# Optimized Management of Cardio-Renal-Metabolic (CRM) Conditions in Patients With T2D

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## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

- Describe cardio-renal-metabolic (CRM) conditions and their impact on health and patient-centered outcomes.
- Recognize current gaps in screening, risk factor management, and utilization of guideline-directed therapies in patients with CRM conditions.
- Select appropriate guideline-directed therapies for patients with type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease based on current guidelines and clinical evidence.
- Recognize the importance of multidisciplinary care when managing patients with CRM conditions.

### KEY TAKEAWAYS

- People with type 2 diabetes (T2D) are at increased risk for cardiovascular and kidney comorbidities, which dramatically increase morbidity and mortality risk.
- Chronic kidney disease (CKD) is largely underrecognized and undertreated in the primary care setting due to suboptimal screening and lack of awareness by both clinicians and patients.
- Agents from the sodium-glucose cotransporter-2 (SGLT2) inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, and mineralocorticoid receptor antagonist (MRA) classes are now considered standard-of-care therapies to mitigate risk in patients with cardio-renal-metabolic (CRM) conditions.
- Primary care providers play an important role in multidisciplinary CRM management teams to address key barriers to optimized care of patients with CRM conditions.

### TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of CRM.

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## INTRODUCTION

### CASE SCENARIO

AW is a 65-year-old cisgender female presenting to the primary care clinic to establish care after moving to the area to be closer to family. AW's medical records indicate a history of type 2 diabetes (T2D), hypertension, dyslipidemia, obesity, and myocardial infarction. AW reports taking all of her medications as prescribed but can't remember the last time she saw a healthcare provider.

***Vitals:*** Body mass index: 34 kg/m$^2$, blood pressure: 138/90 mm Hg (average of 3 seated measurements in clinic today)

***Current Medications:*** Metformin 1000 mg twice daily, linagliptin 5 mg once daily, lisinopril 40 mg once daily, atorvastatin 40 mg once daily, aspirin 81 mg once daily

***Key Lab Values:*** Glycated hemoglobin (A1c): 7.5%; estimated glomerular filtration rate (eGFR): 52 mL/min/1.73 m$^2$; urinary albumin-to-creatinine ratio (UACR): 220 mg/g; lipid panel and electrolytes all within normal ranges. Medical records indicate an eGFR of 58 mL/min/1.73 m$^2$ measured 13 months prior.

This patient has T2D, established atherosclerotic cardiovascular disease (ASCVD), and, as identified via recommended screening of eGFR and UACR, chronic kidney disease (CKD). AW represents a relatively common patient encountered in the primary care setting: a patient with T2D and multiple cardiorenal comorbidities. It is long established that cardiovascular and kidney disease are important diabetes-related complications and a highly interdependent relationship exists between heart and kidney health.[1,2] Optimized metabolic risk factor management to prevent and/or delay progression of heart and kidney disease in patients with diabetes is stressed within major guidelines due to the substantial increased risk for morbidity, decreased quality of life, and premature mortality observed in patients with cardiorenal comorbidities.[1]

Fortunately for patients with cardio-renal-metabolic (CRM) conditions (and the clinicians caring for them), a number of evidence-based therapies are now available to target key cardiorenal risk factors and to improve ASCVD, CKD, and/or heart failure (HF) outcomes.[1] While recent advancements provide options for patients with CRM conditions, important gaps in screening, treatment, and optimized use of guideline-directed therapies persist.[3] Indeed, screening and identification rates of CKD in people with diabetes are low, with estimates suggesting that less than 50% of patients with T2D receive recommended annual albuminuria screening in the primary care setting.[4] Evidence further illustrates that improvements are needed in management of traditional diabetes risk factors. Although promoting smoking cessation and optimization of glucose, blood pressure, and lipid management have been foundational components of diabetes management for decades, current estimates from the Centers for Disease Control and Prevention (CDC) indicate that less than 20% of adults achieve all general A1c, blood pressure, cholesterol, and smoking cessation goals.[5]

While optimization of glycemic control is a central component of diabetes management, some glucose-lowering agents are now recognized for their robust heart and kidney benefits. Specifically, major guidelines recommend agents from the sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 (GLP-1) receptor agonist classes to reduce cardiorenal risk.[1,6-8] Many patients who could benefit from use of these agents, however, do not receive them. For example, recent data suggest that less than 8% of older adults with diabetes and CKD were receiving SGLT2 inhibitors in 2020, and fewer than 14% of people with diabetes and cardiovascular disease received a GLP-1 receptor agonist between 2018 and 2020.[9]

Suboptimal use of evidence-based therapies in T2D is not new. Underutilization of renin-angiotensin system (RAS) inhibitors continues to persist in patients with T2D and CKD despite being a standard of care for more than 3 decades.[10] Factors contributing to these and other gaps in CRM care are numerous and often complicated by clinician time constraints, patient preferences and priorities, and/or access/cost limitations.[3] Indeed, cost is a notable barrier to use of newer agents—including SGLT2 inhibitors and GLP-1 receptor agonists. According to cost information provided in the American Diabetes Association's (ADA's) 2023 Standards of Care in Diabetes, the monthly average wholesale price (AWP) for SGLT2 inhibitors and GLP-1 receptor agonists ranges from $390 to $685 and $814 to $1278, respectively, depending on the agent selected.[1] Although AWP prices do not account for insurance, discounts, rebates, or other price adjustments that impact the actual cost incurred by the patient, patient cost share for these newer agents represents an important barrier often necessitating cost-reduction strategies to improve access.[1]

Guidelines from organizations including, but not limited to, the ADA, Kidney Disease: Improving Global Outcomes (KDIGO), American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) stress the importance of multidisciplinary approaches to CRM care, with primary care clinicians playing a critical role within the multidisciplinary team to improving outcomes by optimizing recommended screening, risk factor management, and initiation of agents with proven cardiorenal benefit (**TABLE 1**).[1,6,7]

**TABLE 1. Recommendations for multidisciplinary/team-based approaches to optimize management of CRM conditions[1,6,7]**

| Organization/guideline | Recommendations |
|---|---|
| ADA 2023 Standards of Care in Diabetes | • People with diabetes can benefit from a coordinated multidisciplinary team that may include and is not limited to diabetes care and education specialists (DCESs), primary care and specialty clinicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, and mental health professionals. |
| KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease | • Policymakers and institutional decision-makers should implement team-based, integrated care focused on risk evaluation and patient empowerment to provide comprehensive care in patients with diabetes and CKD. |
| AHA/ACC/HFSA 2022 Guideline for the Management of Heart Failure | • Patients with HF should receive care from multidisciplinary teams to facilitate the implementation of guideline-directed medical therapy, address potential barriers to self-care, reduce the risk of subsequent rehospitalization for HF, and improve survival.<br>• Patients with HF should receive specific education and support to facilitate HF self-care in a multidisciplinary manner. |

## EVIDENCE REVIEW: GUIDELINE-DIRECTED THERAPIES TO IMPROVE OUTCOMES FOR CRM CONDITIONS

A discussion of evidence supporting use of current guideline-directed therapies to improve ASCVD, CKD, and HF outcomes follows.

### Atherosclerotic cardiovascular disease (ASCVD)

Owing in part to the 2008 US Food and Drug Administration (FDA) guidance for industry requiring manufacturers of new glucose-lowering medications to demonstrate cardiovascular safety through conduct of large cardiovascular outcome trials (CVOTs), treatment with most SGLT2 inhibitors and GLP-1 receptor agonists on the US market have been evaluated in large CVOTs for risk of major adverse cardiovascular events (MACE).[11]

#### *SGLT2 inhibitors*

The EMPA-REG OUTCOME trial with empagliflozin was the first CVOT published, not only establishing cardiovascular safety but also demonstrating a 14% relative risk reduction in 3-point MACE with empagliflozin treatment (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.74-0.99) in people with T2D and established ASCVD.[12] CVOTs with canagliflozin and dapagliflozin shortly thereafter reported benefits of SGLT2 inhibition on MACE and on a composite of cardiovascular death or HF hospitalization, respectively.[13,14] The VERTIS CV outcome trial with ertugliflozin, however, did not report a benefit of treatment on the primary MACE outcome (HR: 0.97; 95% CI: 0.85-1.11) but did report benefit on a key secondary outcome of HF hospitalization.[15] These findings resulted in the FDA granting expanded cardiovascular indications for empagliflozin, canagliflozin, and dapagliflozin. Importantly, these CVOTs also reported consistent benefits on secondary kidney and HF outcomes, thus supporting the need for subsequent dedicated kidney and HF outcome trials.

#### *GLP-1 receptor agonists*

All GLP-1 receptor agonists evaluated in large CVOTs have demonstrated cardiovascular safety.[11] However, a recent meta-analysis of 8 GLP-1 CVOTs, reported a statistically significant class benefit of 14% reduction in MACE (HR: 0.86; 95% CI: 0.79-0.94; $P = 0.006$).[16] GLP-1 receptor agonists that have demonstrated MACE benefit within individual CVOTs and have subsequently received expanded ASCVD indications include liraglutide, injectable semaglutide, and dulaglutide.[11,17-19]

### Chronic kidney disease (CKD)

#### *SGLT2 inhibitors*

In follow-up to consistently positive secondary kidney outcomes observed in CVOTs, 3 SGLT2 inhibitors available in the US have been studied prospectively in dedicated kidney outcome trials (**TABLE 2**).[20-22] All 3 trials were stopped early during planned interim analyses due to overwhelming benefit, with median durations of follow-up ranging from 2.0 to 2.6 years. Of note, all 3 trials evaluated SGLT2 inhibitor therapy in patients with CKD as add-on to background optimized RAS inhibitor therapy.[20-22] While the CREDENCE trial with canagliflozin specifically enrolled participants with T2D and CKD,[20] the DAPA-CKD and EMPA-KIDNEY trials with dapagliflozin and empagliflozin, respectively, included patients with CKD with and without T2D.[21,22] Notably, the kidney benefits observed within these trials were consistent among patients with and without diabetes and without regard to baseline eGFR. Observed benefits in both people without T2D and in those with relatively low eGFRs indicate that the cardiorenal benefits of SGLT2 inhibitors are not entirely attributable to their beneficial effects on traditional metabolic risk factors (eg, glycemia).[23] Indeed, multiple putative mechanisms of cardiorenal benefit have been proposed with SGLT2 inhibition, highlighting the interrelatedness of heart and kidney disease pathophysiology. An illustra-

**TABLE 2. Summary of key SGLT2 inhibitor kidney outcome trials[20-22]**

| Trial | CREDENCE (n = 4401) | DAPA-CKD (n = 4304) | EMPA-KIDNEY (n = 6609) |
|---|---|---|---|
| **Treatment** | Canagliflozin vs Placebo | Dapagliflozin vs Placebo | Empagliflozin vs Placebo |
| **Key inclusion criteria** | • T2D<br>• A1c 6.5 to 12.0%<br>• eGFR 30 to <90 mL/min/1.73 m$^2$<br>• UACR >300 to 5000 mg/g<br>• Treated with RAS inhibitor | • eGFR 25 to 75 mL/min/1.73 m$^2$<br>• UACR of 200 to 5000 mg/g<br>• Treated with RAS inhibitor | • eGFR 20 to <45 mL/min/1.73 m$^2$ OR eGFR ≤45 to <90 mL/min/1.73 m$^2$ with UACR ≥200 mg/g<br>• Treated with RAS inhibitor |
| **Baseline diagnosis of T2D (%)** | 100 | 67 | 46 |
| Median follow-up (years) | 2.6 | 2.4 | 2.0 |
| **Primary outcome** | | | |
| **Primary outcome; HR (95% CI)** | **ESKD, doubling of SCr, or renal or CV death**<br>0.70<br>(0.59-0.82) | **≥50% decline in eGFR, ESKD, or renal or CV death**<br>0.61<br>(0.51-0.72) | **≥40% decline in eGFR, sustained decrease in eGFR to <10 mL/min/1.73 m$^2$, ESKD, or renal or CV death**<br>0.72<br>(0.64-0.82) |

**Abbreviations:** CV, cardiovascular; ESKD, end-stage kidney disease; SCr, serum creatinine.

tion of SGLT2 inhibitor-mediated kidney and heart protection can be accessed here: https://pubmed.ncbi.nlm.nih.gov/36506243/#&gid=article-figures&pid=figure-4-uid-3.[23]

### *Finerenone*

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) FDA approved to improve cardiorenal outcomes in people with CKD associated with T2D.[24] The approval of finerenone was based primarily on findings from 2 large outcome trials studying finerenone as add-on to optimized RAS inhibitor therapy: FIDELIO-DKD and FIGARO-DKD.[25,26] In the FIDELIO-DKD trial, finerenone treatment reduced the risk for its primary kidney disease composite outcome by 18% (HR: 0.82; 95% CI: 0.73-0.93; $P$ = .001).[25] The complimentary FIGARO-DKD trial reported a 13% risk reduction for its primary cardiovascular outcome (HR: 0.87; 95% CI: 0.76-0.98; $P$ = .03).[26]

### *GLP-1 receptor agonists*

CVOTs with liraglutide, injectable semaglutide, and dulaglutide included secondary outcomes for "worsening nephropathy."[17-19] While the definitions utilized within the 3 trials varied, all 3 studies reported a benefit on this exploratory outcome, thus suggesting a potential kidney benefit with GLP-1 receptor agonist therapy. Indeed, multiple potential mechanisms by which GLP-1 receptor agonists may prevent CKD progression have been proposed, including improvements in traditional metabolic risk factors and reductions in kidney inflammation, oxidative stress, and fibrosis.[27] Unlike SGLT2 inhibitors, primary evidence of kidney benefit with GLP-1 receptor agonists is not currently available. The ongoing FLOW trial (NCT03819153), however, is a dedicated kidney outcome trial with injectable semaglutide; this trial is expected to be completed in 2024, which will help further define the role of GLP-1 receptor agonists in the setting of CKD.

## Heart failure

Four dedicated HF outcome trials have been completed to date with dapagliflozin and empagliflozin (**TABLE 3**).[28-31] Collectively, these trials included patients ranging from those with reduced ejection fraction HF (HFrEF) to preserved ejection fraction HF (HFpEF). The DAPA-HF trial with dapagliflozin was the first major SGLT2 inhibitor HF outcome trial published, which reported a 26% risk reduction for worsening HF or cardiovascular-related death (HR: 0.74; 95% CI: 0.65-0.85) in participants with HFrEF.[28] The DELIVER trial subsequently reported an 18% risk reduction for worsening HF or cardiovascular death with dapagliflozin in patients with mildly reduced ejection fraction HF (HFmrEF) or HFpEF.[29] The EMPEROR-Reduced and EMPEROR-Preserved trials with empagliflozin similarly reported benefits in patients with HFrEF and HFpEF, respectively (**TABLE 3**).[30,31] Importantly, these trials enrolled patients with HF with or without diabetes, with overall benefits observed regardless of diabetes status or ejection fraction.

## Brief review: Guideline recommendations for management of CRM conditions in T2D

Based on the outcome trial evidence just reviewed, multiple

**TABLE 3. Summary of key SGLT2 inhibitor heart failure outcome trials[28-31]**

| | DAPA-HF (n = 4744) | DELIVER (n = 6263) | EMPEROR-Reduced (n = 3730) | EMPEROR-Preserved (n = 5988) |
|---|---|---|---|---|
| Treatment | Dapagliflozin vs Placebo | Dapagliflozin vs Placebo | Empagliflozin vs Placebo | Empagliflozin vs Placebo |
| **Key inclusion criteria** | • NYHA class II, III, or IV HF<br>• EF ≤ 40% | • Stabilized HF<br>• EF > 40% | • NYHA class II, III, or IV HF<br>• EF ≤ 40% | • NYHA class II, III, or IV HF<br>• EF > 40% |
| **Baseline diagnosis of T2D (%)** | 42 | 45 | 50 | 49 |
| **Median follow-up (years)** | 1.5 | 2.3 | 1.3 | 2.2 |
| **Primary outcome** | | | | |
| **Primary outcome; HR (95% CI)** | **Worsening HF or CV death**<br>0.74<br>(0.65-0.85) | **Worsening HF, CV death, or urgent visit for HF**<br>0.82<br>(0.73-0.92) | **CV death or HF hospitalization**<br>0.75<br>(0.65-0.86) | **CV death or HF hospitalization**<br>0.79<br>(0.69-0.90) |
| **Key secondary outcome** | | | | |
| **HF hospitalization; HR (95% CI)** | 0.70<br>(0.59-0.83) | 0.77<br>(0.67-0.89) | 0.69<br>(0.59-0.81) | 0.71<br>(0.60-0.83) |

**Abbreviations:** CV, cardiovascular; NYHA, New York Heart Association.

guidelines now recommend SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone as standard-of-care therapies to mitigate cardiorenal risk.[1,6-8] Contemporary recommendations offered by various organizations largely align, with use of these medications recommended without regard to A1c or the need for additional glucose lowering. Importantly, guidelines increasingly stress the importance of multidisciplinary CRM management teams to meet the numerous management and education needs of these patients by leveraging the strengths and abilities of all physician and non-physician team members.

### 2023 ADA Standards of Care in Diabetes

A primary goal stated within the 2023 ADA Standards of Care is to achieve cardiorenal risk reduction in high-risk patients with T2D. To achieve this goal, the ADA offers the following key recommendations[1]:

- **Patients with ASCVD or indicators of high risk:** Initiation of an SGLT2 inhibitor or GLP-1 receptor agonist with proven cardiovascular benefit is recommended. If additional glucose lowering is required after initiation of an agent from one of these classes, the ADA recommends considering the addition of an agent from the other class.
- **Patients with HF:** Initiate an SGLT2 inhibitor with proven HF benefit.
- **Patients with CKD:** It is preferably recommended to initiate an SGLT2 inhibitor with primary evidence of reducing CKD progression in patients with an eGFR ≥20 mL/min/1.73 $m^2$. A GLP-1 receptor agonist with proven cardiovascular benefit is recommended in patients unable to take an SGLT2 inhibitor. The ns-MRA finerenone is additionally recommended for consideration in patients with T2D, CKD, and albuminuria to reduce CKD progression and cardiovascular events.

### 2022 KDIGO Guideline for Diabetes Management in CKD

Recommendations from KDIGO largely align with recommendations from the ADA for patients with T2D and CKD.[6] First-line SGLT2 inhibitor and RAS inhibitor therapy are recommended in patients with T2D and CKD. SGLT2 inhibitor initiation is recommended in patients with an eGFR ≥20 mL/min/1.73 $m^2$, to be continued until kidney transplant or initiation of dialysis, provided the SGLT2 inhibitor continues to be well tolerated. For patients requiring additional glucose lowering to meet individualized glycemic targets, a long-acting GLP-1 receptor agonist is preferentially recommended based on established cardiovascular benefits, preserved glucose-lowering effect at low eGFR, and potential benefits of GLP-1 receptor agonist therapy on CKD progression. KDIGO also recommends finerenone as an option in patients with T2D and CKD with persistent albuminuria (≥30 mg/g) despite RAS inhibitor therapy.[6]

### 2022 AHA/ACC/HFSA Guideline for the Management of HF

Based on the robust benefits observed in dedicated HF outcome trials (**TABLE 3**), the 2022 AHA/ACC/HFSA guideline for the management of HF includes several recommenda-

tions regarding use of SGLT2 inhibitors in patients with or at risk for HF.[7] The guideline recommends SGLT2 inhibitor use in patients with T2D with either established cardiovascular disease or high cardiovascular risk to prevent HF hospitalization. In individuals with established HF, the guideline provides the following additional recommendations[7]:

- **Symptomatic chronic HFrEF:** SGLT2 inhibitor therapy is recommended to reduce HF hospitalization and cardiovascular mortality, irrespective of the presence of T2D.
- **HFmrEF and HFpEF:** SGLT2 inhibitor therapy can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.

### 2022 Diabetes Cardiorenal and Metabolism (DCRM) Multispecialty Practice Recommendations

The 2022 DCRM Multispecialty Practice Recommendations provide clinicians with a succinct set of recommendations and algorithms to guide treatment of CRM conditions.[8] The figure found here: https://pubmed.ncbi.nlm.nih.gov/34922811/ provides a summary of recommendations for use of glucose-lowering agents based on comorbidities in patients with T2D to reduce cardiorenal risk. The recommendations presented within the algorithm largely align with key recommendations from other major guidelines that address CRM management.

## CASE SCENARIO: MANAGEMENT PLAN

Returning to the patient AW, through recommended screening she is now recognized as having CKD in addition to T2D and established ASCVD. Based on her past medical history, physical, and laboratory findings, she is at high risk for kidney disease progression, cardiovascular events, and cardiovascular-related mortality. AW is an ideal candidate for initiation of additional agents to mitigate her cardiorenal risk. To work toward optimal management of her CRM conditions, initial management goals include (1) improved A1c and blood pressure management to slow CKD progression, (2) initiation of SGLT2 inhibitor therapy to slow CKD progression and mitigate cardiovascular risk, and (3) referral for diabetes self-management education to reinforce a healthy lifestyle and to receive education regarding her CKD diagnosis and management options. After addressing these initial goals, her healthcare providers can consider additional interventions to reduce cardiorenal risk, including addition of a GLP-1 receptor agonist and/or finerenone as informed by patient preferences, priorities, and resources.

## CONCLUSION

Patients with T2D and cardiorenal comorbidities are frequently encountered in the primary care setting. Findings from recent cardiovascular, kidney, and HF outcome trials have quickly changed the standard of care for patients with CRM conditions. Current guidelines stress the importance of screening patients for CRM conditions (eg, CKD) and promptly initiating guideline-directed therapies. Primary care providers will continue to play a critical role within the multidisciplinary CRM management team to optimize patient-centered care and outcomes. ●

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