Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

# Role of Sodium-Glucose Transport Protein-2 Inhibitors in Renal Protection: A Narrative Review from the Cardiovascular-Kidney-Metabolic Interconnection

Nan Ye, Hong Cheng

Department of Nephrology, Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China

Correspondence: Hong Cheng, Department of Nephrology, Beijing Anzhen Hospital, Capital Medical University, No. 2, Anzhen Road, Chaoyang District, Beijing, 100029, People's Republic of China, Email drchengh@163.com

Drug Design, Development and Therapy downloaded from https://www.dovepress.com/
For personal use only.

**Abstract:** Cardiovascular-kidney-metabolic (CKM) diseases pose a significant global health burden and are becoming a major healthcare challenge. The intricate interplay among type 2 diabetes mellitus (T2D), cardiovascular disease (CVD) and chronic kidney disease (CKD) has been well established. Therefore, comprehensive management and early intervention are crucial to improving patient outcomes and reducing the strain on medical resources. This narrative review discusses the critical role of renal protection in the context of CKM syndrome, with a focus on the importance of sodium-glucose cotransporter-2 (SGLT-2) inhibitors. These drugs play a significant role in renal protection and in managing a variety of metabolic and cardiovascular disorders or risk factors. Additionally, the review underscores the challenges faced in managing CKM syndrome and suggests potential future directions in China. This reflects a comprehensive approach aimed at enhancing public health strategies in managing the complex interplay among kidney health, cardiovascular function, and metabolic status.

**Keywords:** sodium-glucose cotransporter-2, cardiovascular-kidney-metabolic syndrome, chronic kidney disease, heart failure, cardiovascular disease, type 2 diabetes mellitus

## Introduction

Emerging evidence suggests that there is a strong interplay among type 2 diabetes mellitus (T2D), cardiovascular disease (CVD) and chronic kidney disease (CKD), such that the likelihood of having a second condition will greatly increase if a patient has one of these conditions.[1–4] The cardiovascular-kidney-metabolic (CKM) syndrome, as defined by the American Heart Association (AHA), is a systemic health disorder arising from the interplay of obesity, T2D, CKD, and CVD, including heart failure, atrial fibrillation, coronary heart disease, stroke, and peripheral artery disease. It encompasses individuals at risk for CVD as well as those with established CVD.[5] The AHA defined CKM syndrome stages as a continuum, starting from no CKM risk factors (stage 0), progressing to excess or dysfunctional adiposity (Stage 1), metabolic risk factors or moderate-to-high-risk CKD (Stage 2), subclinical CVD in CKM syndrome or risk equivalents (Stage 3), and finally clinical CVD in CKM syndrome (Stage 4). Each stage reflects an increasing severity of cardiovascular, kidney, and metabolic dysfunction. It is recognized that CKM diseases are emerging as a major healthcare challenge worldwide, which not only affects the health of individual patients but also has a profound impact on public health systems.

Globally, it is estimated that there are 589 million,[6] 64.3 million,[7] and 697.5 million[8] people with diabetes, heart failure (HF), and CKD, respectively. According to the National Health and Nutrition Examination Survey (NHANS) between 2011 and 2018, 14.9% of US adults had diabetes, 38.2% had metabolic syndrome, 12.8% were at risk of CKD, and 9.0% reported CVD.[9] In China, the number of prevalent cases is 115.8 million for T2D,[10] 8.9 million for HF,[11] and 82 million for CKD.[12] CVD (47.1%) and diabetes (2.5%) were among the top four causes of mortality in the Chinese population in 2019.[10] Beyond mortality, each CKM condition contributes substantially to the disease burden of Chinese patients. For instance, T2D

https://doi.org/10.2147/DDDT.S540082
Received: 13 May 2025
Accepted: 20 December 2025
Published: 20 January 2026



© 2026 Ye and Cheng. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

accounted for over 11.5 million disability-adjusted life years.[13] The average annual treatment cost per HF patient was approximately 28,974 renminbi (RMB), with the majority of expenditure spent on inpatient care and only 8.2% spent on HF medication.[14] A study by Yang et al[15] explored the evolving CKD spectrum and its implications for public health. It was estimated that approximately 1.06 million Chinese patients had end-stage kidney disease due to diabetes, resulting in an annual dialysis cost of 1.06 billion RMB.[15]

Epidemiological data have highlighted the prevalence of AHA-defined CKM syndrome stages (Stage 0 to Stage 4) across different populations. Analysis of NHANS data from 2011 to 2020 revealed that nearly 90% of US adults met the criteria for CKM syndrome, with 15% classified in advanced stages. The age-adjusted prevalence of CKM syndrome stages 0 to 4 were 10.6%, 25.9%, 49.0%, 5.4%, and 9.2%, respectively. A similar trend was observed in a prospective UK cohort study, where the distribution of CKM stages was reported as 9%, 6%, 71%, 1%, and 13%.[16,17] In China, the majority of patients with CKM syndrome were found to be in the early stages, with stage 1 and stage 2 accounting for 25.4% and 53.6% of cases, respectively.[18] Since a more advanced stage of the syndrome was significantly associated with an increased risk of all-cause mortality, these findings underscore the need for comprehensive management and early interventions to improve patient outcomes and reduce the medical burden.

Over the past few decades, the development and implementation of clinical practice guidelines have also gradually evolved from focusing on a single disease to a more comprehensive, patient-centered approach.[5,19–21] This approach not only concentrates on treating the disease itself, but also prioritizes the overall health status and quality of life of the patient. The integrated management of CKM diseases exemplifies this patient-centered treatment strategy. A holistic treatment method for these diseases can yield multiple clinical benefits, greatly simplify the treatment plan, and provide a more efficient disease management strategy for patients.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, initially developed as glucose-lowering agents, are characterized by a unique mechanism of action for glycemic control. Over the past decade, accumulating evidence has demonstrated that SGLT-2 inhibitors not only confer cardiorenal protection independent of their glucose-lowering effects, but also slow kidney disease progression in individuals with CKD, regardless of underlying etiology or T2D status. Additionally, SGLT-2 inhibitors improve clinical outcomes in HF patients, irrespective of the ejection fraction level, while maintaining a generally favorable safety profile. In this regard, the expanding clinical applications of SGLT-2 inhibitors in the treatment of T2D, HF and CKD diseases have opened up new possibilities for the integrated management of CKM syndrome and have become an important component of the integrated management plan.

In this narrative review, we aim to summarize the current understanding of the mechanism of action of SGLT-2 inhibitors in CKM syndrome. We also aim to highlight their growing role in the treatment paradigm and provide a reference for nephrologists, endocrinologists, cardiologists, primary care physicians, and other medical specialists to formulate effective clinical management strategies.

To ensure the current literature was available for the review, we searched PubMed, EMBASE, the Cochrane Library, UpToDate, Wanfang Medical Database, China National Knowledge Infrastructure (CNKI), and Baidu Scholar for literature published up to October 2025 on the clinical diagnosis and management of CKM syndrome and the clinical application of SGLT-2 inhibitors. The search was limited to large randomized controlled trials (RCTs), large prospective/retrospective data analyses, systematic reviews, meta-analyses, and clinical management consensuses or guidelines. Duplicate publications, small-sample clinical reports, commentaries, editorials, letters, news reports, narrative reviews, and conference abstracts that were not published in peer-reviewed journals were excluded.

## The Interconnection Among Cardiovascular-Kidney-Metabolic Diseases

It is now recognized that CKM diseases often begin subtly early in life and are closely linked through overlapping risk factors, including hypertension, diabetes, dyslipidemia, obesity, and chronic inflammation. These risk factors share similar pathological mechanisms with CKM diseases, contributing to the activation of inflammatory pathways, oxidative stress, insulin resistance, renin-angiotensin-aldosterone system (RAAS) dysregulation, endothelial dysfunction, and a tendency for thrombosis. These conditions often coexist and exacerbate one another, forming a complex network for disease progression. Disorders like T2D and obesity contribute to systemic inflammation, insulin resistance, and dyslipidemia, which increase the risk of endothelial dysfunction, a precursor to cardiovascular diseases and

microvascular kidney damage. Metabolic dysfunction and hypertension drive cardiovascular diseases like atherosclerotic cardiovascular disease (ASCVD), with atherosclerosis impairing blood flow to vital organs, including the kidneys, and leading to CKD. In turn, CKD worsens cardiovascular and metabolic diseases by causing fluid retention, hypertension, electrolyte imbalances, and impairments in glucose and lipid metabolism.[22]

Atherosclerosis plays a central role in the development and progression of CKM diseases, serving as a key etiological factor directly linked to CKM syndrome. Population-based retrospective studies demonstrate that subclinical atherosclerosis, as assessed by the coronary artery calcium (CAC) score, is independently associated with an increased risk of adverse cardiovascular outcomes and all-cause mortality in patients with CKM risk factors, including CKD, diabetes, and metabolic syndrome.[23–25]

Extensive epidemiological and clinical research showing that conditions like T2D, CVD and CKD often coexist and share common pathological mechanisms has shaped the concept of CKM syndrome.[1] In the past 5 years, several Chinese and International Societies have released guidelines or scientific statements that focus on the early prevention and risk factor screening, as well as interdisciplinary care models to effectively manage these interconnected diseases.[26–37] In 2023, the American Heart Association (AHA) convened a multidisciplinary group of experts and issued a presidential advisory for CKM,[5] concluding that CKM syndrome represents a multidirectional pathophysiology leading to increased morbidity and mortality, exceeding the mere aggregate of its components. Chinese researchers have proposed a sixth innovative cardiorenal syndrome (CRS) subtype, based on the concept of "chronic co-impairment" of the heart and kidneys. This subtype is characterized by the onset of chronic systemic conditions such as diabetes, hypertension, amyloidosis, and systemic lupus, followed by a gradually progressive decompensation and decline in cardiac and renal function, ultimately leading to cardiac and renal failure.[38] This novel type 6 CRS definition closely aligns with the concept of CKM disease.

## Kidney Sits at the Intersection of Cardiovascular-Kidney-Metabolic Diseases

Kidney disease often arises as a secondary condition to cardiovascular (CV) or endocrine disorders. T2D is a major driver of CKD, with approximately 40% of T2D patients also having a diagnosis of CKD.[3] Persistent hyperglycemia and insulin resistance in T2D trigger harmful processes such as glomerular hyperfiltration, oxidative stress, and inflammation, leading to progressive kidney damage characterized by glomerular injury, albuminuria, and declining renal function. Conversely, CKD can lead to metabolic dysregulation, worsening insulin resistance, and contributing to the onset or progression of T2D. The incidence of T2D is significantly higher in patients with CKD compared with the general population.[39,40] Although the underlying mechanism remains unclear, contributing factors may include insulin resistance, metabolic acidosis, vitamin D deficiency, or toxin accumulation due to impaired kidney function.[22]

A similar observation has also been reported in patients with HF, where half of them also experience CKD.[4] Conversely, kidney disease can also lead to multiple complications including an increase in the risk of CV events.[22] CKD patients often have elevated blood pressure, lipid metabolism disorders, anemia, etc. Together, these factors increase the workload on the heart and the risk of myocardial infarction and heart failure.

The CKM AHA Presidential Advisory advocates measurement of the urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) in patients with CKD, diabetes, hypertension or metabolic syndrome. This underscores the increasingly pivotal role of kidney function in CKM diseases.[5] In line with this, kidney protection and delaying CKD progression are crucial components of the comprehensive CKM care model structure.[5]

From a clinical perspective, kidney function can also pose a barrier to the treatment of CV or endocrine disorders. Renal insufficiency can reduce drug clearance and increase the risk of drug accumulation and adverse reactions,[41] thereby impacting the number of drug classes and standard doses that patients can tolerate. Severely reduced renal function will also restrict the application of guideline-recommended medical therapy (GDMT) in managing these diseases.

## Mechanism of Action and Clinical Evidence of the Beneficial Effects of SGLT-2 Inhibitors for Renal Protection in the Context of CKM Disease

### Mechanism of Action

The primary mechanism of action of SGLT-2 inhibitors involves inhibition of the coupled reabsorption of sodium and glucose from the glomerular filtrate in the proximal renal tubule, leading to increased excretion of sodium and glucose in

the urine.[42] Additionally, SGLT-2 inhibitors exhibit a multifaceted mechanism of action that benefits cardiovascular, renal, and metabolic health (Figure 1).

SGLT-2 inhibitors can exert a variety of nephroprotective effects by direct effects on kidney function. They can increase distal sodium delivery, restore tubule-glomerular feedback, and decrease intraglomerular pressure, which subsequently reduces albuminuria. By reducing the solute transport load in proximal tubules, SGLT-2 inhibitors can potentially alleviate their energy burden. SGLT-2 inhibitors may also boost oxygen supply via increased ketone production and erythropoietin secretion, further reducing the risk of hypoxia. Lastly, SGLT-2 inhibitors can prevent inflammation and fibrosis, and ameliorate kidney mitochondrial metabolism to protect renal function.[43,44]

SGLT-2 inhibitors also demonstrate beneficial effects beyond the kidney. Firstly, they improve metabolism by reducing glucotoxicity, which helps decrease HbA1c levels by 0.7%.[45,46] Additionally, they are also capable of lowering uric acid levels. Furthermore, SGLT-2 inhibitors can reduce afterload through arterial vasodilation and diminish preload via natriuresis and diuresis, leading to a decrease in effective circulating volume and blood pressure. They can also prevent cardiac remodeling, enhance cardiac function, and improve cardiac efficiency.[47,48]

## SGLT-2 Inhibitors Can Improve a Range of Metabolic and Cardiovascular Risk Factors Associated with CKD

As medications primarily used to manage T2D, SGLT-2 inhibitors not only improve glycemic control, but also positively impact body weight, uric acid levels, and lipid profiles, and provide CV benefits, all of which are risk factors for CKD development.

The CV benefits of SGLT-2 inhibitors, including a reduction in major adverse CV events such as heart failure, myocardial infarction, and stroke, have been substantiated by a series of Phase 3 RCTs (Table 1). [49–62] A recent meta-analysis involving 90,943 patients demonstrated that, compared with standard of care, SGLT-2 inhibitors resulted in a 14% reduction in CV mortality, a 12% reduction in all-cause mortality, an 11% reduction in major adverse CV events, a 30% reduction in HF hospitalizations, and a 23% reduction in the combined outcome of CV death or HF hospitalization.[63] A retrospective study further indicated that the use of SGLT-2 inhibitors in patients with T2D and CKD was associated with a 20% reduction in the risk of new-onset stroke compared with non-users.[64]

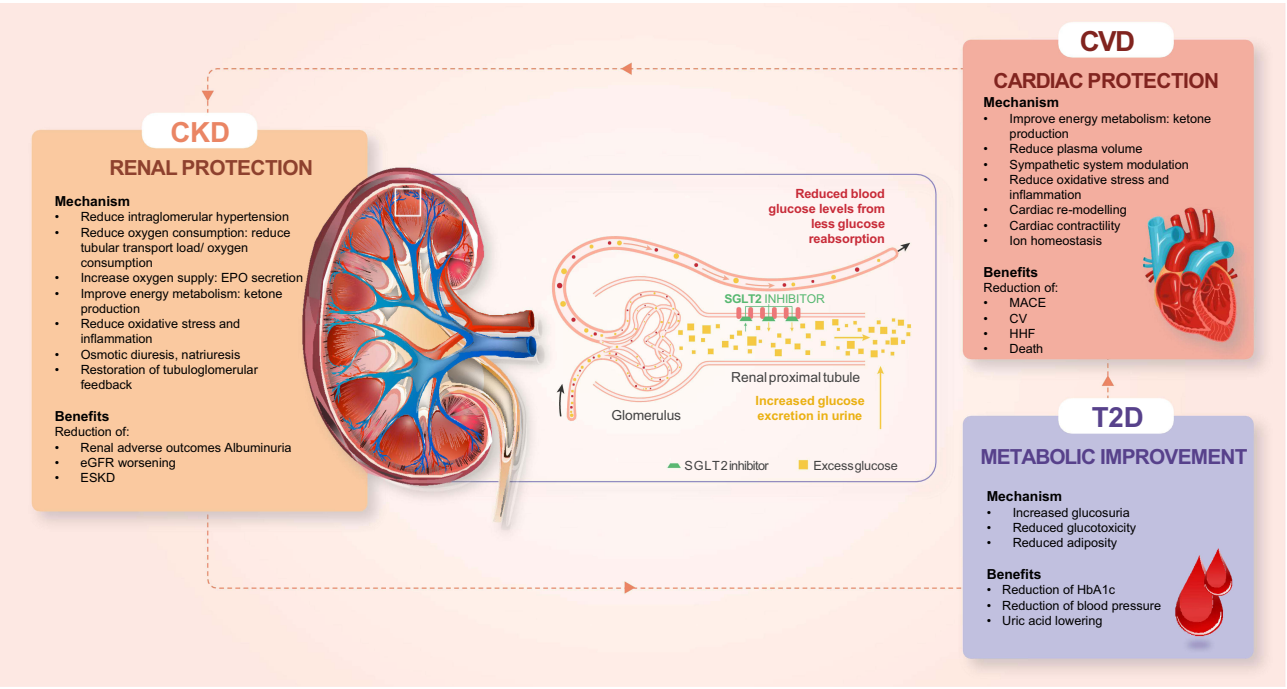


**Figure 1** Mechanism of action and clinical benefits of SGLT-2 inhibitors.

**Table 1** Summary of Key Randomized Clinical Trials of SGLT-2 Inhibitors

| Clinical Trials | Patients (n) | Median Follow-Up (Years) | Trial Population | Primary Endpoint (s) | Effect of SGLT-2 Inhibition on Glycemic Control | Effect of SGLT-2 Inhibition on Kidney Related Outcomes | Effect of SGLT-2 Inhibition on Cardiovascular Related Outcomes |
|---|---|---|---|---|---|---|---|
| **CV outcome trials** | | | | | | | |
| EMPA-REG OUTCOME[49,50] (empagliflozin 10 mg or 25 mg) | 7020 | 3.1 | Type 2 diabetes with established cardiovascular disease | Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | HbA1c: adjusted mean difference vs placebo at week 12: empagliflozin 10 mg: −0.54 percentage points (95% CI −0.58 to −0.49); empagliflozin 25 mg: −0.60 percentage points (95% CI −0.64 to −0.55) | Incident or worsening nephropathy; HR, 0.61; 95% CI 0.53 to 0.70; *P*<0.001<br>Doubling of the serum creatinine level: empagliflozin: 1.5% vs placebo 2.6%<br>Renal-replacement therapy: empagliflozin 0.3% vs placebo 0.6% | The composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: empagliflozin 10.5% vs placebo 12.1% (HR, 0.86; 95.02% CI 0.74 to 0.99; *P*=0.04 for superiority) |
| DECLARE-TIMI 58[52] (dapagliflozin 10 mg) | 17,160 | 4.2 | Type 2 diabetes with established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease | Primary safety endpoint: MACE (cardiovascular death, myocardial infarction, ischemic stroke)<br>Primary efficacy endpoints: MACE and a composite of cardiovascular death or hospitalization for heart failure | HbA1c: average least-squares mean absolute difference vs placebo: −0.42%; 95% CI 0.40 to 0.45 | Renal composite (≥40% decrease in eGFR to <60 mL/min/1.73 $m^2$, new ESRD, or death from renal or cardiovascular causes): HR, 0.76; 95% CI,0.67 to 0.87<br>Kidney-specific outcome in low KDIGO risk category: HR, 0.54 (95% CI 0.38 to 0.77, *P*<0.001)<br>Slope of eGFR decline in low KDIGO risk category: between-arm differences of 0.87 [chronic] and 0.55 [total] mL/min/1.73 $m^2$/year; *P*<0.0001 | MACE: HR, 0.93; 95% CI, 0.84 to 1.03; P=0.17 for superiority)<br>Cardiovascular death or hospitalization for HF: HR, 0.83; 95% CI, 0.73 to 0.95; P=0.005 for superiority) |
| CANVAS Program[51] (canagliflozin 100–300 mg) | 10,142 | 2.4 | Type 2 diabetes with a history of symptomatic atherosclerotic cardiovascular disease or risk factors for cardiovascular disease | Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | $HbA1_C$: mean difference vs placebo: −0.58% (95% CI –0.61 to –0.56) | The composite outcome (a sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes): HR, 0.60; 95% CI 0.47 to 0.77<br>Progression of albuminuria: HR, 0.73; 95% CI 0.67 to 0.79 | The composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR, 0.86; 95% CI 0.75 to 0.97; *P*<0.001 for noninferiority; *P*=0.02 for superiority |

(*Continued*)

https://doi.org/10.2147/DDDT.S540082

**Table 1** (Continued).

| Clinical Trials | Patients (n) | Median Follow-Up (Years) | Trial Population | Primary Endpoint (s) | Effect of SGLT-2 Inhibition on Glycemic Control | Effect of SGLT-2 Inhibition on Kidney Related Outcomes | Effect of SGLT-2 Inhibition on Cardiovascular Related Outcomes |
|---|---|---|---|---|---|---|---|
| VERTIS CV[61] (ertugliflozin 5 mg or 15 mg) | 8246 | 3.0 | Type 2 diabetes with established atherosclerotic cardiovascular disease involving the coronary, cerebrovascular, or peripheral arterial systems | MACE: death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke | HbA1c: least-squares mean difference from baseline at week 18: ertugliflozin 5 mg: −0.70% (95% CI –0.73 to –0.67); ertugliflozin 15 mg: −0.72% (95% CI –0.75 to –0.69); vs placebo −0.22% (95% CI –0.25 to –0.19) | Composite renal outcome event (death from renal causes, renal replacement therapy, or doubling of the serum creatinine level): HR, 0.81; 95% CI 0.63 to 1.04) Placebo-adjusted eGFR slope >0.75 mL/min/ 1.73 $m^2$ per year across all baseline kidney status | MACE: HR, 0.97; 95.6% CI 0.85 to 1.11; *P*<0.001 for noninferiority |
| **HF trials** | | | | | | | |
| DAPA-HF[54] (dapagliflozin 10 mg) | 4744 | 1.5 | Heart failure with an ejection fraction of 40% or less, and New York Heart Association (NYHA) class II, III, or IV symptoms | Composite of worsening heart failure (unplanned hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death | HbA1c from baseline to 8 months vs placebo: −0.24, 95% CI −0.34 to −0.13, *P*<0.001 | Worsening renal function (composite outcome of sustained decline in the eGFR of 50% or greater, end-stage renal disease, or renal death): HR, 0.71, 95% CI 0.44 to 1.16 | The composite of worsening heart failure: HR, 0.74; 95% CI 0.65 to 0.85; *P*<0.001) |
| EMPEROR-REDUCED[65] (empagliflozin 10 mg) | 3730 | 1.3 | Chronic heart failure (functional class II, III, or IV) with a left ventricular ejection fraction of 40% or less | Composite of cardiovascular death or hospitalization for worsening heart failure | HbA1c from baseline to week 52 vs placebo: −0.16, 95% CI −0.25 to −0.08 | Composite renal outcome: HR, 0.50, 95% CI 0.32 to 0.77 Rate of annual eGFR decline, between group difference vs placebo: 1.73 mL/min/1.73 $m^2$ per year, *P*<0.001 | The composite of cardiovascular death or hospitalization for worsening heart failure: HR, 0.75; 95% CI 0.65 to 0.86; *P*<0.001 |
| EMPEROR-PRESERVED[66] (empagliflozin 10 mg) | 5988 | 2.2 | New York Heart Association functional class II–IV chronic heart failure with a left ventricular ejection fraction of more than 40% | Composite of cardiovascular death or hospitalization for heart failure | $HbA1_C$ from baseline to week 52 (adjusted mean difference vs placebo): −0.19, 95% CI −0.25 to −0.14 | Annual eGFR decline rate: empagliflozin –1.25 vs placebo –2.62 mL/ min/1.73 $m^2$ per year, *P*<0.001 Incidence of new macroalbuminuria (EMPEROR-Pooled[67]): HR 0.81, 95% CI 0.70 to 0.94; *P*=0.005 | The composite of cardiovascular death or hospitalization for heart failure: HR, 0.79; 95% CI, 0.69 to 0.90; *P*<0.001 |
| DELIVER[55] (dapagliflozin 10 mg) | 6263 | 2.3 | Stabilized heart failure with a left ventricular ejection fraction of more than 40% | Composite of worsening heart failure (unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death | Not reported | Mean difference in eGFR decline vs placebo: 1.4 (95% CI 1.0 to 1.8) (*P*<0.001) [chronic] and 0.5 (95% CI 0.1 to 0.9) mL/min/1.73$m^2$ per year (*P*=0.01) [total] | The composite of worsening heart failure: HR, 0.82; 95% CI 0.73 to 0.92; *P*<0.001 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SOLOIST-WHF[62] (sotagliflozin 200–400 mg) | 1222 | 0.8 | Type 2 diabetes hospitalized for worsening heart failure (presence of signs and symptoms of heart failure and received treatment with intravenous diuretic therapy) | The total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events) | Not reported | Least-squares mean change in eGFR vs placebo: −0.16 mL/min/ 1.73 $m^2$ (95% CI −1.30 to 0.98) in favor of placebo | The total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure: HR, 0.67; 95% CI 0.52 to 0.85; *P*<0.001 |
| **CKD trials** | | | | | | | |
| CREDENCE[60] (canagliflozin 100 mg) | 4401 | 2.6 | Type 2 diabetes with chronic kidney disease (an eGFR of 30 to <90 mL/min/1.73 $m^2$ and UACR >300 to 5000 mg/g) | Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL/min/ 1.73 $m^2$), a doubling of the serum creatinine level, or death from renal or cardiovascular causes | HbA1c overall mean difference vs placebo throughout the trial: −0.25% (95% CI −0.20 to −0.31) | The composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL /min/ 1.73 $m^2$), a doubling of the serum creatinine level, or death from renal or cardiovascular causes: HR, 0.70; 95% CI 0.59 to 0.82; *P*=0.00001<br>Least-squares mean change in eGFR slope vs placebo: 1.52 mL/ min/ 1.73 $m^2$ per year (95% CI 1.11 to 1.93) [total] and 2.74 mL/ min/<br>1.73 $m^2$ per year (95% CI 2.37 to 3.11) [chronic] | Cardiovascular death or hospitalization for heart failure: HR, 0.69; 95% CI 0.57 to 0.83; *P*<0.001Cardiovascular death, myocardial infarction, or stroke: HR, 0.80; 95% CI 0.67 to 0.95; *P* = 0.01Hospitalization for heart failure: HR, 0.61; 95% CI, 0.47 to 0.80; *P*<0.001 |
| SCORED[68] (sotagliflozin 200–400 mg) | 10,584 | 1.3 | Type 2 diabetes with chronic kidney disease (eGFR, 25 to 60 mL/min/1.73 $m^2$) and risks for cardiovascular disease | Composite of the total number of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure | HbA1c mean difference vs placebo: −0.42% (−0.47 to −0.38) | First occurrence of a sustained decrease of ≥50% in the eGFR from baseline (for ≥30 days), long-term dialysis, renal transplantation, or sustained eGFR of <15 mL/min/1.73 $m^2$ (for ≥30 days): HR, 0.71; 95% CI 0.46 to 1.08; *P*<0.001<br>eGFR mean change from baseline vs placebo: −1.25 mL/min/1.73 $m^2$ (95% CI, −1.51 to −0.99) | The composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure: HR, 0.74; 95% CI 0.63 to 0.88; *P*<0.001 |

(*Continued*)



https://doi.org/10.2147/DDDT.S540082

**Table 1** (Continued).

| Clinical Trials | Patients (n) | Median Follow-Up (Years) | Trial Population | Primary Endpoint (s) | Effect of SGLT-2 Inhibition on Glycemic Control | Effect of SGLT-2 Inhibition on Kidney Related Outcomes | Effect of SGLT-2 Inhibition on Cardiovascular Related Outcomes |
|---|---|---|---|---|---|---|---|
| DAPA-CKD[59] (dapagliflozin 10 mg) | 4304 | 2.4 | Chronic kidney disease with or without type 2 diabetes, with an eGFR of 25 to 75 mL/min/ 1.73 $m^2$ and a UACR of 200 to 5000 mg/g | Composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes | Not reported | The composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular cause: HR, 0.61; 95% CI 0.51 to 0.72; *P*<0.001)<br>Renal-specific composite outcome (a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes): HR, 0.56; 95% CI 0.45 to 0.68; *P*<0.001<br>Annual change in mean eGFR between-group difference vs placebo: 1.92 mL/min/1.73 $m^2$ per year (95% CI 1.61 to 2.24) [chronic] and 0.93 mL/min/1.73 $m^2$ per year (95% CI 0.61 to 1.25) [total] | The composite of death from cardiovascular causes or hospitalization for HF: HR, 0.71; 95% CI 0.55 to 0.92; *P*=0.009 |
| EMPA-KIDNEY[58] (empagliflozin 10 mg) | 6609 | 2.0 | Chronic kidney disease with an eGFR of at least 20 but less than 45 mL/min/1.73 $m^2$, regardless of the level of albuminuria, or with an eGFR of at least 45 but less than 90 mL/min/1.73 $m^2$ with a UACR of at least 200 mg/g | Composite of progression of kidney disease (end-stage kidney disease, a sustained decrease in eGFR to <10 mL/min/1.73 $m^2$, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes | HbA1c from baseline to 18 months vs placebo: −0.39 mmol (95% CI −0.77 to −0.01 [−0.04%; 95% CI −0.07 to 0.00]) | Progression of kidney disease or death from cardiovascular causes: HR, 0.72; 95% CI 0.64 to 0.82; *P*<0.001<br>Progression of kidney disease: HR, 0.71; 95% CI 0.62 to 0.81<br>Changes of eGFR slope vs placebo: 0.75 mL/min/1.73 $m^2$ per year (95% CI 0.54 to 0.96) [total] and 1.37 mL/min/ 1.73 $m^2$ per year (95% CI 1.16 to 1.59) [chronic] | Hospitalization for heart failure or death from cardiovascular causes: HR, 0.84; 95% CI 0.67 to 1.07; *P*=0.15 |

**Abbreviations**: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; MACE, major adverse cardiovascular event; SGLT-2, sodium-glucose cotransport protein-2; UACR, urinary albumin to creatine ratio.


https://doi.org/10.2147/DDDT.S540082

Cardiovascular outcome trials (CVOTs) of SGLT-2 inhibitors have enrolled varying proportions of patients with ASCVD. While these trials did not specifically target atherosclerosis-related endpoints, the observed improvements in CV outcome indirectly suggest a potential benefit of SGLT-2 inhibitors in mitigating atherosclerosis. A meta-analysis involving 23,987 patients without established ASCVD demonstrated that, among those with coexisting CKD and T2D, SGLT-2 inhibitors resulted in a 26% reduction in atherosclerotic major adverse CV events.[69] SGLT-2 inhibitors may potentially slow the progression of atherosclerosis and reduce the risk of related cardiovascular events through mechanisms such as improving vascular function, exerting anti-inflammatory and antioxidant effects, and regulating metabolism. However, direct evidence of plaque regression remains limited and requires further investigation. Some animal studies and clinical observations have suggested that SGLT-2 inhibitors may reduce the size of early atherosclerotic lesions or stabilize them,[69,70] as well as improve atherosclerosis-related markers.[71] Analysis of a large real-world dataset from Israel revealed that in patients with T2D and established ASCVD, compared with no use of SGLT-2 inhibitors or GLP-1RAs, SGLT-2 inhibitor monotherapy, GLP-1RA monotherapy, and their combination reduced the risk of all-cause mortality by 72% (HR 0.28; 95% CI 0.27–0.29), 61% (HR 0.39; 95% CI 0.37–0.40), and 83% (HR 0.17; 95% CI 0.16–0.18), respectively.[72] The relevant clinical outcomes of SGLT-2 inhibitors in ASCVD populations from RCTs are summarized in Table 2. SGLT-2 inhibitors may confer arterial protection via multiple mechanisms, including improved glycemic control, body weight reduction, antihypertensive effects, and antifibrotic actions. They also modulate inflammatory pathways, enhance vascular function, and attenuate oxidative stress.[73] Findings from observational studies and RCTs further demonstrate that SGLT-2 inhibitors favorably influence various markers of subclinical atherosclerosis, such as intima-media thickness (IMT), epicardial adipose tissue (EAT), endothelial function, and arterial stiffness.[74]

Furthermore, the CREDENCE trial showed that patients with T2D and CKD can benefit from canagliflozin therapy in lowering systolic blood pressure. This benefit was observed across all patient subgroups based on blood pressure, and patients on canagliflozin treatment required fewer interventions for blood pressure control.[76]

Real-world evidence also supports the utility of SGLT-2 inhibitors. A retrospective multi-ethnic cohort study reported that SGLT-2 inhibitors were associated with a 12% reduction in all-cause hospitalizations and a 34% reduction in all-cause mortality compared with DPP-4 inhibitors.[77] Another large international study of T2D patients from the Asia Pacific region, the Middle East, and North America showed that SGLT-2 inhibitors were associated with lower risks of death (HR 0.51; $P < 0.001$), hospitalization for HF (HR 0.64; $P = 0.001$), death or hospitalization for HF (HR 0.60; $P < 0.001$), myocardial infarction (HR 0.81; $P < 0.001$), and stroke (HR 0.68; $P < 0.001$).[67]

**Table 2** Clinical Outcomes of SGLT-2 Inhibitors in ASCVD Populations

| Clinical Trials | ASCVD Subgroup, n (%) | Comorbidities | Clinical Outcomes | | |
|---|---|---|---|---|---|
| | | | CV Death | HHF | MACE |
| EMPA-REG OUTCOME[49,50,75] | Empagliflozin: 4687 (100%)<br>Placebo: 2333 (100%) | T2D | HR 0.62; 95% CI 0.49–0.77 | HR 0.65; 95% CI 0.50–0.85 | HR 0.86; 95% CI 0.74–0.99 |
| CANVAS Program[51,75] | Canagliflozin: 3756 (64.8%)<br>Placebo: 2900 (66.7%) | T2D | HR 0.86; 95% CI 0.70–1.06 | HR 0.68; 95% CI 0.51–0.90 | HR 0.82; 95% CI 0.72–0.95 |
| DECLARE-TIMI 58[52,75] | Dapagliflozin: 3474 (40.5%)<br>Placebo: 3500 (40.8%) | T2D | HR 0.94; 95% CI 0.76–1.18 | HR 0.78; 95% CI 0.63–0.97 | HR 0.90; 95% CI 0.79–1.02 |
| CREDENCE[60,75] | Canagliflozin: 1113 (50.5%)<br>Placebo: 1107 (50.3%) | CKD, T2D | HR 0.79; 95% CI 0.58–1.07 | HR 0.61; 95% CI 0.44–0.85 | HR 0.85; 95% CI 0.69–1.06 |
| VERTIS CV[61,75] | Ertugliflozin: 5499 (100%)<br>Placebo: 2747 (100%) | T2D | HR 0.92; 95% CI 0.77–1.10 | HR 0.70; 95% CI 0.54–0.90 | HR 0.99; 95% CI 0.88–1.12 |

**Abbreviations**: ASCVD, atherosclerotic cardiovascular disease; T2D, type 2 diabetes; CKD, chronic kidney disease; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular event.


https://doi.org/10.2147/DDDT.S540082

## Early Use of SGLT-2 Inhibitors to Reduce the Risk of CKD Development

The AHA Presidential Advisory pointed out that SGLT-2 inhibitors can consistently benefit the reduction of CKD progression, the need for kidney replacement therapies, and incident CVD.[19] The following text summarizes the accumulating evidence from randomized clinical trials suggesting that early use of SGLT-2 inhibitors may have the potential to prevent the onset of CKD, ultimately improving overall patient outcomes (Table 1).

The EMPA-REG OUTCOME study was the first CV outcomes trial that demonstrated the benefit of SGLT-2 inhibitors on CV mortality, all-cause mortality, and hospital admission for heart failure,[49] as well as an association with slower progression of kidney disease and lower rates of clinically relevant renal events.[50] The empagliflozin group had a decrease in the prespecified renal composite outcome of incident or worsening nephropathy compared with the placebo group (hazard ratio [HR] 0.61; 95% CI 0.53 to 0.70, $P < 0.0001$).[50] For patients with a baseline eGFR ≥60 mL/min/1.73 $m^2$, the eGFR remained stable in the empagliflozin groups while it declined steadily in the placebo group during long-term follow-up[50] (Table 1).

Subsequently, the CANVAS[51] and DECLARE-TIMI 58[52] studies have reported similar outcomes. In the CANVAS study, 79.9% of the enrolled patients did not have CKD at baseline.[78] In those with a baseline eGFR≥60 mL/min/1.73 $m^2$, canagliflozin reduced the risk of the composite renal outcome (a 40% decrease in eGFR, end-stage kidney disease, or renal death) by 47% (95% CI 0.39 to 0.73). Canagliflozin also helped preserve renal function in these patients, as evidenced by the annual change in eGFR.[78] Dapagliflozin also appeared to prevent and reduce the progression of kidney disease compared with placebo in patients enrolled in the DECLARE-TIMI study, most of whom had preserved renal function.[53] For patients with a baseline eGFR ≥90 mL/min/1.73 $m^2$ or 60 to <90 mL/min/1.73 $m^2$, dapagliflozin reduced the risk of the composite renal-specific outcome (a sustained decrease in eGFR by at least 40% to less than 60 mL/min/1.73 $m^2$, end-stage renal disease, or renal death) by 50% (95% CI 0.34 to 0.73) and 46% (95% CI 0.40 to 0.73), respectively. The change in mean eGFR was also less in the dapagliflozin groups after 2 years of treatment in patients with an eGFR≥60 mL/min/1.73 $m^2$.[53]

From a series of studies conducted in patients with HF, including EMPEROR-Reduced,[65] EMPEROR-Preserved,[66] DAPA-HF,[54] and DELIVER,[55] it has been shown that SGLT-2 inhibitors can provide kidney protection in patients with HF across all ranges of ejection fraction, including those without CKD. The EMPEROR-Reduced study enrolled 3730 HF patients, including 1978 (53%) with concomitant CKD and 1752 (47%) without. Subgroup analysis showed that the risk of a prespecified composite kidney outcome (sustained profound decline in eGFR, chronic dialysis, or transplantation) was reduced in the empagliflozin group with an HR of 0.46 (95% CI 0.22 to 0.99). Additionally, empagliflozin slowed the decline of eGFR, one of the key secondary outcomes, by 2.41 mL/min/1.73 $m^2$/year (95% CI 1.49 to 3.32) in patients without CKD.[56] The pre-specified analysis of the EMPEROR-Preserved trial also demonstrated that empagliflozin effectively slowed the decline in eGFR and reduced the risk of composite kidney outcomes across the entire spectrum of baseline kidney function, including patients without prevalent CKD.[79] Dapagliflozin has shown similar benefits in slowing the rate of eGFR decline in HF patients without CKD, as observed in the DAPA-HF and DELIVER trials.[57,80]

The unexpected and remarkable renal-protective effects of SGLT-2 inhibitors in patients with no evidence of CKD at baseline suggested that the early use of these drugs may bring benefit in reducing the risk of developing CKD.

## SGLT-2 Inhibitors Address the Two Key Treatment Goals in CKD

The Improving Global Outcomes (KDIGO) clinical management guidelines for CKD highlight slowing CKD progression and controlling CV risk as two primary treatment goals for CKD patients.[20] In recent years, SGLT-2 inhibitors have been demonstrated to be a key therapeutic option that addresses both of these goals.

The CREDENCE study (n = 4401) was the first confirmatory trial to explore the effect of SGLT-2 inhibitors on slowing CKD progression in patients with T2D and CKD.[60] The enrolled patients had an eGFR of 30 to <90 mL/min/1.73 $m^2$ and UACR of >300 to 5000 mg/g. After a median follow-up of 2.62 years, there was a significant reduction in the risk of the composite primary endpoint, which included end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or CV causes, in comparison with placebo (HR 0.70; 95% CI 0.59 to 0.82, $P = 0.00001$).[60]

The DAPA-CKD study, which included 4304 CKD patients with or without T2D, enrolled those with an eGFR of 25 to 75 mL/min/1.73 $m^2$ and a UACR of 200 to 5000 mg/g.[59] Patients were randomized to receive either dapagliflozin or placebo. After a median follow-up of 2.4 years, the dapagliflozin group experienced a 39% risk reduction in the composite endpoint of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or vascular causes (HR 0.61; 95% CI 0.51 to 0.72, $P < 0.001$).[59] The HR for the renal-specific composite outcome (a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal causes) was 0.56 (95% CI 0.45 to 0.68, $P < 0.001$).[59]

The EMPA-KIDNEY study, which is presently the largest confirmatory study with 6609 participants, investigated the effects of empagliflozin in CKD patients with different primary diseases and albuminuria statuses.[58] The study found that progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to less than 10 mL/min/1.73 $m^2$, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) and death from CV causes, occurred less frequently in the empagliflozin group compared with the placebo group, with an HR of 0.72 (95% CI 0.64 to 0.82). Additionally, the HR for progression of kidney disease alone also favored the empagliflozin group (HR 0.71; 95% CI 0.62 to 0.81).[58] Prespecified exploratory analyses showed that the rate of decline in eGFR, after an initial decrease, was slower in the empagliflozin group across all key subgroups, including those with a low UACR. In patients with CKD and albuminuria, the empagliflozin group exhibited a reduced annual eGFR decline of 2 to 2.5 mL/min/1.73 $m^2$, while in those with normal albumin levels, the annual eGFR decline was lowered to 0.1 mL/min/1.73 $m^2$, well below the aging-related GFR loss.[81] A hypothetical scenario based on chronic eGFR decline rates across different eGFR subgroups in the EMPA-KIDNEY trial suggests that, empagliflozin could delay the progression to end-stage kidney disease by an estimated 1.9 years (when initiating treatment at an eGFR of 20 mL/min/1.73 $m^2$) to 26.6 years (when initiating treatment at an eGFR of 85 mL/min/1.73 $m^2$).[81]

In the CREDENCE, DAPA-CKD, and EMPA-KIDNEY trials, 50.4%, 37.4%, and 26.7%, respectively, of the patients presented with comorbid CVD.[58–60] Overall results from these studies demonstrated that SGLT-2 inhibitors treatment reduced the risk of cardiovascular mortality by 22%, 19%, and 16%, respectively, compared with placebo.[58–60] Furthermore, the EMPA-KIDNEY Post-Trial Follow-Up (PTFU) indicated that empagliflozin continued to provide additional cardiorenal benefits for up to 12 months after treatment discontinuation. A 25% reduction in cardiovascular mortality risk was observed (HR 0.75; 95% CI 0.59 to 0.95).[82] It was proposed that the preservation and protective effect on renal function following empagliflozin therapy may have partially mediated the cardiovascular mortality benefit observed after the trial period.[82]

The Nuffield Department of Population Health Renal Studies Group conducted a comprehensive meta-analysis of SGLT-2 inhibitors, encompassing 13 randomized controlled trials (RCTs) with a total of 90,413 patients.[83] The analysis found that SGLT-2 inhibitor treatment reduced the risk of kidney disease progression by 37%. This meta-analysis provides robust evidence that SGLT-2 inhibitors can modify the risk of kidney disease progression across various patient settings, irrespective of diabetes status, primary kidney disease, or renal function.

In addition to RCTs, emerging data from real-world studies support the use of SGLT-2 inhibitors in patients with CKD. A group of Japanese researchers selected a more elderly diabetic kidney disease population (patient age ≥75 years), with a total of 696 patients identified from the Japan Chronic Kidney Disease Database. Compared with other glucose-lowering drug groups (top 3 classes: dipeptidyl peptidase 4 [DPP-4] inhibitors 77.9%, biguanides 34.2%, sulfonylureas 28.4%), SGLT-2 inhibitors were associated with a delayed eGFR decline (annual difference: 0.99 mL/min/1.73 $m^2$).[84]

## Safety of SGLT-2 Inhibitors

Data from large RCTs indicate that SGLT-2 inhibitors generally exhibit a favorable safety profile. A meta-analysis of 13 large RCTs reported the following relative risks (RR) associated with SGLT-2 inhibitors: urinary tract infections (RR 1.08; 95% CI 1.02 to 1.15), serious urinary tract infections (RR 1.07; 95% CI 0.90 to 1.27), fungal genital infections (RR 3.57; 95% CI 3.14 to 4.06), fractures (RR 1.07; 95% CI 0.99 to 1.14), and severe hypoglycemia (RR 0.89; 95% CI 0.80 to 0.98).[83] The overall relative risk of ketoacidosis with SGLT-2 inhibitor treatment was 2.12 (95% CI 1.49 to 3.04); however, only one ketoacidosis event occurred in non-diabetic patients during nearly 30,000 patient-years of follow-up.[83] After excluding data from the CANVAS trial (which reported a two-fold increase in lower limb amputation risk with

SGLT-2 inhibitor treatment and showed significant heterogeneity compared with other trials), no significant association was observed between SGLT-2 inhibitor use and the risk of lower limb amputation (RR 1.06; 95% CI 0.93 to 1.21).[83] However, nationwide registry data from Denmark and Sweden (2013–2016) indicated that, compared with GLP-1 receptor agonists (GLP-1RAs), SGLT-2 inhibitor use was associated with a higher risk of lower limb amputation and diabetic ketoacidosis.[85] SGLT-2 inhibitors may also increase the risk of urinary frequency and dehydration, as well as rare but serious adverse events, such as Fournier gangrene.[86]

A mild and reversible decline in eGFR (commonly referred to as an "eGFR dip") is often observed within weeks after initiating SGLT-2 inhibitors. This decline occurs due to tubuloglomerular feedback and reduced intraglomerular pressure. However, this early reduction in eGFR does not increase the risk of acute kidney injury (AKI), negatively impact long-term renal outcomes, or compromise the efficacy of SGLT-2 inhibitors.[87–90] A meta-analysis showed that SGLT-2 inhibitor use was associated with a 23% reduction in the risk of AKI compared with the placebo.[83]

## Guideline Recommendations for SGLT-2 Inhibitors in CKM

The AHA presidential statement introduced a new staging system for CKM syndrome: stage 0 (no CKM risk factors), stage 1 (excess or dysfunctional adiposity), stage 2 (metabolic risk factors or moderate/high-risk CKD), stage 3 (subclinical CVD in CKM), and stage 4 (clinical CVD in CKM).[5] Patients in later stages (Stage 3 or 4) represent advanced disease with significant organ damage. The statement highlights the importance of initiating CKM-related screening early and maintaining it throughout life-course with monitoring protocols comprehensively, considering the common pathological mechanisms of CKM syndrome. In childhood, body weight and blood pressure should be monitored at each clinic visit starting from age 3, while lipid profile screening is recommended once at ages 9–11 and again at ages 17–21. High-risk children who are overweight or obese should also undergo testing for glucose tolerance and liver function. In adulthood, screening frequency should be based on the CKM stage: stage 0 individuals should be assessed every 3–5 years, stage 1 every 2–3 years, and stage 2 or higher, annually for metabolic syndrome components (blood pressure, lipids, blood glucose). Patients in stage 2 or higher should also undergo annual renal function assessment (eg urine albumin-to-creatinine ratio and estimated glomerular filtration rate) and targeted screening for subclinical atherosclerotic cardiovascular disease and heart failure in high-risk populations.[5]

With robust evidence supporting the benefits of SGLT-2 inhibitors in patients with T2D, CVD and CKD, SGLT-2 inhibitors are recommended for the holistic management of CKM disease throughout its different stages. Chinese researchers advocate that the management of patients with type 6 cardiorenal syndrome requires an integrated approach targeting both the cardiac and renal systems, with a focus on novel treatments such as SGLT-2 inhibitors.[38] Several Chinese and international Societies that have developed clinical management guidelines or scientific statements for the management of CKM syndrome consistently recommend SGLT-2 inhibitors as a cornerstone therapy in this clinical setting.[21,33–35,91]

Table 3 summarizes the recommendations from condition-specific guidelines, as well as guidelines covering multiple CKM diseases. SGLT-2 inhibitors now serve three key roles: (1) achieving glycemic control, cardiovascular protection, and renal benefits in T2D patients, especially those with comorbidities; (2) serving as first-line therapy to slow kidney disease progression, even in non-diabetic patients; and (3) providing effective treatment for chronic HF, regardless of ejection fraction or diabetes status.

## Challenges in GDMT Implementation and Future Directions in China

Guideline-recommended medical therapies are designed to improve clinical outcomes and streamline treatment regimens. The recently issued AHA recommendations have established a framework for various therapeutic approaches.[5] In addition to SGLT-2 inhibitors which are endorsed for their ability to prevent kidney failure and provide cardioprotective effects, GLP-1RAs and RAAS inhibitors are also advocated. The recommendation is based on the observed multiple benefits on metabolic risk factors, kidney function, and the CV system. Despite the heavy burden of CKM syndrome, the implementation of these guideline-recommended therapies in real-world settings is suboptimal, leading to an adverse prognosis for patients with CKM diseases.[98,99] It is important to point out that SGLT-2 inhibitors are one of the most underutilized guideline-recommended therapies globally. Only a minority of T2D patients with comorbidities (ASCVD, HF, CKD) receive an SGLT-2 inhibitor, with the proportion ranging from 6.0% to 28.0%.[100] In China, a single

**Table 3** Guideline Recommendation for SGLT-2 Inhibitors in Patients with Different CKM Disease Conditions

| Guideline Clinical Domain | Guideline | Populations | Recommendations |
|---|---|---|---|
| **Diabetes** | **2025 ADA Standards of Care in Diabetes**[21] | T2D with established or high risk of ASCVD | Treatment plan should include SGLT-2 inhibitors for glycemic management and comprehensive CV risk reduction (irrespective of $HbA1_c$). (A) |
| | | T2D and HF with either preserved or reduced ejection fraction | An SGLT-2 inhibitor is recommended for glycemic management and prevention of HF hospitalizations (irrespective of $HbA1_c$), reduce the risk of worsening HF and CV death (A) |
| | | T2D with CKD | An SGLT-2 inhibitor with demonstrated benefit in adults with T2D who have CKD (with confirmed eGFR 20–60 mL/min/1.73 $m^2$ and/or albuminuria) should be used for both glycemic management (irrespective of $HbA1_c$) and for slowing progression of CKD and reduction in cardiovascular events. The glycemic benefits of SGLT2 inhibitors are reduced at eGFR <45 mL/min/1.73 $m^2$. (A) |
| | **Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2024 edition)**[92] | T2D with established or high risk of ASCVD | An SGLT-2 inhibitor with demonstrated benefit in adults with ASCVD should be prescribed. (A) |
| | | T2D with HF | SGLT-2 inhibitors are recommended. (A) |
| | | T2D with CKD | SGLT-2 inhibitors with evidence of CKD benefit should be selected for slowing progression of CKD and reduction in cardiovascular events. (A) |
| **CVD** | **2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure**[35] | HF | An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF or HFpEF to reduce the risk of HF hospitalization or CV death. (I, A) |
| | | HF with T2D and CKD | For the patients with symptomatic HF with preserved ejection fraction, SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death. (I, A) |
| | **China National Heart Failure Guideline 2023**[93] | HF stage A (at high risk for HF) | In patients with T2D, SGLT-2 inhibitors are recommended to reduce the risk of HF and the associated hospitalization. In patients with T2D and CKD, SGLT-2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death. (I, A) |
| | | HF stage B (pre-HF) | For patients after AMI revascularization, early administration of SGLT-2 inhibitors should be considered to ameliorate adverse ventricular remodeling.(IIa, C) |
| | | Symptomatic chronic HF | For patients with symptomatic (NYHA class II–IV) HFrEF, SGLT-2 inhibitors (dapagliflozin or empagliflozin) with evidence-based support are recommended to reduce the risk of HF hospitalization or CV death, regardless of diabetic status. (I, A) |
| | | | For patients with symptomatic (NYHA class II–IV) HFmrEF, SGLT-2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death, regardless of diabetic status. (I, A) |
| | | | For all patients with HFpEF, SGLT-2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death. (I, A) |

(*Continued*)


https://doi.org/10.2147/DDDT.S540082

**Table 3** (Continued).

| Guideline Clinical Domain | Guideline | Populations | Recommendations |
|---|---|---|---|
| CVD | **Chinese guidelines for the diagnosis and treatment of heart failure 2024**[94] | Symptomatic chronic HF | For patients with HFrEF, SGLT-2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or death, unless contraindicated or not tolerated. (I, A) |
| | | | For patients with HFmrEF, SGLT-2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death. (I, A) |
| | | | For patients with HFpEF, SGLT-2 inhibitors are recommended to reduce the risk of the composite endpoint of HF hospitalization or CV death (I, A) |
| | | HF with T2D | The recommended approach incorporates SGLT-2 inhibitor treatment. |
| | | T2D with established or high risk of CVD | SGLT-2 inhibitors are recommended to reduce the risk of HF hospitalization. (I, A) |
| | **2022 AHA/ACC/HFSA Guideline for the Management of HF**[34] | HF stage A (at high risk for HF) | In patients with T2D and either established CVD or at high CV risk, SGLT-2 inhibitors should be used to prevent hospitalizations for HF. (I, A) |
| | | Symptomatic chronic HF | In patients with symptomatic chronic HFrEF, SGLT-2 inhibitors are recommended to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2D.(I, A) |
| | | | In patients with HFmrEF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and CV mortality.(2a,BR) |
| | | | In patients with HFpEF, SGLT-2 inhibitors can be beneficial in decreasing HF hospitalizations and CV mortality. (2a,BR) |
| | | HF with T2D | Use of SGLT-2 inhibitors is recommended for the management of hyperglycemia and to reduce HF related morbidity and mortality. (I, A) |
| | **2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with CCD**[95] | CCD with T2D | In patients with CCD who have T2D, the use of either an SGLT-2 inhibitor or a GLP-1 receptor agonist with proven CV benefit is recommended to reduce the risk of MACE. (I, A) |
| | | CCD with HF | In patients with CCD and HF with LVEF ≤40%, use of an SGLT-2 inhibitor is recommended to reduce the risk of CV death and HF hospitalization and to improve QOL, irrespective of diabetes status. (I, A) |
| | | | In patients with CCD and heart failure with LVEF >40%, use of an SGLT-2 inhibitor can be beneficial in decreasing heart failure hospitalizations and to improve QOL,irrespective of diabetes status. (2a,BR) |

(*Continued*)

**Table 3** (Continued).

| Guideline Clinical Domain | Guideline | Populations | Recommendations |
|---|---|---|---|
| CVD | **2023 ESC Guidelines for the Management of CVD in Patients with Diabetes**[96] | HF with T2D | SGLT-2 inhibitors (dapagliflozin, empagliflozin, or sotagliflozin) are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death. (I, A) |
| | | | Empagliflozin or dapagliflozin are recommended in patients with T2D and LVEF >40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death. (I, A) |
| | | T2D and CKD, with or without HF | An SGLT-2 inhibitor (canagliflozin, empagliflozin, or dapagliflozin) is recommended in patients with T2DM and CKD with an eGFR ≥20 mL/min/1.73 $m^2$ to reduce the risk of CVD and kidney failure. (I, A) |
| | | T2D with established or high risk of ASCVD | SGLT-2 inhibitors with proven CV benefits are recommended in patients with T2D and ASCVD to reduce CV events, independent of baseline or target HbA1c and independent of concomitant glucose-lowering medication. (I, A) |
| | | | In patients with T2DM without ASCVD or severe TOD but with a calculated 10-year CVD risk ≥10%, treatment with an SGLT-2 inhibitor or GLP-1 RA may be considered to reduce CV risk. (2b, C) |
| **CKD** | **2024 KDIGO Guidelines for the Evaluation and Management of CKD**[20] | CKD | SGLT-2 inhibitors are recommended for the adults with CKD, and an eGFR ≥20 mL/min/1.73 $m^2$ with urine ACR ≥200 mg/g (≥20 mg/mmol).(I, A)<br>SGLT-2 inhibitors are suggested for the adults with eGFR 20 to 45 mL/min/1.73 $m^2$ with urine ACR <200 mg/g (<20 mg/mmol). (2, B) |
| | | CKD with HF | SGLT-2 inhibitors are recommended for adults with CKD and heart failure, irrespective of level of albuminuria. (I, A) |
| | | CKD with T2D | SGLT-2 inhibitors are recommended for the patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 mL/min/1.73 $m^2$ (I, A). |
| | **Guidelines for early evaluation and management of chronic kidney disease in China 2023**[97] | CKD | SGLT-2 inhibitors are recommended for CKD patients with or without diabetes.(I, A) |
| | | CKD with T2D | Metformin (2a, B) and SGLT-2 inhibitors (1a, A) are recommended as first-line antihyperglycemic therapy in patients with CKD and diabetes and can be combined with other glucose-lowering agents as needed.<br>SGLT-2 inhibitors are recommended for patients with CKD and T2D who have an eGFR ≥25 mL/min/1.73$m^2$. (1a, A). |
| | | CKD with HF | SGLT-2 inhibitors are recommended for patients with CKD and symptomatic chronic HF, regardless of ejection fraction. (1a, A)<br>SGLT2 inhibitors are suggested for the treatment of CKD with concomitant HFrEF. (1b, A) |
| | | T2D with established ASCVD | SGLT-2 inhibitors are recommended for primary prevention of CKD (1b, A). |

(*Continued*)


https://doi.org/10.2147/DDDT.S540082

**Table 3** (Continued).

| Guideline Clinical Domain | Guideline | Populations | Recommendations |
|---|---|---|---|
| **CKM** | **2023 Clinical Practice Guideline for the Diagnosis and Treatment of Cardiorenal Syndrome**[91] | CRS with HF | SGLT-2 inhibitors are recommended for patients with acute or chronic CRS complicated by HFrEF. However, they should be avoided in patients with a GFR below 30 mL/min/1.73m², ESRD, or those on dialysis. (1a, A). |
| | | | SGLT-2 inhibitors are recommended for patients with acute or chronic CRS complicated by HFmrEF or HFpEF. However, they should be avoided in patients with a GFR<30 mL/min/1.73m², ESRD, or those on dialysis. (1a, A). |
| | | CRS with hyperkalemia | ACEIs, ARBs, ARNIs, and MRAs are all associated with an increased risk of hyperkalemia, whereas SGLT-2 inhibitors reduce the incidence of severe hyperkalemia and are recommended for the treatment of CRS. (1a, A). |
| | **2023 CKM Health: A Presidential Advisory From the AHA**[5] | CKM syndrome stage 2 | SGLT-2 inhibitors are recommended for CKD patients regardless of diabetes status. |
| | | | SGLT-2 inhibitors are recommended for T2D patients with CKD. |
| | | CKM syndrome stage 3 | SGLT-2 inhibitors are recommended for subclinical HF patients with diabetes. |
| | | | SGLT-2 inhibitors are recommended for T2D patients with CKD. |
| | | CKM syndrome stage 4 | SGLT-2 inhibitors are recommended for CKD patients regardless of diabetes status. |
| | | | SGLT-2 inhibitors are recommended for T2D patients with ASCVD. |
| | | | SGLT2 inhibitors are recommended for patients with CKD and HF, regardless of ejection fraction, diabetes status, and baseline UACR. |
| | | | An SGLT-2 inhibitor is indicated for all patients with HF regardless of diabetes status. |

**Note**: The strength of the ratings for each guideline recommendation is shown in parentheses.
**Abbreviations**: ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CCD, chronic coronary disease; CDS, Chinese Diabetes Society; CKD, chronic kidney disease; TOD, target organ damage; CKM, cardiovascular-kidney-metabolic; CRS, cardiorenal syndrome; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESRD, end stage renal disease; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; T2D, type 2 diabetes.

institutional study reported similar findings: SGLT-2 inhibitors were used in only 12.3% of diabetic kidney disease patients.[101] A multivariate logistic regression was also performed in the study to identify factors that are associated with the use of SGLT-2 inhibitors; they included age, body mass index (BMI), HbA1c level, eGFR, dyslipidemia, and hypertension history.[101]

Several other factors may also limit compliance with guideline recommendations in real-world CKM management settings. Treatment-related factors, such as adverse reactions and renal function, as well as healthcare service-related factors (including clinical inertia and insufficient interdisciplinary collaboration) may hinder the optimal selection and use of guideline-recommended therapies, such as SGLT-2 inhibitors, in China.

Addressing these challenges is crucial to guiding future efforts and shaping innovative strategies that can further enhance clinical outcomes. In addition to the comprehensive benefits of SGLT-2 inhibitors in CKM syndrome mentioned above, exploring their combination with other drugs may provide additional advantages. Evidence supports the use of

SGLT-2 inhibitors with other agents, such as RAAS inhibitors, GLP-1 RAs, angiotensin receptor-neprilysin inhibitors, nonsteroidal mineralocorticoid receptor antagonists (eg finerenone), and aldosterone synthase inhibitors (eg vicadrostat). These combinations, tailored to specific comorbidities, can enhance cardiorenal protection and improve glucolipid metabolism.[49,51,52,58–62,65,66,68,102,103] Analyses of clinical trial data indicate that for patients with CKD, a regimen comprising a RAAS inhibitor and an SGLT-2 inhibitor or finerenone may provide additive benefits by effectively slowing the rate of eGFR decline to levels comparable to or even below those with natural aging.[104,105] Future research is warranted to delineate standardized protocols and precautions for the application of these SGLT-2 inhibitor combination therapies within CKM clinical practice.

The therapeutic potential of SGLT-2 inhibitors beyond CKM also represents a noteworthy research direction. Recent evidence suggests a potential role for SGLT-2 inhibitors in suppressing tumor growth, indicating that they might synergize with conventional anticancer therapies to enhance efficacy and reduce toxicity.[106,107] Further investigation is required to elucidate their mechanisms of action and clinical applications.

Considering that CKM-related diseases are predominantly managed by specialists rather than primary care physicians in China, enhancing multidisciplinary team (MDT) collaboration may potentially ameliorate the suboptimal utilization of GDMT and overall management of CKM diseases. Given the critical role of renal protection in the pathogenesis and therapy of CKM diseases, nephrologists should serve as pivotal coordinators within the MDT. They can raise awareness of kidney diseases and their implications for CV and metabolic health, disseminate information about current evidence-based treatments, and share experiences in managing patients with renal dysfunction.

Last but not least, patient and caregiver education is crucial for the success of CKM management. Promoting a healthy diet, regular physical activity, and weight management is a fundamental and an effective part of CKM treatment. Education should be prioritized for patients at higher risk of CKM, as well as for under-resourced families and communities. Enhancing physician-patient cooperation throughout the entire CKM disease journey is also essential.

## Limitations

This narrative review synthesizes pivotal recent research to provide a comprehensive overview of the renal protective effects of SGLT-2 inhibitors in the context of CKM syndrome. The aim was to enhance understanding of their role in these connections. However, the inherent limitations of this narrative review must be acknowledged, including the lack of reproducible conclusions, potential for bias, and subjectivity stemming from a non-standardized and often non-exhaustive search approach. Additionally, the insights regarding GDMT implementation and its associated challenges are primarily based on the Chinese clinical context and may not be directly applicable to other geographic regions.

## Conclusions

Diabetes, CVD, and kidney disease are closely interconnected disorders and are core components of CKM syndrome, making proactive early screening and intervention essential to slow their progression and improve outcomes.

SGLT-2 inhibitors provide significant benefits in CKD protection, including controlling risk factors for CKD development and slowing its progression. They also contribute to improvements in CV and metabolic health. As part of a comprehensive management strategy, SGLT-2 inhibitors may help to reduce the risk of cardiovascular-renal-metabolic diseases. For patients with CKD, T2D, or heart failure (irrespective of ejection fraction), especially those with concomitant CKM risk factors such as obesity, ASCVD, or high cardiovascular risk, SGLT-2 inhibitors should be considered when selecting pharmacotherapy.

Interdisciplinary approaches are critical to optimize the management of CKM diseases in China. Given that kidney function is at the core intersection of CKM diseases, nephrologists are well-positioned to spearhead the creation of an interdisciplinary team of clinicians for the co-management of patients with CKM diseases.

## Data Sharing Statement

All data used for this publication are presented in the main article.

## Acknowledgments

Editorial assistance was provided by Content Ed Net, Shanghai, with funding from Boehringer Ingelheim China.

## Funding

Nan Ye was funded by Beijing Municipal Hospital Scientific Research and Cultivation Program (PX2022024), and Beijing Hospital Authority Young Talent Cultivation "Qingmiao" Program (QML20230601). Hong Cheng was funded by Special Project for Scientific Research on Health Development of the Capital (2022-2-2066).

## Disclosure

The authors declare no conflicts of interests for this work.

## References

1. Maack C, Lehrke M, Backs J, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the translational research committee of the heart failure association-European society of cardiology. *Eur Heart J*. 2018;39:4243–4254. doi:10.1093/eurheartj/ehy596
2. Seferovic PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20:853–872. doi:10.1002/ejhf.1170
3. Usman MS, Khan MS, Butler J. The interplay between diabetes, cardiovascular disease, and kidney disease, in chronic kidney disease and type 2 diabetes. In: *Chronic Kidney Disease and Type 2 Diabetes*. Arlington (VA): American Diabetes Association; 2021. ADA Clinical Compendia Series 13-18; 2021.
4. Damman K, Valente MA, Voors A, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455–469. doi:10.1093/eurheartj/eht386
5. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic health: a Presidential Advisory from the American Heart Association. *Circulation*. 2023;148(20):1606–1635. doi:10.1161/CIR.0000000000001184
6. Duncan BB, Magliano DJ, Boyko EJ. IDF diabetes atlas 11th edition 2025: global prevalence and projections for 2050. *Nephrol Dial Transplant*. 2025;41:7–9. doi:10.1093/ndt/gfaf177
7. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail*. 2020;22:1342. doi:10.1002/ejhf.1858
8. Bikbov B, Purcell CA, Levey AS; GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2020;395:709–733. doi:10.1016/S0140-6736(20)30045-3
9. Kim JE, Joo J, Kuku KO, et al. Prevalence, Disparities, and mortality of cardiovascular-kidney-metabolic syndrome in US Adults, 2011-2018. *Am J Med*. 2025;138(6):970–979.e7. doi:10.1016/j.amjmed.2025.01.031
10. Peng W, Chen S, Chen X, et al. Trends in major non-communicable diseases and related risk factors in China 2002-2019: an analysis of nationally representative survey data. *Lancet Reg Health West Pac*. 2023;20(43):100809.
11. Hao G, Wang X, Chen Z, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012-2015. *Eur J Heart Fail*. 2019;21:1329–1337. doi:10.1002/ejhf.1629
12. Wang L, Xu X, Zhang M, et al. Prevalence of chronic kidney disease in China results from the sixth China Chronic Disease and Risk Factor Surveillance. *JAMA Intern Med*. 2023;183:298–310. doi:10.1001/jamainternmed.2022.6817
13. Deng W, Zhao L, Chen C, et al. National burden and risk factors of diabetes mellitus in China from 1990 to 2021: results from the Global Burden of Disease Study 2021. *J Diab*. 2024;16:e70012. doi:10.1111/1753-0407.70012
14. Huang J, Yin H, Zhan M, Ni Q, Xuan J. Understanding the economic burden of heart failure in China: impact on disease management and resource utilization. *J Med Econ*. 2017;20:549–553. doi:10.1080/13696998.2017.1297309
15. Yang C, Wang H, Zhao X, et al. CKD in China: evolving spectrum and public health implications. *Am J Kidney Dis*. 2020;76:258–264. doi:10.1053/j.ajkd.2019.05.032
16. Aggarwal R, Ostrominski JW, Vaduganathan M. Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011-2020. *JAMA*. 2024;331(21):1858–1860. doi:10.1001/jama.2024.6892
17. Mayne KJ, Walker H, Elyan BMP, et al. Cardiovascular-kidney-metabolic syndrome and mortality in a prospective UK cohort study. *Eur J Prev Cardiol*. 2025. doi:10.1093/eurjpc/zwaf514
18. Li N, Li Y, Cui L, et al. Association between different stages of cardiovascular-kidney-metabolic syndrome and the risk of all-cause mortality. *Atherosclerosis*. 2024;397:118585. doi:10.1016/j.atherosclerosis.2024.118585
19. Ndumele CE, Neeland IJ, Tuttle KR, et al. A synopsis of the evidence for the science and clinical management of cardiovascular-kidney-metabolic (CKM) syndrome: a Scientific Statement from the American Heart Association. *Circulation*. 2023;148:1636–1664. doi:10.1161/CIR.0000000000001186
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105:S117–S314. doi:10.1016/j.kint.2023.10.018
21. ElSayed NA, McCoy RG, Aleppo G; American Diabetes Association Professional Practice Committee. Introduction and Methodology: standards of Care in Diabetes-2025. *Diabetes Care*. 2025;48:S1–S5. doi:10.2337/dc25-SINT
22. Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. *Cardiovasc Diabetol*. 2023;22:195. doi:10.1186/s12933-023-01937-x
23. Jung CY, Yun HR, Park JT, et al. Association of coronary artery calcium with adverse cardiovascular outcomes and death in patients with chronic kidney disease: results from the KNOW-CKD. *Nephrol Dial Transplant*. 2023;38:712–721. doi:10.1093/ndt/gfac194

24. Matsushita K, Sang Y, Ballew SH, et al. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. *J Am Soc Nephrol*. 2015;26:439–447. doi:10.1681/ASN.2014020173
25. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the multi-ethnic study of atherosclerosis. *JAMA Cardiol*. 2017;2:1332–1340. doi:10.1001/jamacardio.2017.4191
26. Joseph JJ, Deedwania P, Acharya T, et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a Scientific Statement From the American Heart Association. *Circulation*. 2022;145:e722–e759. doi:10.1161/CIR.0000000000001040
27. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;74:e177–e232. doi:10.1016/j.jacc.2019.03.010
28. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur J Prev Cardiol*. 2022;29:5–115. doi:10.1093/eurjpc/zwab154
29. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13–e115. doi:10.1161/HYP.0000000000000065
30. Grundy SM, Stone NJ, Bailey AL, et al. 2018 HA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi:10.1161/CIR.0000000000000625
31. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129:S102–S138. doi:10.1161/01.cir.0000437739.71477.ee
32. Hall ME, Cohen JB, Ard JD, et al. Weight-loss strategies for prevention and treatment of hypertension: a Scientific Statement From the American Heart Association. *Hypertension*. 2021;78:e38–e50. doi:10.1161/HYP.0000000000000202
33. Disease K, Improving Global Outcomes Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2022;102:S1–S127.
34. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi:10.1161/CIR.0000000000001063
35. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44(37):3627–3639. doi:10.1093/eurheartj/ehad195
36. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498. doi:10.1093/eurheartj/ehaa612
37. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi:10.1161/CIR.0000000000000665
38. Zhang Y, Jiang Y, Yang W, Shen L, He B. Chronic secondary cardiorenal syndrome: the sixth innovative subtype. *Front Cardiovasc Med*. 2021;8:639959. doi:10.3389/fcvm.2021.639959
39. Jepson C, Hsu JY, Michael J, et al. Incident type 2 diabetes among individuals with CKD: findings from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis*. 2019;73:72–81. doi:10.1053/j.ajkd.2018.06.017
40. Thornley-Brown D, Wang X, Wright JT Jr, et al. Differing effects of antihypertensive drugs on the incidence of diabetes mellitus among patients with hypertensive kidney disease. *Arch Intern Med*. 2006;166:797–805. doi:10.1001/archinte.166.7.797
41. Vondracek SF, Teitelbaum I, Kiser TH. Principles of kidney pharmacotherapy for the nephrologist: core curriculum 2021. *Am J Kidney Dis*. 2021;78:442–458. doi:10.1053/j.ajkd.2021.02.342
42. Evans M, Morgan AR, Bain SC, et al. Defining the role of SGLT2 inhibitors in primary care: time to think differently. *Diabetes Ther*. 2022;13:889–911. doi:10.1007/s13300-022-01242-y
43. Yau K, Dharia A, Alrowiyti I, Cherney DZI. Prescribing SGLT2 inhibitors in patients with CKD: expanding indications and practical considerations. *Kidney Int Rep*. 2022;7:1463–1476. doi:10.1016/j.ekir.2022.04.094
44. Larmour K, Levin A. Slowing progression in CKD: DAPA CKD and beyond. *Clin J Am Soc Nephrol*. 2021;16:1117–1119. doi:10.2215/CJN.20211220
45. Plosker GL. Canagliflozin: a review of its use in patients with type 2 diabetes mellitus. *Drugs*. 2014;74:807–824. doi:10.1007/s40265-014-0225-5
46. Padda IS, Mahtani AU, Parmar M. Sodium-glucose transport protein 2 (SGLT2) inhibitors. [Updated 2023 Jun 3]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK576405/. Accessed January 12, 2025.
47. Yang F, Meng R, Zhu DL. Cardiovascular effects and mechanisms of sodium-glucose cotransporter-2 inhibitors. *Chronic Dis Transl Med*. 2020;6:239–245. doi:10.1016/j.cdtm.2020.07.002
48. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care*. 2016;39:1108–1114. doi:10.2337/dc16-0330
49. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi:10.1056/NEJMoa1504720
50. Wanner C, Inzucchi SE, Lachin JM. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. doi:10.1056/NEJMoa1515920
51. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657. doi:10.1056/NEJMoa1611925

52. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357. doi:10.1056/NEJMoa1812389
53. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7:606–617. doi:10.1016/S2213-8587(19)30180-9
54. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi:10.1056/NEJMoa1911303
55. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098. doi:10.1056/NEJMoa2206286
56. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-reduced. *Circulation*. 2021;143:310–321. doi:10.1161/CIRCULATIONAHA.120.051685
57. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;143:298–309. doi:10.1161/CIRCULATIONAHA.120.050391
58. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–127. doi:10.1056/NEJMoa2204233
59. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. doi:10.1056/NEJMoa2024816
60. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306. doi:10.1056/NEJMoa1811744
61. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435. doi:10.1056/NEJMoa2004967
62. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128. doi:10.1056/NEJMoa2030183
63. Ali MU, Mancini GBJ, Fitzpatrick-Lewis D, et al. The effectiveness of sodium-glucose co-transporter 2 inhibitors on cardiorenal outcomes: an updated systematic review and meta-analysis. *Cardiovasc Diabetol*. 2024;23:72. doi:10.1186/s12933-024-02154-w
64. Jong GP, Lin TK, Liao PL, Huang JY, Yang TY, Pan LF. Risk of new-onset stroke in patients with type 2 diabetes with chronic kidney disease on sodium-glucose co-transporter-2 inhibitor users. *Transl Stroke Res*. 2024;15(6):1098–1107. doi:10.1007/s12975-023-01174-0
65. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424. doi:10.1056/NEJMoa2022190
66. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461. doi:10.1056/NEJMoa2107038
67. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol*. 2018;71:2628–2639. doi:10.1016/j.jacc.2018.03.009
68. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384:129–139. doi:10.1056/NEJMoa2030186
69. Rahman H, Khan SU, Lone AN, et al. Sodium-glucose cotransporter-2 inhibitors and primary prevention of atherosclerotic cardiovascular disease: a meta-analysis of randomized trials and systematic review. *J Am Heart Assoc*. 2023;12(16):e030578. doi:10.1161/JAHA.123.030578
70. D'Onofrio N, Sardu C, Trotta MC, et al. Sodium-glucose co-transporter2 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of sodium-glucose co-transporter2 inhibitor treatment. *Mol Metab*. 2021;54:101337. doi:10.1016/j.molmet.2021.101337
71. Nomura S, Shouzu A, Taniura T, et al. Effects of tofogliflozin and anagliptin alone or in combination on glucose metabolism and atherosclerosis-related markers in patients with type 2 diabetes mellitus. *Clin Pharmacol*. 2023;15:41–55. doi:10.2147/CPAA.S409786
72. Arow Z, Hornik-Lurie T, Hilu R, et al. SGLT2 inhibitors and GLP-1 receptor agonists: impact on mortality in diabetic patients with cardiovascular disease. *Cardiovasc Diabetol*. 2025;24(1):353. doi:10.1186/s12933-025-02874-7
73. Ceasovschih A, Balta A, Aldeen ES, et al. Sodium-glucose cotransporter 2 inhibitors and atherosclerosis. *Am J Prev Cardiol*. 2025;23:101061. doi:10.1016/j.ajpc.2025.101061
74. Stachteas P, Karakasis P, Patoulias D, Clemenza F, Fragakis N, Rizzo M. The effect of sodium-glucose co-transporter-2 inhibitors on markers of subclinical atherosclerosis. *Ann Med*. 2023;55(2):2304667. doi:10.1080/07853890.2024.2304667
75. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2021;6(2):148–158. doi:10.1001/jamacardio.2020.4511
76. Ye N, Jardine MJ, Oshima M, et al. Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: insights from the CREDENCE trial. *Circulation*. 2021;143:1735–1749. doi:10.1161/CIRCULATIONAHA.120.048740
77. Goh LGH, Sun J, Ong BSK, et al. Real-world evaluation of sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors for managing type 2 diabetes mellitus: a retrospective multi-ethnic cohort study. *J Diabetes Metab Disord*. 2022;21:521–555. doi:10.1007/s40200-022-01004-4
78. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation*. 2018;138:1537–1550. doi:10.1161/CIRCULATIONAHA.118.035901
79. Sharma A, Ferreira JP, Zannad F, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from the EMPEROR-preserved trial. *Eur J Heart Fail*. 2023;25:1337–1348. doi:10.1002/ejhf.2857
80. McCausland FR, Claggett BL, Vaduganathan M, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: a prespecified analysis of the DELIVER randomized clinical trial. *JAMA Cardiol*. 2023;8:56–65. doi:10.1001/jamacardio.2022.4210
81. Fernández-Fernandez B, Sarafidis P, Soler MJ, et al. EMPA-KIDNEY: expanding the range of kidney protection by SGLT2 inhibitors. *Clin Kidney J*. 2023;16(8):1187–1198. doi:10.1093/ckj/sfad082
82. Group EMPA-KIDNEYC, Herrington WG, Staplin N, et al. Long-term effects of empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2025;392(8):777–787.
83. Baigent C, Emberson J, Haynes R; Nuffield Department of Population Health Renal Studies Group. SGLT2 Inhibitor Meta-analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium-glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet*. 2022;400:1788–1801. doi:10.1016/S0140-6736(22)02074-8

84. Kitaoka K, Yano Y, Nagasu H, et al. Kidney outcomes of SGLT2 inhibitors among older patients with diabetic kidney disease in real-world clinical practice: the Japan chronic kidney disease database ex. *BMJ Open Diab Res Care*. 2024;12:e004115. doi:10.1136/bmjdrc-2024-004115
85. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ*. 2018;363:k4365. doi:10.1136/bmj.k4365
86. Bersoff-Matcha SJ, Chamberlain C, Cao C, et al. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. *Ann Intern Med*. 2019;170(11):764–769. doi:10.7326/M19-0085
87. Adamson C, Docherty KF, Heerspink H, et al. Initial decline (Dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from DAPA-HF. *Circulation*. 2022;146(6):438–449. doi:10.1161/CIRCULATIONAHA.121.058910
88. Jongs N, Chertow GM, Greene T, et al. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. *J Am Soc Nephrol*. 2022;33(11):2094–2107. doi:10.1681/ASN.2022030306
89. Kraus BJ, Weir MR, Bakris GL, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int*. 2021;99(3):750–762. doi:10.1016/j.kint.2020.10.031
90. Oshima M, Jardine MJ, Agarwal R, et al. Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int*. 2021;99(4):999–1009. doi:10.1016/j.kint.2020.10.042
91. Cardiorenal Syndrome Guidelines Working Group of Chinese Nephrologist Association of Chinese Medical Doctor Association. [Clinical practice guideline for the diagnosis and treatment of cardiorenal syndrome (2023 Edition)] − Article in Chinese. *Zhonghua Yi Xue Za Zhi*. 2023;103:3705–3759. doi:10.3760/cma.j.cn112137-20230822-00277
92. Chinese Diabetes Society. Guideline for the prevention and treatment of diabetes mellitus in China (2024 edition). *Chin J Diab*. 2025;17(1):16–139.
93. National Center for Cardiovascular Diseases, China National Heart Failure Society, Chinese Heart Failure Association of Chinese Medical Doctor Association, et al. National Heart Failure Guideline 2023. *Chin Circul J*. 2023;38(12):1207–1238.
94. Chinese Society of Cardiology, Chinese Medical Association; Chinese College of Cardiovascular Physician; Chinese Heart Failure Association of Chinese Medical Doctor Association, et al. Chinese guidelines for the diagnosis and treatment of heart failure 2024.*Chinese J Cardiol*.2024;52(3):235–275. doi:10.3760/cma.j.cn112148-20231101-00405
95. Members WC, Virani SS, Newby LK, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2023;82(9):833–955. doi:10.1016/j.jacc.2023.04.003
96. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44(39):4043–4140. doi:10.1093/eurheartj/ehad192
97. Chinese Preventive Medicine Association for Kidney Disease. Guidelines for early evaluation and management of chronic kidney disease in China. *Chin J Int Med*. 2023;62(8):902–930. doi:10.3760/cma.j.cn112138-20221013-00755
98. Zhang Z, Wang, Tu T, et al. Advancing guideline-directed medical therapy in heart failure: overcoming challenges and maximizing benefits. *Am J Cardiovasc Drugs*. 2024;24:329–342. doi:10.1007/s40256-024-00646-4
99. Nicholas SB, Daratha KB, Alicic RZ, et al. Prescription of guideline-directed medical therapies in patients with diabetes and chronic kidney disease from the CURE-CKD registry, 2019-2020. *Diab Obes Metab*. 2023;25:2970–2979. doi:10.1111/dom.15194
100. Scheen AJ. Real-life underuse of SGLT2 inhibitors for patients with type 2 diabetes at high cardiorenal risk. *Diab Epidemiol Manag*. 2024;13:100184. doi:10.1016/j.deman.2023.100184
101. Fang L, Li G, Ren J, et al. Integrated analysis for treatment scheme of sodium-glucose cotransporter 2 inhibitors in patients with diabetic kidney disease: a real-world study. *Sci Rep*. 2023;13:5969. doi:10.1038/s41598-023-33211-1
102. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219–2229. doi:10.1056/NEJMoa2025845
103. Tuttle KR, Hauske SJ, Canziani ME, et al. Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, Phase 2 trial. *Lancet*. 2024;403(10424):379–390. doi:10.1016/S0140-6736(23)02408-X
104. Rossing P, Anker SD, Filippatos G, et al. Finerenone in patients with chronic kidney disease and type 2 diabetes by sodium-glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care*. 2022;45:2991–2998. doi:10.2337/dc22-0294
105. Sarafidis P. Use of ACEi/ARBs, SGLT2 inhibitors and MRAs can help us reach the therapeutic ceiling in CKD. *Clin Kidney J*. 2024;17(2):sfae014. doi:10.1093/ckj/sfae014
106. Miao X, Zhang J, Huang W, et al. Research progress of SGLT2 inhibitors in cancer treatment. *Drug Des Devel Ther*. 2025;19:505–514. doi:10.2147/DDDT.S485755
107. Naeimzadeh Y, Tajbakhsh A, Nemati M, Fallahi J. Exploring the anti-cancer potential of SGLT2 inhibitors in breast cancer treatment in pre-clinical and clinical studies. *Eur J Pharmacol*. 2024;978:176803. doi:10.1016/j.ejphar.2024.176803



**Drug Design, Development and Therapy**

**Dovepress**
Taylor & Francis Group

**Publish your work in this journal**

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

**Submit your manuscript here:** https://www.dovepress.com/drug-design-development-and-therapy-journal