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REVIEW ARTICLE

A Systematic Review of Pharmacodynamics and Cardio-Renal Outcomes of SGLT-2 and DPP-4 Inhibition in Type 2 Diabetes Mellitus

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Abstract: Type 2 Diabetes Mellitus is a principal driver of global morbidity, requiring pharmacological interventions that transcend simple glycemic control. While both Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors and Dipeptidyl Peptidase-4 (DPP-4) inhibitors serve as important components of the modern antihyperglycemic armamentarium, their clinical impacts diverge significantly. SGLT-2 inhibitors facilitate glucose excretion through insulin-independent pathways in the renal proximal tubule, concurrently promoting natriuresis and caloric loss. These physiological changes translate into robust reductions in hospitalization for heart failure, attenuation of chronic kidney disease progression, and decreased cardiovascular mortality. Conversely, DPP-4 inhibitors augment the incretin effect by prolonging the half-life of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, leading to glucose-dependent insulin secretion and suppressed glucagon release. These agents exhibit a high degree of tolerability and weight neutrality but lack the transformative cardio-protective and renoprotective benefits observed with SGLT-2 inhibition. Systematic evaluation of randomized controlled trials and large-scale outcome data confirms that SGLT-2 inhibitors represent the preferred therapeutic choice for patients with established or high-risk cardiovascular and renal complications. DPP-4 inhibitors maintain clinical relevance as safe, second-line options for individuals requiring simplified glycemic management without the need for significant hemodynamic modification. The integration of these two classes in combination therapy offers additive glycemic efficacy without increasing hypoglycemia risk, though the long-term survival advantages remain largely driven by the SGLT-2 inhibitory component. Strategic selection between these classes allows for a personalized approach that addresses both metabolic targets and the overarching risk of organ damage.

Keywords: Type 2 Diabetes Mellitus; SGLT-2 inhibitors; DPP-4 inhibitors; Cardiovascular Outcomes; Renal Protection

1. Introduction

The traditional approach for the management of Type 2 Diabetes Mellitus (T2DM) focused almost exclusively on the maintenance of glycated hemoglobin (HbA1c) levels below 7% to prevent microvascular complications. This traditional approach focused almost exclusively on the maintenance of glycated hemoglobin (HbA1c) levels below a stringent threshold of 7.0%, a strategy largely derived from evidence suggesting that such control effectively mitigated microvascular complications like retinopathy and nephropathy. However, the longitudinal results from pivotal trials such as ACCORD, ADVANCE, and VADT necessitated a profound re-evaluation of this paradigm. These studies demonstrated that intensive glycemic control, while beneficial for microvascular endpoints, did not provide a commensurate reduction in macrovascular events or cardiovascular mortality; in some instances, intensive therapy was even associated with an increased risk of adverse outcomes [1].

This clinical realization triggered a radical realignment of therapeutic objectives. Contemporary management has moved beyond a purely glucocentric perspective, now prioritizing a multi-factorial strategy that targets the systemic drivers of diabetic morbidity. The understanding of T2DM has evolved from a simple disorder of carbohydrate metabolism to a complex vascular and metabolic

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syndrome. Consequently, modern strategies emphasize the selection of antihyperglycemic agents based on their proven capacity to reduce the burden of heart failure, attenuate the progression of renal decline, and lower the incidence of major adverse cardiovascular events (MACE). This shift represents a fundamental change in the "Standard of Care," where the intrinsic properties of a drug class are now considered as important as its glucose-lowering potency [2].

While metformin persists as the foundational pharmacological intervention for the majority of patients, the selection of subsequent therapeutic agents has become a critical inflection point in clinical decision-making. As clinicians seek to individualize therapy, the choice of the subsequent agent must account for the patient's underlying comorbidities, particularly cardiovascular and renal health. Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors and Dipeptidyl Peptidase-4 (DPP-4) inhibitors are both characterized by a low intrinsic risk for hypoglycemia, but they represent two fundamentally distinct philosophies of care [3, 4].

SGLT-2 inhibitors are increasingly categorized as "disease-modifying" agents due to their pleiotropic effects that extend far beyond the renal proximal tubule. They provide a unique hemodynamic "unloading" effect that preserves myocardial and renal integrity by inducing a state of controlled glucosuria and natriuresis. Conversely, DPP-4 inhibitors are valued for their "metabolic fine-tuning" and excellent tolerability. They optimize the body's endogenous hormonal response to nutrient intake through the incretin axis, offering a weight-neutral and highly reliable method of achieving glycemic stability without the systemic hemodynamic shifts associated with SGLT-2 inhibition. This divergence creates a clear therapeutic choice: the use of SGLT-2 inhibitors for proactive organ protection in high-risk individuals, or the use of DPP-4 inhibitors for safe, simplified metabolic control in patients where hemodynamic modification is less urgent [5,6].

2. Selection and Appraisal of Evidence

2.1. Structured Literature Interrogation

This appraisal utilized a rigorous methodology to identify and synthesize evidence from diverse clinical sources. Systematic searches were conducted across PubMed, Scopus, Web of Science, and the Cochrane Library for data published between January 2010 and December 2025. The inclusion criteria prioritized Phase III randomized controlled trials (RCTs), cardiovascular outcome trials (CVOTs), and dedicated renal outcome trials to ensure that the findings reflect the highest level of clinical certainty.

2.2. Data Validation and Outcome Metrics

Primary endpoints analyzed included MACE, hospitalization for heart failure (HHF), all-cause mortality, and hard renal endpoints such as a sustained 50% decline in estimated glomerular filtration rate (eGFR) or progression to end-stage kidney disease (ESKD). Meta-analyses of high-quality data were scrutinized to identify class-level effects versus drug-specific anomalies, providing a comprehensive view of how these pharmacological classes perform in real-world and controlled clinical settings [7,8].

3. Mechanisms of Action

3.1. Renal Glucose Transport and SGLT-2 Inhibition

3.1.1. The Role of the Proximal Tubule in Metabolic Homeostasis

SGLT-2 inhibitors, including empagliflozin, canagliflozin, and dapagliflozin, target the SGLT-2 transport protein located in the S1 segment of the renal proximal tubule. Under normal physiological conditions, this transporter is responsible for the reabsorption of approximately 90% of filtered glucose [9,10]. These agents lower the renal threshold for glucose by competitively inhibiting this pathway, promoting significant daily glucosuria (typically 60–100 grams). Because this mechanism is independent of insulin secretion or action, it remains effective across various stages of T2DM progression, including cases of severe insulin resistance [11].

3.1.2. Hemodynamic Consequences and Tubuloglomerular Feedback

Beyond glycemic control, the inhibition of SGLT-2 prevents the co-reabsorption of sodium, which increases sodium delivery to the macula densa. This activation of tubuloglomerular feedback results in the constriction of the afferent arteriole, effectively reducing intraglomerular hypertension [12]. Moreover, the resulting natriuresis and osmotic diuresis lead to a reduction in plasma volume, decreased arterial stiffness, and a lowering of both cardiac preload and afterload. These systemic hemodynamic modifications are believed to underpin the rapid and sustained cardiovascular benefits observed in clinical populations [13].

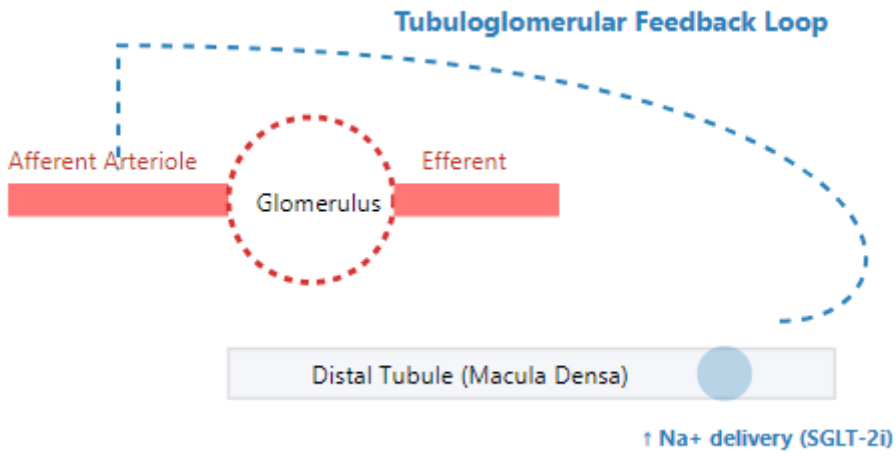
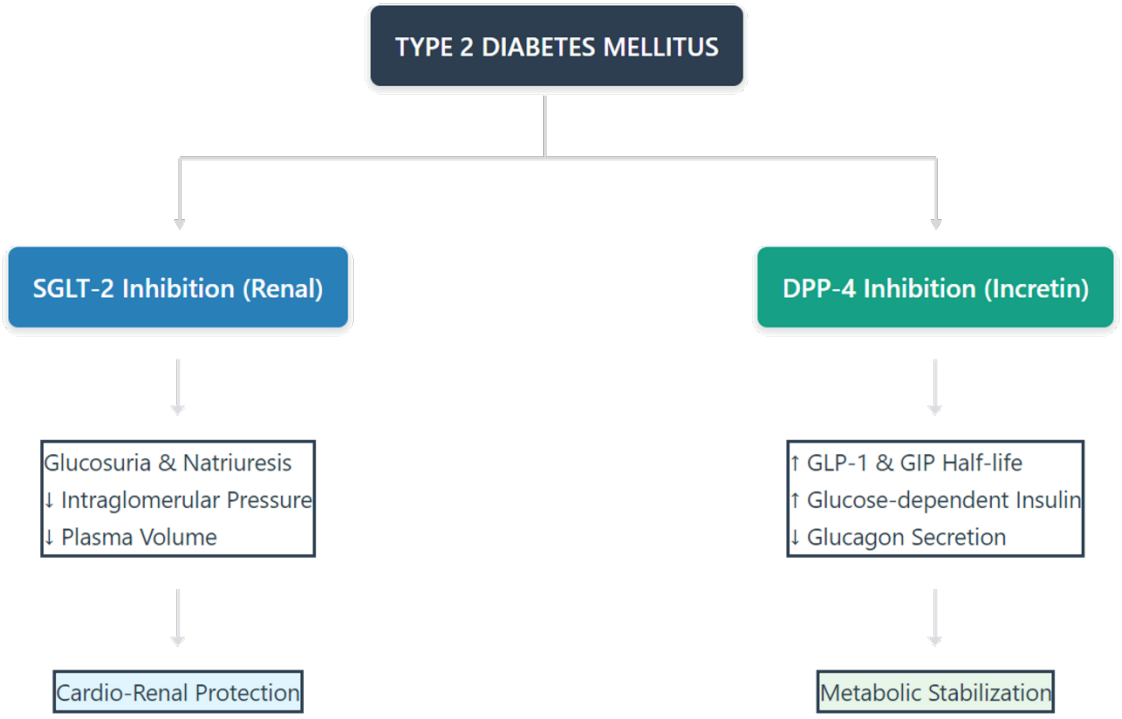


Figure 1. Renal Protection via Tubuloglomerular Feedback

3.2. Enhancement of the Incretin Axis via DPP-4 Inhibition

3.2.1. Stabilization of GLP-1 and GIP Dynamics

DPP-4 inhibitors, such as sitagliptin, vildagliptin, and linagliptin, exert their effects by blocking the dipeptidyl peptidase-4 enzyme, which is the primary mediator for the degradation of incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [14]. By extending the half-life of these hormones, these agents potentiate the glucose-dependent insulin response to meal ingestion, effectively addressing the postprandial glucose excursions that characterize early-stage T2DM.



Legend: HHF: Hospitalization for Heart Failure; CKD: Chronic Kidney Disease; GLP-1: Glucagon-like Peptide-1.

Figure 2. Mechanism of Action for SGLT-2 Inhibition and DPP-4 inhibition

3.2.2. Endocrine Regulation of Insulin and Glucagon

The stabilization of endogenous GLP-1 levels promotes pancreatic beta-cell insulin secretion while simultaneously suppressing alpha-cell glucagon release [15]. Unlike the hemodynamic "unloading" effect of SGLT-2 inhibitors, the impact of DPP-4 inhibition is largely confined to the endocrine regulation of nutrient metabolism. This targeted action results in a clinical profile defined by weight neutrality, excellent gastrointestinal tolerability, and a lack of significant effect on systemic blood pressure or renal hemodynamic parameters [16].

3.3. Molecular Comparison of Therapeutic Targets

The fundamental distinction between these classes resides in their physiological site of impact. SGLT-2 inhibitors function as "metabolic and hemodynamic modifiers" that remove excess glucose and sodium from the body via the renal pathway. Conversely, DPP-4 inhibitors act as "endocrine fine-tuners" that optimize the body's existing hormonal architecture in response to nutrient intake [17]. While both classes successfully lower HbA1c, the systemic physiological changes triggered by SGLT-2 inhibition provide a broader spectrum of extra-glycemic benefits that are inherently absent in the localized enzymatic action of DPP-4 inhibitors.

Table 1. Pharmacological and Physiological Properties of SGLT-2 Inhibitors and DPP-4 Inhibitors

Feature	SGLT-2 Inhibitors	DPP-4 Inhibitors
Primary Biological Target	SGLT-2 protein (S1 segment of proximal tubule)	Dipeptidyl peptidase-4 enzyme (Systemic)
Metabolic Pathway	Insulin-independent renal glucose excretion	Incretin-mediated glucose-dependent insulin secretion
Effect on Glucagon	Potential compensatory increase	Direct suppression of alpha-cell secretion
Natriuresis & Osmosis	Significant; promotes volume contraction	Negligible; hemodynamically neutral
Glomerular Dynamics	Afferent vasoconstriction (reduces intraglomerular pressure)	No consistent effect on renal hemodynamics
Daily Caloric Loss	~240–320 kcal/day (via glucosuria)	Neutral

4. Metabolic and Hemodynamic Impact

4.1. Glycemic Control and HbA1c Reduction

4.1.1. Efficacy Profiles and Renal Dependency

SGLT-2 inhibitors typically achieve a reduction in HbA1c ranging from 0.5% to 1.0% when used as monotherapy or add-on therapy. However, because their primary mechanism relies on the filtration of glucose, their glycemic efficacy is intrinsically linked to the estimated glomerular filtration rate (eGFR) [18]. As renal function declines, the filtered load of glucose decreases, leading to a diminished HbA1c response. Conversely, DPP-4 inhibitors provide a consistent HbA1c reduction of 0.5% to 0.8% across a broader range of renal function. Notably, agents like linagliptin maintain their efficacy and do not require dose adjustment even in advanced stages of chronic kidney disease (CKD), making them a versatile option for patients with impaired renal clearance [19].

4.1.2. Synergistic Potential of Combination Therapy

The integration of SGLT-2 and DPP-4 inhibitors in a single therapeutic regimen leverages complementary pathways: the insulin-independent excretion of glucose via the kidneys and the glucose-dependent stimulation of insulin via the incretin axis. Clinical data suggest that this combination results in additive glycemic lowering without an increased risk of hypoglycemia. Meta-analyses have indicated that fixed-dose combinations can achieve superior glycemic targets compared to up-titrating either agent as monotherapy, particularly in patients with higher baseline HbA1c levels [20].

4.2. Body Weight and Anthropometric Modifications

A primary clinical differentiator between these classes is their impact on body weight. SGLT-2 inhibitors promote a caloric deficit through daily glucosuria, typically resulting in a weight loss of 2 to 3 kilograms over the first six months of therapy. This weight reduction is predominantly characterized by a decrease in visceral adiposity and total body fat mass rather than lean muscle tissue [21]. In contrast, DPP-4 inhibitors are characterized by metabolic weight neutrality. While they do not promote weight loss, they also do not cause the weight gain frequently associated with sulfonylureas or thiazolidinediones, making them a safe choice for maintaining weight stability [22].

4.3. Blood Pressure and Cardiovascular Hemodynamics

SGLT-2 inhibitors exert a modest but clinically significant reduction in systolic blood pressure (SBP), generally ranging from 3 to 5 mmHg. This effect is attributed to the combination of natriuresis-induced volume contraction and improvements in arterial stiffness [23]. These hemodynamic changes occur early in the treatment course and contribute to the reduction in cardiovascular workload. DPP-4 inhibitors, however, do not exhibit consistent effects on systemic blood pressure. While some experimental models suggested potential vasodilation, clinical trials have confirmed that DPP-4 inhibition remains hemodynamically neutral in human populations [24].

Table 2. Comparative Metabolic and Anthropometric Impact

Parameter	SGLT-2 Inhibitor Profile	DPP-4 Inhibitor Profile
HbA1c Reduction	0.5% – 1.0% (Dependent on eGFR)	0.5% – 0.8% (eGFR independent)
Body Weight Change	Loss of 2.0 – 3.0 kg (Primarily adipose)	Weight Neutral
Systolic BP Change	Reduction of 3 – 5 mmHg	Neutral
Lipid Profile Effect	Modest increase in HDL and LDL	Neutral
Visceral Adiposity	Significant reduction	No significant change
Hypoglycemia Risk	Very low (Glucose-independent)	Very low (Glucose-dependent)

5. Cardiovascular Clinical Outcomes

5.1. The Cardioprotective Evidence for SGLT-2 Inhibition

5.1.1. Mitigation of Heart Failure and Mortality

The most striking evidence for SGLT-2 inhibitors lies in their ability to reduce hospitalization for heart failure (HHF). Landmark trials such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 consistently demonstrated a 27% to 35% reduction in HHF [25,26]. These benefits are observed rapidly after initiation and extend across the spectrum of heart failure, including those with reduced (HFrEF) and preserved (HFpEF) ejection fraction. Moreover, meta-analyses confirm that SGLT-2 inhibition significantly reduces cardiovascular death and all-cause mortality in patients with established atherosclerotic disease [27].

5.1.2. Primary and Secondary Prevention

While the greatest absolute benefits are seen in patients with established cardiovascular disease, evidence from the DECLARE-TIMI 58 trial suggests that SGLT-2 inhibitors also offer protective benefits in patients with multiple risk factors but no established disease. This suggests a role for SGLT-2 inhibitors earlier in the treatment algorithm to prevent the first occurrence of heart failure or renal decline [28].

5.2. Cardiovascular Safety and Neutrality of DPP-4 Inhibitors

5.2.1. Analysis of Major Outcome Trials

Large-scale CVOTs, including TECOS (sitagliptin), EXAMINE (alogliptin), and CARMELINA (linagliptin), have definitively established the cardiovascular safety of DPP-4 inhibitors.

Table 3. Landmark Cardiovascular Outcome Trials (CVOTs)

Trial (Agent)	Population	MACE (HR; 95% CI)	HHF (HR; 95% CI)	CV Death (HR; 95% CI)
EMPA-REG (Empagliflozin)	T2DM + Established ASCVD	0.86 (0.74–0.99)	0.65 (0.50–0.85)	0.62 (0.49–0.77)
DECLARE (Dapagliflozin)	T2DM + ASCVD/Risk Factors	0.93 (0.84–1.03)	0.73 (0.61–0.88)	0.98 (0.82–1.17)
DAPA-HF (Dapagliflozin) [28]	HFrEF ± T2DM	N/A	0.70 (0.59–0.83)*	0.82 (0.69–0.98)
TECOS (Sitagliptin)	T2DM + Established ASCVD	0.98 (0.88–1.09)	1.00 (0.83–1.20)	1.03 (0.89–1.19)
SAVOR (Saxagliptin)	T2DM + High CV Risk	1.00 (0.89–1.12)	1.27 (1.07–1.51)	1.03 (0.87–1.22)
CARMELINA (Linagliptin)	T2DM + High CV/Renal Risk	1.02 (0.89–1.17)	0.90 (0.74–1.08)	0.94 (0.76–1.15)

**Reported as composite of HHF or urgent HF visit.*

These trials showed that DPP-4 inhibitors do not increase the risk of MACE compared to placebo [29,30]. However, they also failed to show any superiority in terms of reducing myocardial infarction, stroke, or cardiovascular death, positioning them as "safety-neutral" agents.

5.2.2. The Saxagliptin Anomaly and Heart Failure Concerns

The SAVOR-TIMI 53 trial identified a statistically significant increase in the risk of hospitalization for heart failure with the use of saxagliptin [31]. While this signal was not observed with sitagliptin or linagliptin, regulatory agencies have maintained a cautious approach, often recommending against saxagliptin or alogliptin in patients with existing heart failure or high risk for the condition. This clinical nuance further prioritizes SGLT-2 inhibitors in patients where heart failure is a primary concern.

6. Renal Preservation and Outcomes

6.1. SGLT-2 Inhibition as a Renoprotective Strategy

Dedicated renal outcome trials, such as CREDENCE and DAPA-CKD, have established SGLT-2 inhibitors as a foundational therapy for chronic kidney disease. These agents significantly reduce the risk of a composite endpoint consisting of a 50% decline in eGFR, end-stage kidney disease (ESKD), or renal-related death [32]. The reduction in intraglomerular pressure, as discussed in the mechanistic section, provides a "hemodynamic rest" for the nephrons, effectively slowing the progressive decline of renal function over years of therapy [33].

6.2. The Role of DPP-4 Inhibitors in Renal Management

DPP-4 inhibitors have demonstrated a modest ability to reduce the progression of albuminuria, particularly in the CARMELINA trial with linagliptin. However, they do not impact hard renal endpoints such as doubling of serum creatinine or progression to dialysis [34]. Their primary utility in renal disease remains their safety profile; linagliptin, in particular, serves as a vital tool for managing glycemia in patients with advanced ESKD where many other agents, including SGLT-2 inhibitors, are either ineffective or contraindicated [35]

Table 4. Evidence from Renal Outcome Trials

Trial (Agent)	Primary Renal Endpoint (Composite)	RRR / Result	Impact on eGFR Slope
CREDENCE (Canagliflozin)	ESKD, Doubling of Creatinine, Renal/CV Death	30% Reduction	Significant attenuation of decline
DAPA-CKD (Dapagliflozin)	≥50% eGFR decline, ESKD, Renal/CV Death	39% Reduction	Significant attenuation of decline
EMPA-KIDNEY (Empagliflozin)	Progression of Kidney Disease or CV Death	28% Reduction	Significant attenuation of decline
CARMELINA (Linagliptin)	Renal Death, ESKD, Sustained eGFR decline	Neutral	Neutral
MARLINA (Linagliptin)	Change in Albuminuria (UACR)	6% Reduction	Neutral

7. Safety Profiles and Therapeutic Tolerability

7.1. Adverse Events Associated with SGLT-2 Inhibition

7.1.1. Genitourinary Infections and Volume Depletion

The primary safety concern with SGLT-2 inhibitors is the increased incidence of genitourinary tract infections, specifically mycotic vulvovaginitis and balanitis, resulting from the high concentration of glucose in the urinary tract. These infections are typically mild to moderate and manageable with standard antifungal therapy [36]. Moreover, due to the osmotic diuretic effect, some patients particularly the elderly or those on loop diuretics may experience symptoms of volume depletion, such as orthostatic hypotension or dizziness. Clinical vigilance is required to monitor hydration status and adjust concomitant diuretic dosages upon initiation [37].

7.1.2. Rare but Serious Complications: Euglycemic DKA and Fournier's Gangrene

A rare but clinically significant adverse event is euglycemic diabetic ketoacidosis (DKA), where patients present with metabolic acidosis despite relatively normal blood glucose levels. This condition is often precipitated by illness, surgery, or extreme carbohydrate restriction and requires immediate cessation of the SGLT-2 inhibitor [38]. Additionally, rare cases of necrotizing fasciitis of the perineum (Fournier's gangrene) have been reported, necessitating prompt surgical evaluation if patients present with perineal pain or swelling [39].

7.2. Tolerability and Risks of DPP-4 Inhibition

7.2.1. General Safety and Gastrointestinal Profile

DPP-4 inhibitors are among the best-tolerated antihyperglycemic agents, with a safety profile comparable to placebo in many clinical trials. They do not cause significant gastrointestinal distress, weight gain, or volume-related issues [40]. This makes them an ideal choice for frail patients, the elderly, or those who have had poor experiences with other oral therapies.

7.2.2. Pancreatitis and Musculoskeletal Concerns

Early observational data raised concerns regarding a potential link between incretin-based therapies and acute pancreatitis. However, large-scale CVOTs and pooled meta-analyses have largely refuted this, showing no significant increase in pancreatitis risk compared to placebo [41]. Some post-marketing reports have identified severe joint pain (arthralgia) associated with DPP-4 inhibitors, which typically resolves upon discontinuation of the drug. Physicians should consider this possibility in patients presenting with new-onset joint symptoms [42].

8. Clinical Utility and Guidelines

8.1. Prioritizing Organ Protection in High-Risk Populations

Current international guidelines from the ADA, EASD, and KDIGO have evolved to recommend SGLT-2 inhibitors as a preferred second-line and in some cases first-line therapy for patients with established atherosclerotic cardiovascular disease, heart failure, or CKD [43,44]. The decision to initiate an SGLT-2 inhibitor in these populations is now made independently of baseline HbA1c or metformin use, recognizing that the cardio-renal benefits are distinct from the glycemic effects.

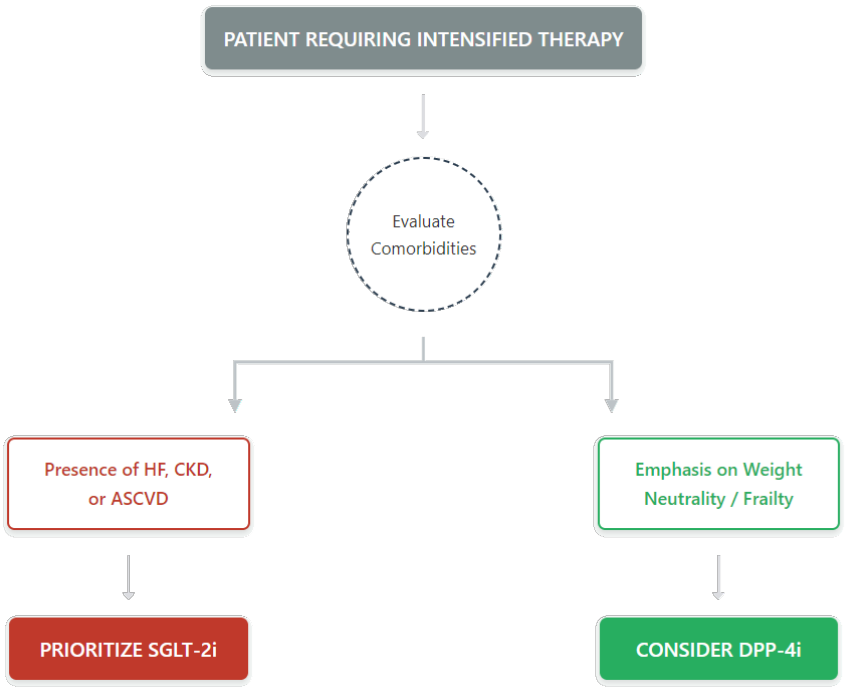


Figure 3. Clinician's Decision-Making in Type 2 Diabetes Mellitus

8.2. The Sustained Role of DPP-4 Inhibitors in Personalized Care

While SGLT-2 inhibitors are favored for their disease-modifying properties, DPP-4 inhibitors remain essential tools in the diabetic clinic. They are particularly valuable for:

- Patients with contraindications to SGLT-2 inhibitors (e.g., recurrent severe urinary infections or high risk for DKA).
- Individuals where weight loss or blood pressure reduction is not clinically desirable.
- Simplifying regimens in elderly patients where the risk of dehydration or orthostasis must be minimized.
- Providing safe glycemic control in advanced ESKD (specifically linagliptin) [45].

Table 5. Therapeutic Selection Matrix based on Patient Phenotype

Patient Clinical Phenotype	Preferred Class	Rationale
Established Heart Failure (HFrEF/HFpEF)	SGLT-2 Inhibitor	Superiority in HHF reduction and CV survival.
Chronic Kidney Disease (UACR >200mg/g)	SGLT-2 Inhibitor	Proven renoprotection and slowing of eGFR decline.
Obesity (BMI >30 kg/m²)	SGLT-2 Inhibitor	Promotes caloric loss and visceral fat reduction.
Advanced Age/Frailty	DPP-4 Inhibitor	High tolerability; minimal risk of orthostasis/dehydration.
Advanced ESKD (eGFR <15 ml/min)	DPP-4 Inhibitor*	Linagliptin is safe/effective; SGLT-2i loses glycemic efficacy.
Recurrent Genital Mycotic Infections	DPP-4 Inhibitor	Avoids increased risk of urinary glucose-mediated infections.

**Specifically Linagliptin due to non-renal excretion.*

9. Conclusion

The management of Type 2 Diabetes Mellitus has transitioned from a glucose-centric approach to a more complex, outcome-driven strategy. SGLT-2 inhibitors represent a transformative advancement, offering systemic hemodynamic and metabolic modifications that provide robust protection against heart failure and chronic kidney disease progression. Their ability to improve survival and reduce hospitalizations makes them indispensable for patients with existing or high-risk comorbidities. In contrast, DPP-4 inhibitors offer a highly tolerable, safe, and weight-neutral option that ensures effective glycemic control without increasing cardiovascular risk. Although they lack the organ-protective benefits of SGLT-2 inhibitors, their clinical versatility and safety profile ensure their continued relevance in personalized diabetes care. Optimal clinical outcomes in T2DM are increasingly dependent on the strategic selection of these agents, prioritizing SGLT-2 inhibition for cardiovascular and renal risk reduction while utilizing DPP-4 inhibitors to support stable, well-tolerated glycemic management. This individualized approach represents the current standard of care in achieving long-term disease modification and improving the quality of life for patients living with Type 2 Diabetes Mellitus.

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