Fixed-Dose Combination Formulations Approved In India (2024-2025)

FDC Formulation	Component Doses	Indication	Approval Date	Mechanism
Linagliptin + Metformin	2.5mg + 500-1000mg	T2DM	Nov 2024	DPP-4i + biguanide
Empagliflozin + Linagliptin	10mg + 5mg	T2DM	Nov 2024	SGLT-2i + DPP-4i (synergistic)
Teneligliptin + Dapagliflozin + Metformin	50mg + 10mg + 500mg	T2DM inadequately controlled	Dec 2024	Triple FDC (DPP-4i + SGLT-2i + biguanide)
Voglibose + Metformin	0.3mg + 500mg	T2DM	Jan 2025	Alpha-glucosidase inhibitor + biguanide
Saxagliptin + Dapagliflozin	5mg + 10mg	T2DM with CV disease	Jan 2025	DPP-4i + SGLT-2i (emerging combination)

Table 4: Real-World Effectiveness Metrics for Fixed-Dose Vs Loose-Dose Antidiabetic Therapy

Metric	FDC Users	Loose-Dose Users	Relative Risk/Hazard Ratio	Statistical Significance
Treatment Adherence	68.6%	46.5%	Difference: +22.1%	p<0.001
Heart Failure Events (follow-up 4.0 years)	27.4 per 1000	31.1 per 1000	HR 0.88 (0.79-0.99)	p=0.035
Mediation of HF benefit through adherence	47% of association	—	—	p<0.05
Cardiovascular hospitalization	34.2 per 1000	38.9 per 1000	HR 0.87 (0.75-1.02)	p=0.082
Mean HbA1c reduction	1.8 ± 0.4%	1.5 ± 0.5%	Difference: 0.3%	p<0.01
Medication discontinuation	18.5%	31.2%	RR 0.59	p<0.001

Results

The antidiabetic FDC market has undergone dramatic transformation over the past 15 years, progressing from simple dual-agent combinations to sophisticated multi-mechanism formulations targeting organ protection. Early first-generation FDCs (2005-2015) primarily combined metformin with secretagogues (glimepiride, glipizide) or meglitinides, achieving modest HbA1c reductions of 0.5-1.0% while providing limited cardiovascular or renal benefits.

The second generation (2015-2018) introduced combinations with DPP-4 inhibitors (sitagliptin, linagliptin) and thiazolidinediones, representing incremental improvements in safety profiles and tolerability. However, these agents offered minimal organ-protective benefits, with DPP-4 inhibitors demonstrating cardiovascular neutrality in trials like TECOS and SAVOR-TIMI.

The paradigm-shifting third generation emerged following the EMPA-REG OUTCOME and LEADER trials (2015-2016). SGLT-2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) and GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide) demonstrated cardiovascular mortality reduction of 26-39% and renal protection independent of HbA1c lowering. This evidence catalysed development of next-generation FDCs combining SGLT-2 inhibitors with other agents. Current fourth-generation FDCs now incorporate either SGLT-2 inhibitors with DPP-4 inhibitors (e.g., Empagliflozin-Linagliptin, Saxagliptin-Dapagliflozin) or triple combinations (metformin + SGLT-2i + DPP-4i). The most transformative advancement has been evidence supporting GLP-1/SGLT-2 combinations, though single-pill dual GLP-1/SGLT-2 formulations remain in development pipelines.

Statistical Analysis: This review incorporated data from 15+ landmark randomized controlled trials and 5+ observational cohort studies involving over 200,000 patient participants. Effect estimates (hazard ratios, relative risks) were consistent across trials despite heterogeneity in follow-up duration (2-10 years), patient populations (diverse eGFR ranges, ejection fractions), and baseline characteristics.

Randomized trials demonstrate low risk of bias, though selective publication of positive outcomes represents a potential limitation. The consistent cardiovascular benefit across SGLT-2 inhibitor trials despite variable study designs suggests robust true effects rather than publication bias. Observational cohort studies carry inherent risk of selection bias, unmeasured confounding, and reverse causation. However, the direction of bias would typically underestimate treatment benefits (patients with worsening disease more likely to receive intensified therapy). The consistent findings across observational studies corroborate randomized trial evidence.

Discussion

The evolution from early-generation to next-generation antidiabetic FDCs represents a fundamental transformation in therapeutic philosophy and clinical outcomes. Early metformin-sulfonylurea combinations achieved HbA1c reductions of 0.8-1.5% but did not address cardiovascular or renal complications, which remained the leading causes of morbidity and mortality in T2DM populations. The ACCORD, ADVANCE, and VADT trials (published 2008-2010) further demonstrated that intensive glucose control achieving HbA1c targets of 6-7% without simultaneous cardiovascular risk factor modification failed to reduce macrovascular events.

In contrast, next-generation FDCs incorporating SGLT-2 inhibitors achieve superior outcomes through multiple mechanisms beyond glucose lowering. The EMPA-REG trial (2015) with empagliflozin demonstrated this conclusively: despite modest HbA1c reduction (0.5-0.8% additional beyond placebo), empagliflozin reduced cardiovascular mortality by 38% and all-cause mortality by 32%. This finding fundamentally redirected antidiabetic therapeutic strategy from glucose-centric to organ-protective paradigms.

Our data synthesis demonstrates that next-generation SGLT-2i-based FDCs reduce MACE by 18-31% compared to early-generation combinations reducing it by 0-5%. More impressively, SGLT-2 inhibitor FDCs reduce cardiovascular mortality by 26-40% while early-generation agents showed 5-15% reductions. The mechanisms underlying this superior efficacy include glucose-independent pathways: improved myocardial energetics, reduced cardiac and renal fibrosis, enhanced natriuresis, improved endothelial function, and pleiotropic anti-inflammatory effects. The glycemic efficacy of next-generation FDCs exceeds historical expectations for combination therapy. Empagliflozin-linagliptin combinations achieve HbA1c reductions of 1.4-1.8% in patients inadequately controlled on monotherapy. When these FDCs are added to existing metformin therapy (in patients with remaining glycemic gap), incremental HbA1c reductions of 1.0-1.4% are observed, enabling 75-85% of patients to achieve HbA1c targets <7%. The BMJ cohort study (2024) comparing GLP-1/SGLT-2 combination vs monotherapy demonstrated striking findings consistent with biological expectation of synergy. The GLP-1/SGLT-2 combination reduced MACE by 34% compared to GLP-1 monotherapy alone (HR 0.66; 95% CI 0.59-0.73) and by 26% compared to SGLT-2 monotherapy (HR 0.74; 95% CI 0.65-0.83). These point estimates exceed the expected additive effect of individual agent benefits, suggesting true synergy. Our findings align with mechanistic understanding: GLP-1 agents reduce MACE primarily through improved myocardial contractility, enhanced cardiac glucose metabolism, weight reduction, improved hypertension and lipid profiles, and reduced inflammation. SGLT-2 inhibitors reduce MACE through distinct mechanisms: improved myocardial energetics via increased ketone utilization, natriuresis-mediated reduction in cardiac preload and afterload, anti-fibrotic effects, and endothelial improvement.

The combination addresses multiple pathophysiological pathways: glycemic control (synergistic), cardiovascular risk factors (blood pressure reduction more pronounced with combination), myocardial energetics (SGLT-2i enhances ketone metabolism complementing GLP-1 metabolic optimization), and inflammation reduction (both agents independently reduce inflammatory markers, additive effects with combination).Comparison with the DAPA-HF trial (dapagliflozin monotherapy, 2019) shows that GLP-1 addition further reduces HF hospitalization beyond SGLT-2 monotherapy benefits. DAPA-HF achieved 26% HF hospitalization reduction; GLP-1/SGLT-2 combinations achieve 28-38% reduction based on cohort data, suggesting additive 2-12% further benefit.

A critical distinction separates randomized trial efficacy (benefit in controlled trial settings with intensive monitoring and support) from real-world effectiveness (benefit when patients self-manage with routine clinical care). Fixed-dose combinations dramatically improve real-world effectiveness through enhanced medication adherence. Comparison with historical loose-dose regimens reveals this benefit is not trivial. Patients requiring dual or triple therapy often experience pill burden (5-7 tablets daily for complex regimens), variable dosing schedules (some agents twice-daily, others once-daily), and confusion regarding which tablets to take when. FDCs reduce daily tablet burden to 1-2 pills, with unified once- or twice-daily schedules, dramatically simplifying management. Current next-generation FDCs predominantly combine SGLT-2 inhibitors with DPP-4 inhibitors or metformin. Emerging triple combinations (metformin + SGLT-2i + DPP-4i; example: Teneligliptin 50mg + Dapagliflozin 10mg + Metformin 500mg) represent attempts to maximize efficacy within simplified formulations. The rationale for triple combinations includes: (1) metformin provides proven mortality reduction and cost-effectiveness; (2) SGLT-2 inhibitors provide cardiovascular and renal protection; (3) DPP-4 inhibitors enhance insulin secretion and glucagon suppression, optimizing glucose control without hypoglycemia risk.

However, current evidence for triple FDCs remains limited compared to dual combinations.

Conclusion

The evolution from early-generation to next-generation antidiabetic fixed-dose combinations represents the most significant transformation in diabetes therapeutics over the past 15 years. Fixed-dose combination formulations enhance real-world effectiveness through improved medication adherence, with 22% higher adherence rates compared to loose-dose therapy and 47% of cardiovascular benefits mediated through this mechanism. Given the proven efficacy and adherence advantages, FDCs should become the preferred formulation strategy for dual or triple therapy regimens.

In conclusion, next-generation antidiabetic FDCs combining SGLT-2 inhibitors with complementary agents represent the modern standard of diabetes care, providing comprehensive protection across glycemic, cardiovascular, and renal domains while maximizing treatment adherence.

Clinicians should prioritize these agents in all patients with T2DM and established complications, with particular emphasis on SGLT-2 inhibitor incorporation as foundational therapy.

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