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Research Paper

Pharmacological management of type 2 diabetes mellitus and diabetic kidney disease: a multi-pillar cardiorenal-protective approach

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is the most common cause of chronic kidney disease (CKD) all over the world, and diabetic kidney disease (DKD) is the single most common cause of end-stage kid disease (ESKD). Pharmacological treatment of T2DM primarily focused on glycemic control for the past 20 years, but monotherapy with glycaemic control has failed to halt progressive loss of nephrons as well as cardiovascular mortality in people with T2DM.
Objective: This narrative review summarises the pharmacology of the different classes of antihyperglycemic drugs and reviews the evidence for four cardinal strategies for the prevention, diagnosis and treatment of cardiorenal disease with T2DM: renin-angiotensin system (RAS) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RA), and non-steroidal mineralocorticoid receptor antagonists (ns-MRA).
Methods: A structured narrative search was performed of the PubMed/MEDLINE and Cochrane Library databases and ClinicalTrials.gov for landmark RCTs, regulatory labelling and current or recent American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO) guidance issued from 2008 to 2025.
Results: More than 32,000 participants have been included in six landmark cardiorenal outcome trials that all showed hazard ratio reductions between 13% and 39% (hazard ratios of 0.61-0.87) with SGLT2 inhibitors, the non-steroidal mineralocorticoid receptor antagonist, and GLP-1 receptor agonist, with few of these benefits attributed to glycated hemoglobin levels. The mechanism of action - tubuloglomerular feedback restoration, natriuresis, and anti-fibrotic mineralocorticoid-receptor blockade - which accounts for the resulting clinical benefit, is presented with a comparative synthesis of ten classes of antihyperglycemic drugs and their pharmacodynamic, pharmacokinetic properties and adverse effects, including those of renal dosing.
Conclusions: This has changed from a diabetes-centric approach to a multi-pillar, organ-protective approach, where the use of

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SGLT2 inhibitors, GLP-1 receptor agonists and ns-MRAs is for independent cardiorenal benefits rather than just for glycemic control. Converting evidence into the prescription of drugs routinely, especially under resource-limited conditions, is still an untapped need for human disease prevention, diagnosis and management.

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1. INTRODUCTION

It is estimated that currently 537 million adult people have diabetes mellitus and that the vast majority of them suffer from type 2 diabetes mellitus (T2DM) [1]. Diabetic kidney disease (DKD) is a common complication of T2DM, present in 30–40% of individuals with T2DM and is the leading cause of chronic kidney disease (CKD) and end stage kidney disease (ESKD) in the world. Hyperglycemia and hyperfiltration cause the cells to become enlarged; the basement membrane becomes thicker, and interstitial fibrosis ensues, with the consequent onset of albuminuria and reduction in the GFR. The presence of both T2DM and CKD significantly increases the risk of cardiovascular mortality, hospitalization for heart failure, and mortality from any cause [2] which led to an idea of linking them together as a cardiovascular-kidney-metabolic (CKM) syndrome by the American Heart Association.

The management of T2DM has been focused almost exclusively on glycated hemoglobin (HbA1c) targets for the majority of the modern era of pharmacology, with choice of drug mainly dependent on glucose lowering efficacy, hypoglycaemic risk and cost. UK Prospective Diabetes Study (UKPDS) demonstrated an only modest decrease in microvascular complications, compared with conventional treatment, in patients treated intensively with sulfonylureas or insulin [3]. Three later, properly powered outcome trials, however, did not demonstrate consistent lower rates of cardiovascular mortality and ACCORD was terminated early owing to greater mortality rates in the intensively treated group [4], [5], [6]. This lead to an obvious unmet need - a strategy that would be effective to preserve the heart and kidney separately from, or in addition to, achieving glycemic control.

This need has been partially met in the last two and a half decades, starting with trials that demonstrated that renin-angiotensin system (RAS) blockade with an angiotensin-receptor blocker (ARB) slows diabetic nephropathy, independent of blood pressure lowering [7] and more recently by two glucose-lowering drug classes, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), as well as the angiotensin-receptor blocker (ARB) called finerenone, a new non-steroidal mineralocorticoid receptor antagonist (ns-MRA) developed specifically for diabetic kidney disease. These independent, placebo-controlled outcome trials have all demonstrated reduction of kidney failure and cardiovascular mortality in T2DM and CKD patients, with T2DM showing significant reduction of composite outcome, largely irrespective of HbA1c levels.

This change is even more significant because of the magnitude of the underlying epidemic. Low- and middle-income countries are disproportionately affected by diabetes and many health systems lack capacity to screen for albuminuria, to monitor eGFR and to be able to provide newer cardiorenal agents.

Given that often pharmacological treatment for DKD is not undertaken until late in the disease process, public-health strategies would better be suited to pharmacological prevention, rather than rescue, as is more realistic, and this applies not only to the drugs that work but to the ones that work for the correct reasons, so that limited resources are spent on drugs with the best organ-protective rationale.

In spite of this evidence, the use of cardiorenal-protective drugs for the management of T2DM and CKD is still not being used in line with guideline recommendations – with many prescribers still choosing glucose-lowering agents based on their glycemic effect alone. Therefore, the aims of this review are (i) to update and summarize the comparative pharmacology (mechanism, pharmacokinetics, renal dose adjustment, adverse-effect profile) of major classes of antihyperglycemic drugs; (ii) to synthesize the clinical trial data regarding cardiorenal-protective pharmacologic therapies for T2DM-associated CKD; (iii) to present this information in a tabulated format that is results-oriented, as appropriate for the scope of this Journal; and (iv) to discuss mechanistic and translational considerations for prevention, diagnosis, and treatment of human disease.

2. RELATED WORK

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) have been the mainstays of the treatment of DKD since the early 2000s. In fact, the RENAAL trial showed that the use of losartan vs placebo was associated with a 16% risk reduction for a composite primary outcome (doubling of serum creatinine, ESKD, or death), as well as a 28% risk reduction for ESKD, which were observed beyond the reduction in blood pressure [7]. This and contemporary, concurrent trials were the basis for the renoprotection principle, thus allowing the use of ACEi (or ARB) at the maximum tolerated doses (MTDs) in patients with T2DM and albuminuria, and the subsequent introduction into the market of the new generation of SGLT1 inhibitors and GLP1 receptor agonists.

This evidence has been translated into clinical guidelines that have been promulgated in successive international guidelines. Based on new outcome-trial data, the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in KD recommends a cascade of interventions including lifestyle, metformin, ACEi/ARB, an SGLT2 inhibitor, and - if appropriate - GLP-1 receptor agonism and finerenone [8]. This was codified in a 2022 consensus document jointly developed by the ADA and the American Kidney Fund (KFF) which shifted the focus of choosing medication in T2DM-CKD from glycemic potency to organ protection [9] and is also reflected in the 2022 annual standards of care in diabetes from the ADA [10]. There is a switch from the glycemia-first, stepwise buildup algorithms that had guided CKD treatment earlier, to recommending an SGLT2 inhibitor as an option at the time of T2DM and CKD diagnosis. This guideline document, along with the pharmacokinetic literature listed in Table 1, makes up the body of knowledge upon which the evidence from the trials in Section 4 should be interpreted.

Table 1 provides some of the comparative clinical pharmacology of the major classes of drugs used for T2DM. Metformin is a biguanide which is almost always used first line, is associated with healthy glucose control, low risk of hypoglycaemia, and low weight gain risk; works by activating AMPK and blocking hepatic gluconeogenesis, and is cleared by the kidneys unchanged and needs to be reviewed when eGFR < 45 mL/min/1.73m^2 due to theoretical lactic-acidosis. Certain sulfonylureas become metabolically active in the body and this active metabolite is cumulative as renal function decreases, causing further increase in the risk of hypoglycemia, which is the primary drawback and a main advantage of the class. Most require dose reduction with decreasing eGFR, while any DPP-4 inhibitors with biliary-fecal clearance are not affected by eGFR decline; all are modest in glycemic efficacy and lack any documented cardiorenal benefit and are well tolerated. Thiazolidinediones work through PPAR-γ agonism and do not require renal dose adjustment and although they are effective at improving insulin sensitivity, have limited use due to fluid retention and the risk of heart failure which increases with reduced eGFR. Insulin should only be used if glycemic goals are not achievable with any other antidiabetic therapy, or in advanced CKD, when lower doses will be required because of reduced renal clearance and when there is an increased risk of hypoglycemia if not lowered as necessary beforehand. SGLT2 inhibitors and GLP-1 receptor activators form a unique class: 'organ-protective' drugs in regard to their renal-dosing and risk profiles, along with their

effects on glycemic control, that are well established and known to come with adverse effects (that are obviously different from other therapeutic groups; see section 4).

Table 1. Comparative Pharmacology of Major Antihyperglycemic Drug Classes

Drug Class	Representative Agents	Mechanism of Action	Typical HbA1c Reduction	Renal Considerations	Principal Adverse Effects
Biguanides	Metformin	Decreases hepatic gluconeogenesis via AMPK activation; decreases mitochondrial glycerophosphate dehydrogenase	1.0-1.5%	Dose review below eGFR 45; avoid below eGFR 30 (lactic acidosis risk)	GI upset, vitamin B12 deficiency, rare lactic acidosis
Sulfonylureas	Glimepiride, Gliclazide	Closes pancreatic beta-cell K-ATP channels, stimulating insulin secretion	1.0-1.5%	Active/renally cleared metabolites accumulate in CKD; hypoglycemia risk rises	Hypoglycemia, weight gain
DPP-4 inhibitors	Sitagliptin, Linagliptin	Inhibits DPP-4, prolonging endogenous GLP-1/GIP activity	0.5-0.8%	Most require dose reduction in CKD (linagliptin an exception)	Generally well tolerated; rare pancreatitis, arthralgia
SGLT2 inhibitors	Empagliflozin, Dapagliflozin, Canagliflozin	Inhibits proximal tubular SGLT2, causing glucosuria and natriuresis; resets tubuloglomerular feedback	0.5-1.0% (attenuates as eGFR falls; cardiorenal benefit persists)	Efficacious and indicated down to eGFR ~20; reduces intraglomerular pressure	Genital mycotic infection, volume depletion, euglycemic DKA (rare), Fournier gangrene (rare)
GLP-1 receptor agonists	Semaglutide, Liraglutide, Dulaglutide	Glucose-dependent insulin secretion, glucagon suppression, delayed gastric emptying, central satiety; direct natriuretic proximal-tubule effect	1.0-1.8%	Renal dose adjustment generally not required; caution with severe GI intolerance and volume loss	Nausea, vomiting, diarrhea, rare pancreatiti, gallbladder disease
Non-steroidal MRA	Finerenone	Selective mineralocorticoid receptor antagonism; reduces renal	Minimal (not a glucose-	Indicated for albuminuric CKD in T2DM on RAS	Hyperkalemia, hypotension

		inflammation and fibrosis independent of blood pressure	lowering agent)	inhibition; monitor potassium	
Thiazolidinediones	Pioglitazone	PPAR-gamma agonism, improves peripheral insulin sensitivity	0.5-1.4%	No renal dose adjustment, but fluid retention worsens with reduced eGFR	Weight gain, fluid retention, heart failure, fracture risk
Insulin	Basal and prandial analogues	Exogenous replacement/supplementation of endogenous insulin	Variable, dose-titratable, most potent	Requirements fall as eGFR declines (reduced renal clearance); hypoglycemia risk rises	Hypoglycemia, weight gain

The mechanisms of action of the newer classes of drugs is well described in previous mechanistic studies. The SGLT2 inhibitor blocks the SGLT2 co-transporter in the proximal convoluted tubule, resulting in more sodium and chloride delivered to the macula densa which restores tubuloglomerular feedback, and decreases intraglomerular pressure regardless of glycaemic control [11]. In fact, aldosterone-mineralocorticoid receptor signaling has been defined as a fourth pillar of therapy that is linked to renally pathogenic, inflammatory, fibrotic, and anti-natriuretic mechanisms in patients in whom BP alone is not implicated [12].

3. METHODOLOGY

This is a narrative review on the pharmacological aspects of the topic, not a systematic review; no data was collected or analyzed on patients. A structured search was conducted in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov from January 2008 to mid-2025 with the following combinations of search terms: type 2 diabetes, diabetic kidney disease, chronic kidney disease, SGLT2 inhibitor, GLP-1 receptor agonist, mineralocorticoid receptor antagonist, finerenone, cardiorenal outcomes, and randomized controlled trial. Pre-specified primary composite outcome for kidney and cardiovascular endpoints in studies with prospective intervention were given priority. Current guidance from the American Diabetes Association (ADA) and KDIGO (professional societies working on outcomes in kidney disease) were given priority [8], [9], [10]. The mechanistic literature that explained the physiological basis of the observed effect were given priority. Post hoc subgroup analyses with no hypothesis to test, non-English publications, abstracts and narrative commentaries without primary data were not included. Hazard ratios, confidence intervals and event rates were taken directly from the original trial reports, and have been cited appropriately; no statistical calculations were made, pooled or simulated by the authors. To capture the relationship between pharmacological mechanisms and the results of trials, a narrative instead of systematic design approach was taken for four drug classes aimed at a clinical audience. If a drug class had multiple trials dedicated to its treatment, the largest, most recent, and trial event driven trial with a pre-specified composite endpoint provided the basis for the primary discussion for that class of trials, while other trials were noted for context. Direct information from the primary manuscripts was used to construct the trial population characteristics and effect estimates in Table 2 and 3, which have been listed as 'like for like' to facilitate easy comparison, and to arrive at the safety and monitoring recommendations that are listed in Table 3, together with current prescribing advice.

4. RESULTS AND DISCUSSION

4.1 SGLT2 Inhibitors: Kidney and Cardiovascular Outcome Trials

The renoprotective effect of SGLT2 inhibition has been proven in three dedicated kidney-outcome trials. The primary composite outcome (doubling of serum creatinine [dSCr] or cases of renal/cardiovascular death) was reduced by 30%, hazard ratio (HR) 0.70 (95% confidence interval [CI] 0.59–0.82) [13] in CREDENCE, which randomized 4,401 participants with T2DM and albuminuria (UACR >300 mg/g) and eGFR 30–90 mL/min/1.73m^2 who were on background RAS blockade. Both diabetic and non-diabetic participants with CKD (eGFR 25–75, UACR ≥200 mg/g) were randomized to dapagliflozin or placebo. The primary composite endpoint of ≥50% eGFR decline or renal/cardiovascular death or renal/ESKD was reduced by 39% (HR 0.61, 95% CI 0.51–0.72) [14]. The broadest trial, EMPA-KIDNEY, included 6,609 participants who had at least moderate CKD (eGFR ≥ 20 mL/min/1.73m^2) with or without diabetes who experienced a 28% relative reduction in primary composite endpoint — a composite of kidney disease progression or cardiovascular death (HR 0.72; 95% CI 0.64–0.82) [15].

These kidney-outcome trials followed previous cardiovascular outcome trials used for glycemic-safety indications that also had a reduction in hospitalization for heart failure (HHFH), and showed a signal of amputation in CANVAS, followed by regulatory monitoring. These data overall suggest a diabetes-independent hemodynamic benefit to SGLT2 inhibition, and the benefit to the renal and cardiovascular system was found to be consistent across the range of eGFR values down to 20 mL/min/1.73m^2. Preplanned subgroup analyses across the 3 individual trials further illustrate benefit to be consistent across albuminuria categories, age subgroups and background dose of RAS-inhibitors.Consistency of benefit across preplanned subgroup analyses of the three trials is confirmed across the albuminuria categories, age categories and background dose of RAS-inhibitors. [16], [17], [18].

4.1.1 Pharmacokinetic and Dosing Implications

The cardiorenal benefits of SGLT2 inhibitors persist, despite a reduction in glycemic benefits - this is the direct implication of the dissociation of the glucosuric vs natriuretic effect from SGLT2 inhibitors - as filtered glucose load decreases, and glycemic effect may also decrease, hence this continues to be the primary rationale for initiating treatment down to an eGFR of ~20mL/min/1.73m^2, albeit with limited residual glucose effect.

4.2 GLP-1 Receptor Agonists

3,533 participants who were not hypocaloric in T2DM and had CKD (eGFR 50-75 with UACR >300 mg/g or eGFR 25-<50 with UACR >100 mg/g) were randomized to once weekly administration of semaglutide 1 mg or placebo in the dedicated kidney-outcome study FLOW. The same primary outcome (≥50% sustained eGFR decline, KD, or KD/CVD) was decreased by 24% (HR 0.76, 95% CI 0.66–0.88) and the secondary outcomes of MCE and deaths of all cause was reduced by 18% and 20%, respectively [19]. Inconsistent with a redundant mechanism, benefits were seen across all baseline SGLT2 inhibitor use groups, extending the broader GLP-1 agonist–mediated cardiometabolic benefit established in SELECT, which compared cardiovascular disease (but without diabetes) outcomes in people with overweight/obesity and hypertension, in whom cardiovascular events were reduced by semaglutide [20]. Mechanistically, GLP-1 receptor agonists act on peripheral GLP-1 receptors in the pancreas, stomach and central GLP-1 receptors to postulate the stimulation of glucose-dependent insulin secretion, suppression of glucagon secretion, slow gastric emptying and as a result of satiety. An additional role for GLP-1 receptor agonists is direct proximal-tubular action to inhibit the sodium-hydrogen exchanger isoform 3 (NHE3), which leads to natriuresis and diuresis without glycemic or weight effects; further proof of GLP-1 receptor agonists' activity on NHE3 has emerged in recent years. Although this effect has not yet been confirmed in a dedicated factorial trial of combined use in these classes, this is probably because of the undeniable difference in mechanism of action of the tubuloglomerular-feedback effect of SGLT2-inhibitors, explaining why these agents are pharmacologically and physiologically distinct yet complementary.

4.3 Non-Steroidal Mineralocorticoid Receptor Antagonism

The primary kidney composite outcome of kidney failure, ≥40% eGFR decrease or renal death was 18% less (HR 0.82, 95% CI 0.73–0.93) with finerenone than with placebo, when added to RAS blockade, in 5,734 patients with T2DM and stage mostly 3–4 CKD and severe albuminuria [21]. There was a significant reduction in the primary cardiovascular composite outcome [22] and a reduction in the secondary kidney composite outcome [23] of 13 (0.76–1.01, with a confidence interval slightly above unity) and 16 (0.84–1.09, with confidence interval crossing unity), respectively, after enrolling 7437 participants with earlier-stage CKD and moderately elevated albuminuria in the study.After enrolment of these 7437 participants with earlier-stage CKD and moderately elevated albuminuria, the primary cardiovascular composite outcome was reduced by 13 (0.76–1.01), narrow enough to even cross unity, and significant reduction in the secondary kidney composite outcome by 16 (0.84–1.09) (with confidence interval crossing unity). A pooled FIDELITY analysis showed the general cardiorenal benefit regardless of the range of severity of CKD studied [23]. Renal inflammation, fibrosis and conservation of sodium are negatively regulated by aldosterone – mineralocorticoid receptor belonging to the immune system and kidney independent of blood pressure. Prior steroidal MR antagonists (spironolactone, eplerenone) decelerate albuminuria, but have significant hyperkalemic and antiandrogenic properties that have restricted their use to CKD. In comparison to steroidal MR antagonists, which have been reported to cause hyperkalemia and lead to withdrawal from treatment, a non-steroidal MR antagonist with more favorable kidney tissue concentrations (balanced versus heart tissue) and a shorter half-life (half-life of 81 hours versus 15.3–15.8 hours) is more likely to be discontinued due to occurrences of hyperkalemia.A non-steroidal, more balanced kidney tissue concentration versus heart tissue, and with a shorter half-life (81 hours versus 15.3–15.8 hours), than steroidal MR antagonists, has been shown to have lower incidence rates of continuing administration due to hyperkalemia.

4.4 Synthesis of Effect Sizes

Table 2 shows the characteristics of the six landmark cardiorenal outcome trials mentioned above with details regarding their design, population and effect estimates. These trials as collectively showed in Table 2 recruited a total number of over 32000 subjects and produced a reduction in the hazard ratio of 13%–39% in each trial for their primary composite outcomes.

Table 2. Landmark Cardiorenal Outcome Trials in Type 2 Diabetes and Chronic Kidney Disease

Trial (Drug)	N	Population	Primary Composite Outcome	HR (95% CI)	Relative Risk Reduction
CREDENCE (canagliflozin)	4,401	T2DM, UACR >300 mg/g, eGFR 30-90	ESKD, doubling of serum creatinine, or renal/CV death	0.70 (0.59-0.82)	30%
DAPA-CKD (dapagliflozin)	4,304	CKD +/- T2DM, eGFR 25-75, UACR >=200 mg/g	>=50% eGFR decline, ESKD, or renal/CV death	0.61 (0.51-0.72)	39%
EMPA-KIDNEY (empagliflozin)	6,609	CKD +/- T2DM, eGFR 20-45, or 45-90 with UACR >=200	Kidney disease progression or CV death	0.72 (0.64-0.82)	28%
FIDELIO-DKD (finerenone)	5,734	T2DM + CKD, UACR 30-5000 mg/g	Kidney failure, >=40% eGFR decline, or renal death	0.82 (0.73-0.93)	18%
FIGARO-DKD (finerenone)	7,437	T2DM + earlier-stage CKD, moderately elevated albuminuria	CV death, MI, stroke, or HF hospitalization	0.87 (0.76-1.01)	13%
FLOW (semaglutide)	3,533	T2DM + CKD, eGFR 50-75/UACR >300 or	>=50% eGFR reduction, kidney	0.76 (0.66-0.88)	24%

		eGFR 25-<50/UACR >100	failure, or kidney/CV death		

This forest plot is a display of the hazard ratios and 95% confidence intervals of the primary composite outcome for the six different trials (Figure 1). The shade of ALL suggests that all six point estimates are in favor of active treatment, and the thinness of the envelope for active treatment in both studies (FIGARO-DKD and cardiovascular) and the width of the envelope for passive treatment in both studies (DAPA-CKD and kidney) represents the range of benefit seen within drug classes and study populations.

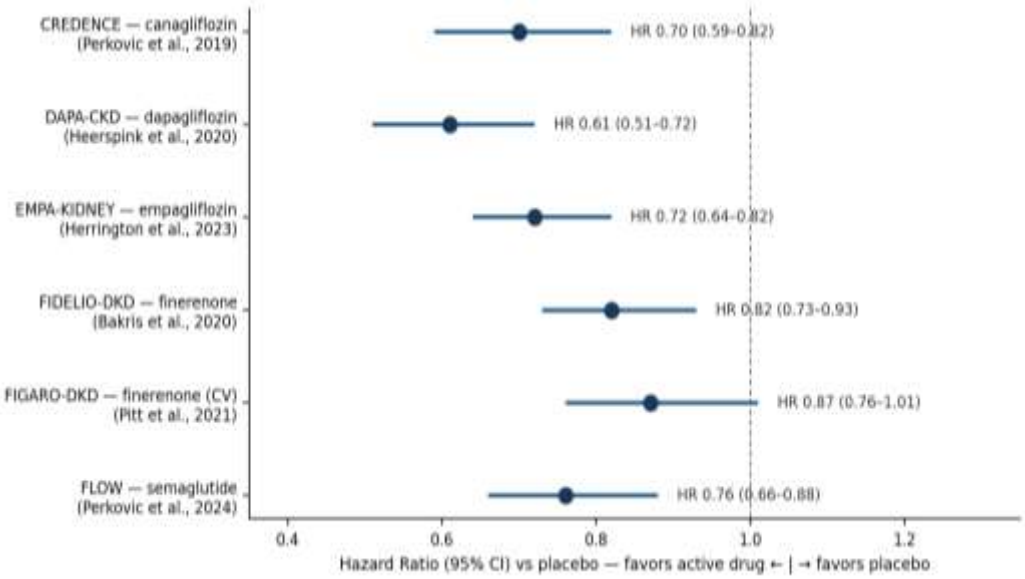

Figure 1. Cardioprotective Effects of Pharmacological Agents on Primary and Cardiovascular Outcomes in Landmark Randomized Trials

Figure 1. Effect of pharmacological cardiorenal-protective agents on primary composite kidney/cardiovascular outcomes in landmark randomized trials. Point estimates and 95% confidence intervals extracted directly from the primary trial publications [13], [15], [19], [21], [22].

4.5 Adverse Effects and Pharmacological Safety Monitoring

In summary, the cardiorenal-protective agents discussed above have a range of clinically relevant safety requirements, which are summarized in Table 3, based on trial-reported safety data and mechanistically predictable risk. Table 3, shown here, highlights areas where counselling is required when patients are taking these drugs: proSGLT2 inhibitors: counselling regarding risks of genital mycotic infections; proRAS inhibitors: counselling regarding risk of interruption of the drug due to sick days; proGLP-1 receptor agonists: counselling regarding gastrointestinal intolerance, which requires gradual titration; and profinerenone: counselling regarding structured potassium monitoring, particularly in the presence of RAS inhibitors.

Table 3. Safety Profile and Monitoring for Cardiorenal-Protective Pharmacotherapy

Drug Class	Key Adverse Effects Observed in Trials	Absolute Incidence Signal	Recommended Monitoring
SGLT2 inhibitors	Genital mycotic infection; volume depletion; rare euglycemic diabetic ketoacidosis; lower-limb	Genital infection ~4-8x placebo rate in pooled trial data	Baseline and periodic eGFR (transient dip expected, not a reason to stop); genital hygiene

	amputation signal (canagliflozin, CANVAS)		counselling; sick-day rules
GLP-1 receptor agonists	Nausea, vomiting, diarrhea (dose-dependent, usually transient); rare acute pancreatitis; gallbladder disease	GI adverse events in 20-40% during titration	Slow dose titration; avoid in personal/family history of medullary thyroid carcinoma or MEN2
Non-steroidal MRA (finerenone)	Hyperkalemia	Hyperkalemia-related discontinuation 2.3% (finerenone) vs 0.9% (placebo), FIDELIO-DKD	Serum potassium at baseline, 4 weeks after initiation, and periodically thereafter; avoid initiation if potassium >5.0 mmol/L
RAS inhibitors (ACEi/ARB)	Hyperkalemia, acute kidney injury with volume depletion, cough (ACEi), angioedema (rare)	Class-established over two decades of use	Serum creatinine and potassium 1-2 weeks after initiation or dose change

None of these tolerability factors was enough to offset the overall cardiorenal advantage at a population level, but may be of importance when considering each individual, especially in cases of baseline hyperkalemia, recurrent genitourinary infection or family history of medullary thyroid carcinoma. The monitoring requirements of the three classes on top of the RAS inhibitors, on which other monitoring is built, are also known, and these additional layers of monitoring can include monitoring potassium and electrolytes 1–2 weeks after the introduction or a change in the dose of both finerenone and RAS inhibitors combined.

4.6 Integrated Pharmacological Management Approach

The consensus guidance updated recently by ADA and KDIGO (2022) [9] recommends using a 'layered' approach as set in the aforementioned Key points/Table 2 whereby the first 3 tiers of therapies (1) Lifestyle intervention and metformin in the background (if possible in eGFR ≥20 mL/min/1.73m^2); (2) titrating an ACEi or ARB to maximum tolerated dose for any patient with hypertension and albuminuria; and (3) initiation of an SGLT2 inhibitor in essentially all patients with T2DM and CKD (eGFR ≥20 mL/min/1.73m^2), regardless of glycemic control) should then be complemented and/or reinforced with a GLP-1 receptor agonist and/or finerenone in those cases where a high risk of cardiorenal or albuminuric adverse event exist despite the above (4). This is a change from a glycemia focused approach to a more organ protection-oriented pharmacology-based approach, and glycemic control is an objective of therapy pitted against others.

4.7 Discussion

Pharmacological evidence presented here indicates that the clinically relevant effect of SGLT2 inhibitors, GLP-1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists on T2DM-associated kidney disease is also primarily through the mechanisms independent of glucose lowering: hemodynamic control of intraglomerular pressure through tubuloglomerular feedback restoration (TGF; SGLT2 inhibitors) [11] and direct natriuretic proximal-tubular signaling (GLP-1 receptor agonists) [12] and anti-inflammatory, anti-fibrotic mineralocorticoid receptor blockade (finerenone) [12]. This mechanistic diversity is responsible for the additivity between the three classes, rather than redundancy, and makes the combination-therapy approach adopted here take more than a note of sense that is recommended by international guidelines.

An important observation across the trials is that glycemic and cardiorenal benefit occurs separately: renal benefit in DAPA-CKD/EMPA-KIDNEY was comparable irrespective of initial HbA1c, and finerenone, with very little glucose lowering effects, had similar impact as glucose lowering medications

[14], [15], [21], [22]. Implication for prescribers: A patient is not more likely to have an unmet glycemic target if they are on an SGLT2 inhibitor, GLP-1 or finerenone for any reason and should not be consistently delayed until the target is incomplete. This also supports biomarker guided selection among the three add-on pillars (baseline eGFR, UACR, cardiovascular risk) to sequence therapy, which aligns with KDIGO practice points, but did not yet submit to specific studies on sequencing.

There are wide-spread "real world" barriers facing implementation of this evidence beyond those addressed in efficacy trials. However, an analysis of the adoption of these drugs across multiple health systems indicates that the use of SGLT2 inhibitors and finerenone is low among eligible patients, driven by clinical inertia, economic considerations, and the impact of cost and formulary constraints, and not by inadequate trial evidence. Whereas pillars one and two, with the generic introduction of entry and expansive availability of cheap intrinsic products (the RAS-inhibitor and the metformin backbone), are feasible in most health systems today, pillars three and four are still aspirational, in particular at very high out-of-pocket costs which remain several times higher than an average patient's monthly income on branded SGLT2 inhibitors and GLP-1 receptor agonists, respectively. This is further hindered by the fact that clinician-level barriers remain prevalent, including many primary-care prescribers—even some specialty trainees—still considering both SGLT2 inhibitors and GLP-1 receptor agonists as glucose-lowering drugs and not realizing that current labelling justifies their clinical benefit for cardiorenal protection, independent of glycemic control.

The role of the four pillars in this type of development is yet to be determined by outcome trials that are still to come in combination pharmacotherapy trials for T2DM-associated kidney disease; next generation dual incretin receptor agonist therapies; and aldosterone synthase inhibitors. Head-to-head and factorial-design trials would help to clarify whether all three are equally effective as add-on regimens – and whether one can clearly prescribe the most cost-effective sequence of teachers – when all three are used concurrently, and would help inform clinical findings.

This is not a systematic review per se; a formal risk-of-bias assessment, PRISMA based selection and meta-analytic pooling were not performed, and readers interested in a systematic synthesis should refer to the specific meta-analysis mentioned below. The hazard ratios shown in Table 2 and Figure 1 were from cross-trial analyses and have important limitations such as differences between the primary-outcome definitions in each trial, eligibility criteria, and background exposure to T2DM therapies (including low exposure to SGLT2 inhibitors in the finerenone trials); caution should be exercised when attempting to directly conduct a cross-trial comparison. This review did not explore extent to which real-world effectiveness, adherence, and cost-related access barriers, especially in low- and middle-income countries, exist and exists as a priority for future implementation research.

5. CONCLUSION

There are more and more progressed steps for the pharmacological management of T2DM that have shifted from a glycemia-centered to a multi-pillar, cardiorenal-protective model. In addition to renin-angiotensin system medication, each of SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone, a potential non-steroidal MRAs, appear to work through unique, additive mechanisms to decrease the composite outcome of kidney failure and cardiovascular death in T2DM and CKD, with a TG2 action largely independent of glycemic control. One of the biggest challenges in current internal medicine and clinical pharmacology is turning this evidence into earlier, more widespread and more consistent prescriptions. Future studies should place a greater emphasis on implementation research in the real world, equity for resources scarce patients, and dedicated sequential or combination trials, establishing the order of the four pharmacological pillars. In the individual prescriber, the bottom line is simple: Consider the drugs in parallel with achieving the glycemic goals in patients with T2DM and CKD to avoid the cost of delay, and avoid nephron loss in addition to the associated excess cardiovascular events; the cardiorenal benefits of these drugs are independent of glycemic control.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Dr. Mosrur Ahmed	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study and their voluntary consent was obtained prior to data collection.

Ethical Approval

Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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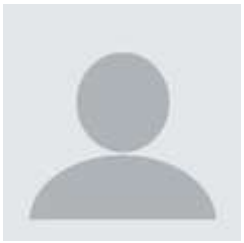

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