Research Open

Endocrinology, Diabetes and Metabolism Journal

Volume 9 Issue 2

Research Article

Beyond Diabetes Care, Sodium-Glucose Co-transporter-2 (SGLT2) Inhibitors in Cardiovascular and Renal Health: Evidence and Implementation

Lucianne West PharmD[1], **Brittany Chapman** MD[2,3], **Harsh Patolia** MD[2], **Rachel Stulock** PharmD[4], **Rachel Carroll** PharmD MS[4], **Jessica Hohman** MD MSc MSc[5], **Hunter Block-Beach** BS[5], **Amanda R. Vest** MBBS MPH[2,3], **Ankeet S. Bhatt** MD MBA[6] **and Trejeeve Martyn,** MD MsC[2,3]*

[1]Department of Transplant Surgery, Tufts Medical Center, Boston, MA, USA

[2]Department of Cardiovascular Medicine, Heart Vascular Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA

[3]Kaufman Center for Heart Failure Treatment and Recovery, Cleveland Clinic, Cleveland, OH, USA

[4]Department of Pharmacy, Cleveland Clinic, Cleveland, OH, USA

[5]Center for Value-Based Care Research, Cleveland Clinic, Cleveland, OH, USA

[6]Department of Cardiovascular Medicine, Kaiser Permanente Northern California, San Francisco, CA, USA

Corresponding author: Trejeeve Martyn, MD MSc, Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, 9500 Euclid Ave, J3-4 Cleveland, OH 44195, USA, Phone: (216)-704-2458

Received: March 20, 2025; **Accepted:** March 26, 2025; **Published:** March 30, 2025

Abstract

Multiple studies have established the benefits of sodium-glucose co-transporter-2 (SGLT2) inhibitors in heart failure and chronic kidney disease (CKD) in patients with type 2 diabetes. Following these studies, additional large randomized controlled trials were conducted to assess their efficacy across various stages of heart failure and CKD and demonstrated benefit in patients regardless of diabetes status. While the data supporting the use of SGLT2 inhibitors is robust and national guidelines now recommend their use, the adoption of these treatments in clinical practice remains suboptimal. To improve patient outcomes, leveraging a multidisciplinary team-based approach can help accelerate widespread adoption.

Review of the Evidence in Heart Failure

Numerous randomized controlled trials in patients with type 2 diabetes have demonstrated the benefits of SGLT2 inhibitors in managing cardiovascular disease and chronic kidney disease [1-7]. In the initial SGLT2 inhibitor trials, these therapies significantly reduced heart failure hospitalizations compared to placebo in patients with established cardiovascular disease or those at high risk, a benefit that is primarily attributed to the prevention of incident symptomatic heart failure. Another placebo-controlled study found that initiating a combined SGLT1/2 inhibitor (sotagliflozin) either before or shortly after discharge in patients with diabetes and recent worsening heart failure led to a significant reduction in cardiovascular mortality as well as the number of hospitalizations and urgent visits for heart failure [8]. SGLT2 inhibitors have similarly been shown to slow the progression of kidney disease and reduce the incidence of renal events when added to standard care. The mechanisms underlying these benefits are believed to extend beyond glucose, weight, and blood pressure reduction; they are hypothesized to be driven by reductions in plasma volume, decreased cardiac preload and afterload, alterations in cardiac metabolism, and tubuloglomerular feedback which in turn lowers intraglomerular pressure [9,10].

Given the benefit seen in patients with type 2 diabetes, several landmark large clinical trials were conducted to analyze the benefits of these medications for these indications in patients with or without diabetes. These trials investigated the benefit of SGLT inhibitors in patients with heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, and chronic kidney disease. A summary of these trials and their findings are presented in Table 1.

The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) and Empagliflozin in Heart Failure with a Reduced Ejection Fraction (EMPEROR-Reduced) trials were the two earliest trials to evaluate the benefit of SGLT2 inhibitors in patients with heart failure and reduced ejection fraction (HFrEF) independent of diabetes status [11,12]. These studies compared dapagliflozin and empagliflozin, respectively, with placebo. Participants in both trials were predominantly male with a mean age of approximately 65 years, and less than half had a history of type 2 diabetes. Most patients presented with New York Heart Association (NYHA) class II symptoms and were on background therapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or angiotensin receptor-neprilysin inhibitors (ARNIs). In both studies, the use of an SGLT2 inhibitor resulted in significant improvements in the primary composite outcomes including heart failure-related hospitalizations and cardiovascular mortality. These benefits were consistent across various subgroups, though the effects were particularly pronounced in patients with NYHA class II

Table 1: Summary of randomized controlled trials for non-diabetes indications.

Heart Failure with Reduced Ejection Fraction			
Trial	**Intervention**	**Key Patient Characteristics**	**Results**
DAPA-HF[11]	Dapagliflozin 10 mg once daily (n=2373) or placebo (n=2371)	• NYHA Class II 67.7% (dapa); 67.4% (placebo) • Systolic blood pressure (mmHg) 122.0 ± 16.3 (dapa); 121.6 ± 16.3 (placebo) • Mean LVEF (%) 31.2 ± 6.7 (dapa); 30.9 ± 6.9 (placebo) • Mean eGFR (mL/min/1.73m^2) 66.0 ± 19.6 (dapa); 65.5 ± 19.3 (placebo) o eGFR < 60 40.6% (dapa); 40.7% (placebo) • Background therapy with ACE/ARB/ARNI 95% (dapa); 93.7% (placebo)	Primary composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in IV therapy for heart failure) or death from cardiovascular causes: 16.3% dapa vs 21.2% placebo (HR 0.74 [0.65-0.85]; p<0.001)
EMPEROR-Reduced[12]	Empagliflozin 10 mg once daily (n=1863) or placebo (n=1867)	• NYHA Class II 75.1% (empa); 75.0% (placebo) • Systolic blood pressure (mmHg) 122.6 ± 15.9 (empa); 121.4 ± 15.4 (placebo) • Mean LVEF (%) 27.7 ± 6.0 (empa); 27.2 ± 6.1 (placebo) o LVEF ≤ 30% 71.8% (empa); 74.6% (placebo) • Mean eGFR (mL/min/1.73m^2) 61.8 ± 21.7 (empa); 62.2 ± 21.5 (placebo) o eGFR < 60 48.0% (empa); 48.6% (placebo) • Background therapy with ACE/ARB/ARNI 88.8% (empa); 89.6% (placebo)	Primary composite outcome of death from cardiovascular causes or hospitalization for heart failure: 19.4% empa vs 24.7% placebo (HR 0.75 [0.65-0.86]; p<0.001)
Heart Failure with Preserved Ejection Fraction			
Trial	**Intervention**	**Patient Characteristics**	**Results**
EMPEROR-Preserved[14]	Empagliflozin 10 mg once daily (n=2997) or placebo (n=2991)	• NYHA Class II 81.1% (empa); 81.9% (placebo) • Systolic blood pressure (mmHg) 131.8 ± 15.6 (empa); 131.9 ± 15.7 (placebo) • Mean LVEF (%) 54.3 ± 8.8 (empa; placebo) • Mean eGFR (mL/min/1.73m^2) 60.6 ± 19.8 (empa); 60.6 ± 19.9 (placebo) o eGFR < 60 50.2% (empa); 49.6% (placebo)	Primary composite outcome of death from cardiovascular causes or hospitalization for heart failure: 13.8% empa vs 17.1% placebo (HR 0.79 [0.69-0.90]; p<0.001)
DELIVER[15]	Dapagliflozin 10 mg once daily (n=3131) or placebo (n=3132)	• NYHA Class II 73.9% (dapa); 76.6% (placebo) • Mean LVEF (%) 54.0 ± 8.6 (dapa); 54.3 ± 8.9 (placebo) • Mean eGFR (mL/min/1.73m^2) 61.0 ± 19.0 (dapa; placebo)	Primary composite outcome of worsening heart failure (hospitalization or urgent visit for heart failure) or death from cardiovascular causes: 16.4% dapa vs 19.5% placebo (HR 0.82 [0.73-0.92]; p<0.001)
Chronic Kidney Disease			
Trial	**Intervention**	**Patient Characteristics**	**Results**
DAPA-CKD[20]	Dapagliflozin 10 mg once daily (n=2152) or placebo (n=2152)	• Systolic blood pressure (mmHg) 136.7 ± 17.5 (dapa); 137.4 ± 17.3 (placebo) • Mean eGFR (mL/min/1.73m^2) 43.2 ± 12.3 (dapa; 43.0 ± 12.4 (placebo) o eGFR 30-45 45.5% (dapa); 42.7% (placebo) • Median urinary albumin-to-creatinine ratio(IQR) 965 (472-1903; dapa); 934 (482-1868; placebo) • Serum potassium (mEq/L) 4.6 ± 0.5 (dapa); 4.6 ± 0.6 (placebo) • Background therapy with ACE/ARB 98.4% (dapa); 97.9% (placebo)	Primary composite outcome of sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes: 9.2% dapa vs 14.5% placebo (HR 0.61 [0.51-0.72]; p<0.001)
EMPA-KIDNEY[21]	Empagliflozin 10 mg once daily (n=3304) or placebo (n=3305)	• Systolic blood pressure (mmHg) 136.4 ± 18.1 (empa); 136.7 ± 18.4 (placebo) • Mean eGFR (mL/min/1.73m^2) 37.4 ± 14.5 (empa); 37.3 ± 14.4 (placebo) o eGFR 30-45 44.4% (empa); 44.2% (placebo) • Median urinary albumin-to-creatinine ratio(IQR) 331 (46-1061; empa); 327 (54-1074; placebo) • Background therapy with ACE/ARB 85.7% (empa); 84.6% (placebo)	Primary composite outcome of progression of kidney disease or death from cardiovascular causes: 13.1% empa vs 16.9% placebo (HR 0.72 [0.64-0.82]; p<0.001)

symptoms and an LVEF of less than 30%. Additionally, no significant differences were observed in the incidence of side effects including volume depletion, renal adverse events, or major hypoglycemia in either trial.

With the clear benefits of SGLT inhibitors established in the HFrEF patient population, the question remained whether this benefit persists across the spectrum of heart failure. Left ventricular ejection fraction (LVEF) has historically been used for trial inclusion and exclusion criteria, creating a body of evidence that is therefore subcategorized based on ejection fraction, when the reality is that heart failure is a clinical syndrome that exists along a spectrum of ejection fraction. There is broad agreement on the definitions of HFrEF (LVEF ≤ 40%) and HFpEF (LVEF ≥ 50%) while much ambiguity remains for those with LVEF between 40% and 50% as well as those who previously qualified as HFrEF with subsequent improvement in LVEF to ≥ 40% [13].

The Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR-Preserved) and Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trials sought to assess the potential benefits of SGLT2 inhibitors in patients with heart failure and LVEF > 40%; importantly, DELIVER allowed enrollment of patients with prior LVEF ≤ 40% provided their LVEF was > 40% at the time of study enrollment (a group that has been labeled heart failure with "improved" EF according to the Universal Definition of heart failure) while EMPEROR-Preserved did not [13-15]. These trials involved a slightly older population with a mean age of approximately 72 years, and nearly half of the participants were female. Like EMPEROR-Reduced and DAPA-HF, about half of the patients had a history of type 2 diabetes, although approximately 90% participants enrolled in EMPEROR-Preserved and DELIVER had a history of hypertension. In both trials, patients were evenly distributed across the spectrum of eligible LVEF. The use of SGLT2 inhibitors in both studies resulted in significant improvements in primary composite outcomes including heart failure-related hospitalizations and cardiovascular mortality. These benefits were consistent across subgroups; however, the EMPEROR-Preserved trial showed a signal towards greater benefit in patients with lower-range LVEF, while the DELIVER trial suggested more pronounced

benefits in those with higher-range LVEF. These differences may be attributed to variations in primary outcomes (such as the addition of urgent HF visits to the composite endpoint in DELIVER), patient inclusion criteria (such as the inclusion of patients with heart failure with recovered ejection fraction in DELIVER), and the duration of heart failure symptoms prior to enrollment. While there is likely a class effect of SGLT2 inhibitors in heart failure and there is evidence that canagliflozin can improve activity and patient-reported outcomes compared with placebo, there are currently only three FDA approved SGLT2 inhibitors for broad heart failure use with varying approved eGFR cutoffs based on study inclusion criteria: sotagliflozin (eGFR > 30 ml/min/1.73 m^2), empagliflozin (eGFR > 20 ml/min/1.73 m^2), and dapagliflozin (eGFR > 25 ml/min/1.73 m^2) [16-19].

Review of the Evidence in Chronic Kidney Disease

Another key patient population hypothesized to benefit from SGLT2 inhibitors is those with chronic kidney disease. The DAPA-CKD and EMPA-KIDNEY trials therefore sought to evaluate the potential benefits of SGLT2 inhibitors in patients with chronic kidney disease independent of diabetes status, though the characteristics of participants enrolled in these studies differed in a few key ways [20,21]. The DAPA-CKD trial enrolled a higher proportion of patients with a history of cardiovascular disease and diabetes, while the EMPA-KIDNEY trial included a greater percentage of patients with an eGFR < 30 and a broader range of baseline urinary albumin-to-creatinine ratios (UACR). Both trials demonstrated that SGLT2 inhibitors (dapagliflozin and empagliflozin, respectively) provide significant benefits in slowing CKD progression and reducing cardiovascular risk regardless of diabetes status and across a wide spectrum of renal function. However, in EMPA-KIDNEY, subgroup analysis revealed that the benefits may be more pronounced in patients with lower baseline UACR levels (Table 1).

Guideline Recommendations

As a result of these trial findings, national guidelines for heart failure, chronic kidney disease, and diabetes now recommend initiating SGLT2 inhibitor therapy in eligible patients (Table 2).

Important Considerations for Safe Use and Adverse Events

Many patients do not carry only a single indication for treatment with an SGLT2 inhibitor. In fact, a 2018 study of 530,747 patients with type 2 diabetes found that over 90% had concomitant cardiovascular or kidney disease [25]. Given the interconnectedness of metabolic syndrome, cardiovascular disease, and chronic kidney disease, it is crucial for clinicians managing patients with these conditions to consider initiating SGLT2 inhibitors in eligible individuals from multiple vantage points. Clinicians should be mindful of dual disease purposes and screen appropriately for benefit using UACR and NT-proBNP for CKD and heart failure, respectively.

According to the KDIGO guidelines, once an SGLT2 inhibitor is initiated, it is generally appropriate to continue the therapy even if the eGFR drops below 20 mL/min/1.73m^2, unless the medication is poorly tolerated or kidney replacement therapy (KRT) is require [26]. Additionally, starting or continuing SGLT2 inhibitors does not necessitate a change in the frequency of CKD monitoring. There is often a reversible decrease in eGFR observed at the start of therapy that is typically not a reason to discontinue treatment. It is important to note that while glycemic control may be less effective when eGFR falls below 45 mL/min/1.73m^2, the cardiovascular and renal benefits of SGLT2 inhibitors remain, and therefore these agents should still be initiated as long as the eGFR prior to initiation is >20 mL/min/1.73m^2.[23] In the HFrEF and CKD trials previously described, most patients were already on background therapy with ACE inhibitors, ARBs, or ARNI, suggesting that SGLT2 inhibitors can safely and effectively be added to these guideline-directed medical therapies with few adverse effects. Given the generally favorable hemodynamic and laboratory tolerability of SGLT2 inhibitors, clinicians may consider initiating them before other classes of guideline-directed therapies based on

Table 2: Summary of guideline recommendations.

National Guideline	Class of Recommendation/ Level of Evidence	Recommendation
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[22]	1/A	Initiate SGLT2 inhibitor for patients with type 2 diabetes and CVD or high risk for CVD
	1/A	In patients with symptomatic chronic HFrEF, SGLT2 inhibitors are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes
	2/A	SGLT2 inhibitor use recommended in patients with HF with mildly reduced ejection fraction (HFmrEF; LVEF 41-49%)
	2/A	SGLT2 inhibitor use recommended in patients with HF with preserved ejection fraction (HFpEF; LVEF ≥ 50%)
KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[23]	1/A	Recommend treating patients with type 2 diabetes, CKD, and an eGFR ≥ 20 ml/ min per 1.73 m^2 with an SGLT2 inhibitor
	1/A	Recommend treating adults with CKD with an SGLT2 inhibitor for the following: • eGFR ≥ 20 ml/min per 1.73 m2 with urine ACR ≥ 200 mg/g (≥ 20 mg/mmol) • Heart failure, irrespective of level of albuminuria
	2/B	Treat adults with eGFR 20 to 45 ml/min per 1.73 m2 with urine ACR < 200 mg/g (< 20 mg/mmol) with SGLT2 inhibitor
American Diabetes Association Standards of Care in Diabetes – 2025[24]	A	In adults with type 2 diabetes and established or high risk of atherosclerotic cardiovascular disease, the treatment plan should include medications with demonstrated benefits to reduce cardiovascular events (e.g., GLP-1 and/or SGLT2 inhibitor) for glycemic management and comprehensive cardiovascular risk reduction (irrespective of A1c)
	A	In adults with type 2 diabetes who have heart failure with either preserved or reduced ejection fraction, an SGLT2 inhibitor is recommended for both glycemic management and prevent of HF hospitalizations (irrespective of A1c)
	A	In adults with type 2 diabetes who have CKD (with confirmed eGFR 20-60 mL/min/1.73 m^2 and/or albuminuria), and SGLT2 inhibitor or GLP-1 RA with demonstrated benefit in this population should be used for both glycemic management (irrespective of A1c) 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

individual patient factors. However, special consideration should be made for management of diuretics, anti-hypertensive regimens, and anti-hyperglycemic regimens to reduce risk of side effects and simplify complex medication regimens.

Specifically, because hyperkalemia often limits the use of combination therapy with renin-angiotensin system inhibitors (RASi) and/or mineralocorticoid receptor antagonists (MRAs), the hypokalemic side effect of SGLT2 inhibitors may help balance potassium levels in patients on combination therapy. Indeed, there is evidence that SGLT2 inhibitors reduce hyperkalemic events in patients with and without diabetes making early initiation of this therapy enabling of combination GDMT [27]. With recently published evidence for the non-steroidal MRA finerenone showing clinical benefit in reducing heart failure morbidity, but with higher than expected hyperkalemic events, upfront initiation of SGLT2 inhibitors with MRAs in patients with heart failure and/or CKD indication(s) is an attractive strategy that may improve tolerability [28].

Though not the focus of this review, combination therapy in treating cardiovascular, kidney, and metabolic disease has gained traction over the prior several years. The pathophysiology of both CKD and heart failure are complex with multiple targetable pathways of injury including the renin-angiotensin system, inflammation and fibrosis, and metabolic derangement; as such, a single therapy is highly unlikely to modulate all involved pathways. In addition, cardiovascular disease (including heart failure, stroke, and myocardial infarction [MI]) is a significant cause of morbidity and mortality among patients with metabolic syndrome and those with CKD. However, each of these cardiac comorbidities is affected differently by each class of CKD therapy: SGLT2 inhibitors and ns-MRAs appear to most modulate heart failure outcomes, while RASi more significantly reduce blood pressure and GLP-1 receptor antagonists modulate metabolic syndrome, reduce ASCVD risk, and modify CDK outcomes. Additionally, though efficacy of empagliflozin in HFrEF and HFpEF has been demonstrated, inhibition of these pathway did not demonstrate meaningful impact in patients with MI with regards to first hospitalization for HF or death when compared to placebo. Subsequent post hoc analyses revealed a decreased risk of heart failure (HF) in patients with left ventricular dysfunction or congestion following acute MI, as well as a reduction in both first and total HF hospitalizations among individuals with type 2 diabetes [29-31]. We believe that aggressive and early combination therapy in treating the distinct but interrelated conditions of cardiovascular, kidney, and metabolic disease (align with CKM) should become the norm moving forward.

Although the benefits of SGLT2 inhibitors extend across multiple physiological pathways, this medication class is not without adverse effects. SGLT2 inhibitors have been linked to an elevated risk of genitourinary infections, hypovolemia, and diabetic ketoacidosis (DKA). The increased risk of genitourinary infections is primarily attributed to the glucosuric effects of these medications, a relationship highlighted in previous meta-analyses [32]. The use of canagliflozin, dapagliflozin, and empagliflozin in patients with diabetes is particularly linked to a higher risk of genitourinary tract infections, especially in women, with this risk further heightened in those with a history of urinary tract infections (UTIs) and obesity [33]. Among these patients, there have been reports of Fournier's gangrene; however, the connection between SGLT2 inhibitor therapy and this severe perineal infection remains weak, as patients with diabetes already have a higher baseline risk for such infections. Across all heart failure and CKD trials reviewed, although SGLT2 inhibitor groups exhibited a higher rate of genitourinary tract infections, there were no reported cases of Fournier's gangrene in either the placebo or intervention arms.

Volume depletion has been consistently observed in multiple randomized controlled trials, including those focused on heart failure and CKD, due to osmotic diuresis induced by SGLT2 inhibitors, which may lead to symptomatic hypotension. The induction of DKA by this medication class has been postulated to occur due to different mechanisms, including impairment in ketone clearance. While the overall incidence of DKA remains rare across trials included in this review (<0.1%), the risk may be higher in patients hospitalized on SGLT2 inhibitor therapy, particularly when additional risk factors such as dehydration, infection, or changes in medication regimens including insulin or other glucose-altering agents are present. Due to these concerns, perioperative discontinuation and avoidance of this therapy on sick days has been advocated [34].

Furthermore, earlier concerns regarding potential associations between SGLT2 inhibitors and bone fractures, amputations, or malignancies have not been substantiated by more recent data, with variations in findings depending on the specific medication within the class.

SGLT2 inhibitors have been widely used and an effective therapeutic option for managing diabetes for several years. As our understanding of the potential side effects of this medication class evolves, especially in patients with multiple comorbidities, the benefits of SGLT2 inhibitors remain well-established and significant. These benefits are most pronounced when used in appropriately selected patients, with close monitoring by the multidisciplinary care team.

Translating Evidence to Implementation

A decision-analytic modeling study of heart failure patients in the United States estimated that optimal implementation of SGLT2 inhibitors over three years could prevent or delay approximately 630,000 worsening heart failure events across the entire LVEF spectrum. Of these, roughly 230,000 to 280,000 events would be prevented or postponed in patients with heart failure and LVEF greater than 40% [35]. Population health initiatives focused on managing chronic kidney disease, diabetes, and cardiovascular disease aim to prevent, manage, and reduce the impact of these conditions across diverse populations. These initiatives typically emphasize disease detection, improved access to therapeutics, patient and provider education, and initiation/titration of medical therapy.

Particularly in a value-based care context, wherein there are existing resources targeting better chronic disease management that are sustainable and not simply being used for demonstration projects, access to regularly updated patient, prescribing, and provider data is paramount [36]. Health system data can be leveraged to target therapeutic gaps, reduce practice variation and idiosyncratic use of evidence-based therapy, address disparities in care, and, ultimately

improve health outcomes at scale. Furthermore, multiple strategies can be tested and iteratively improved. As outlined in national guidelines for these diseases, care delivery models at the local level that engage multidisciplinary teams, provide targeted interventions and education, and focus on improving outcomes are essential for achieving these goals (Figure 1). Telehealth strategies may be incorporated to increase utilization of remote monitoring, improve education delivery, and incorporate more frequent touch points to provide care [22-24].

For example, through daily electronic health record (EHR) identification of inpatients with heart failure patients with suboptimal GDMT, the IMPLEMENT-HF trial demonstrated that the integration of pharmacist consultative services into inpatient workflows can improve medication access to novel GDMT. Through streamlined prior authorization and use of patient assistance programs (PAPs), pharmacists and heart failure specialists in collaboration facilitated the safe initiation and titration of heart failure GDMT through targeted recommendations to rounding generalist physicians [37].

Figure 1: Multidisciplinary Management Strategy to Optimize Guideline-Directed Medical Therapy in Patients with Heart Failure.

In the outpatient setting, PROMPT-HF was a pragmatic, EHR-based trial in which 100 healthcare providers treating patients with HFrEF were randomly assigned to receive either an alert or usual care [38]. The alert provided individualized, guideline-directed medical therapy recommendations along with patient-specific details. As a result, the alert group demonstrated significantly higher rates of guideline-directed medical therapy use at 30 days compared to those receiving usual care. The authors emphasized that this low-cost intervention could be quickly integrated into clinical practice, promoting faster adoption of high-value therapies in heart failure.

Another example of an ambulatory study that utilized EHR-identification of patients with GDMT gaps was the DRIVE study that enrolled 200 patients with indications for, but not currently on, an SGLT2 inhibitor or GLP1 receptor agonist [39]. This trial used a remote, team-based education and medication management program either simultaneously with a navigator/pharmacist outreach effort with or prior to navigator/pharmacist outreach effort; patients were randomized in a blinded fashion to one of these strategies. After 6 months, 64% of patients received a new prescription for either SGLT2 inhibitor or GLP1 agonist. These trials highlight how EHRs, telehealth models, and remote multidisciplinary interventions can be leveraged to improve patient care; one example of how to leverage the patient messaging portal to prompt uptake of SGLT2 inhibitor prescription can be seen in Figure 2. Importantly, once patients are in front of clinicians with knowledge and expertise to initiate GDMT, there is a high degree of success. Unfortunately, even with dedicated navigation resources, the ability to identify and connect patients with these expert providers remains a significant challenge. In the aforementioned DRIVE study, 1289 eligible patients were contacted: 771 were unreachable, 288 declined participation, and ultimately 200 patients were enrolled. Though these results show the value of dedicated pharmacists as a strategy to improve GDMT prescription, they also highlight the challenges in activating the pipeline of eligible patients into the pharmacist visit.

Conclusion

While SGLT2 inhibitors began as antihyperglycemic therapy for type 2 diabetes, the indications and benefits of this class of medications have expanded rapidly over the past decade. Despite the broad body of literature supporting their benefits across the spectrums of both heart failure and chronic kidney disease, there remains significant work to be done to improve national adherence to guideline recommendations and increase prescribing of these medications especially as most patients carry at least two indications for treatment with SGLT2 inhibitors. A multidisciplinary, team-based approach to treatment of patients with type 2 diabetes, heart failure, and chronic kidney disease is therefore crucial in the care for these patients. With increasing sophistication in both the ability to identify patients at risk and to provide personalized clinical decision support, remote patient data coupled to multidisciplinary teams can iteratively improve care delivery [40,41].

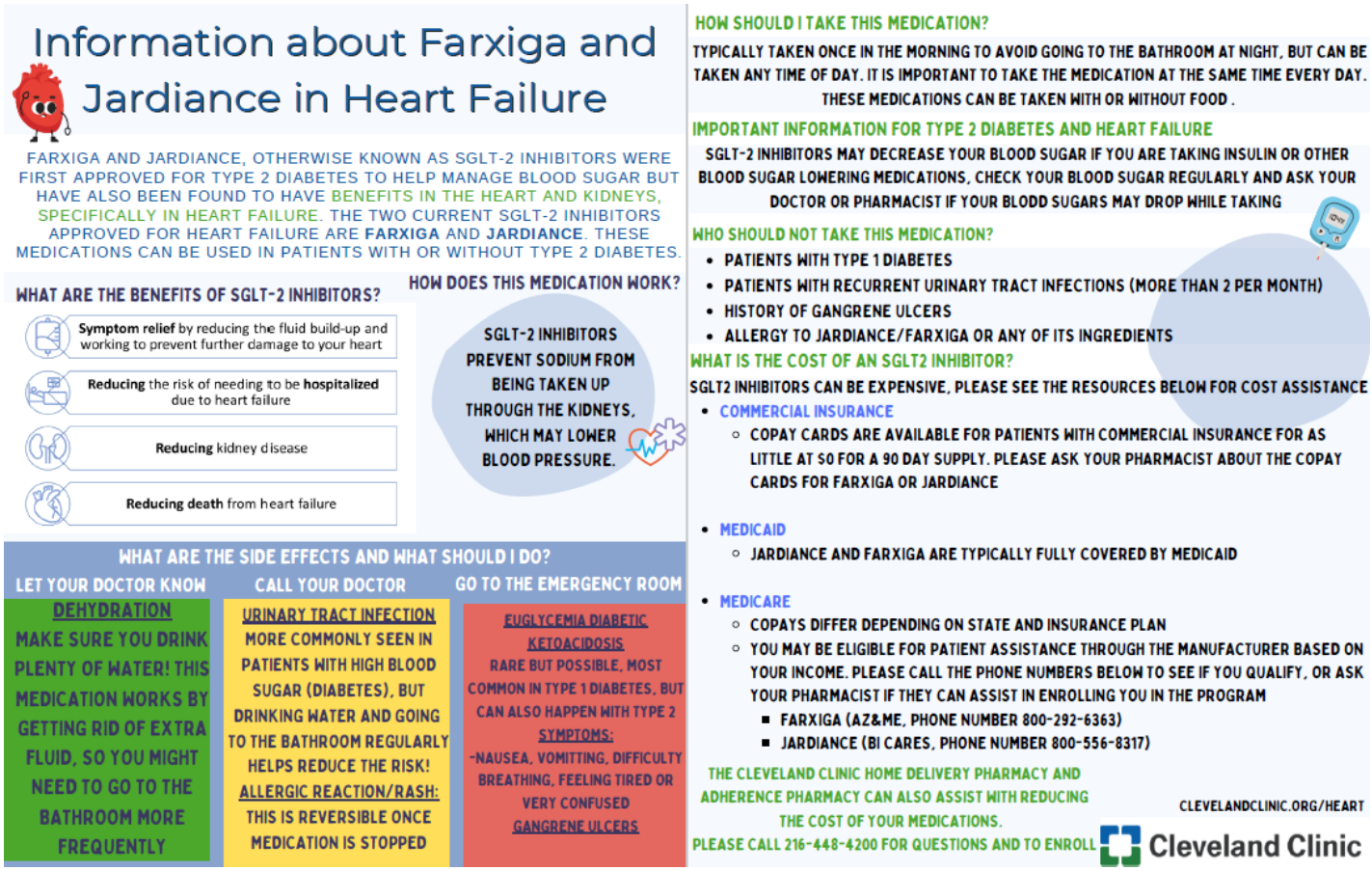

Figure 2: Educational Outreach Embedded In Direct Patient Messaging to Facilitate Uptake of SGLT2 Inhibitors in the Outpatient Setting.

Disclosures

Dr. Bhatt has received research grant support to his institution from National Institutes of Health/National Heart, Lung, and Blood Institute, National Institutes of Health/National Institute on Aging, American College of Cardiology Foundation, and the Centers for Disease Control and Prevention and consulting fees from Heart Health Leaders, Sanofi Pasteur, Merck, Amgen, AstraZeneca, and Novo Nordisk. Dr. Martyn serves as an advisor or receives consulting fees from, Fire1, Prolaio, Boehringer Ingelheim/Eli Lilly, Dyania Health, Novo Nordisk, AstraZeneca, Cleveland Clinic/American Well Joint Venture, BridgeBio, Pfizer, Apricity Robotics, and Kilele health and receives grant support from Ionis Therapeutics, AstraZeneca and the Heart Failure Society of America (HFSA). All other authors report no relevant disclosures.

References

1. Zinman B, Wanner C, Lachin JM, et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *Diabetes Res Clin Pract*. [crossref].
2. Fitchett D, Zinman B, Wanner C, et al. (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *Eur Heart J*. [crossref].
3. Wanner C, Inzucchi SE, Lachin JM, et al. (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. *Diabetes Res Clin Pract*. [crossref].
4. Neal B, Perkovic V, Mahaffey KW, et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *Diabetes Res Clin Pract*. [crossref].
5. Rådholm K, Figtree G, Perkovic V, et al. (2018) Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS program. *Circulation*. [crossref].
6. Wiviott SD, Raz I, Bonaca MP, et al. (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *Diabetes Res Clin Pract*. [crossref].
7. Perkovic V, Jardine MJ, Neal B, et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *Diabetes Res Clin Pract*. [crossref].
8. Bhatt DL, Szarek M, Steg PG, et al. (2021) Sotagliflozin in patients with diabetes and recent worsening heart failure. *Diabetes Res Clin Pract*. [crossref].
9. Lopaschuk GD, Verma S (2020) Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *Diabetes Res Clin Pract*. [crossref].
10. Bailey CJ, Day C, Bellary S (2022) Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. *Curr Diabetes Rep*. [crossref].
11. McMurray JJV, Solomon SD, Inzucchi SE, et al. (2019) Dapagliflozin in patients with heart failure and reduced ejection fraction. *Diabetes Res Clin Pract*. [crossref].
12. Packer M, Anker SD, Butler J, et al. (2020) Cardiovascular and renal outcomes with empagliflozin in heart failure. *Diabetes Res Clin Pract*. [crossref].
13. Bozkurt B, Ahmad T, Alexander K, et al. (2025) HF STATS 2024: heart failure epidemiology and outcomes statistics an updated 2024 report from the heart failure society of America. *J Card Fail*. [crossref].
14. Anker SD, Butler J, Filippatos G, et al. (2021) Empagliflozin in heart failure with a preserved ejection fraction. *Diabetes Res Clin Pract*. [crossref].
15. Solomon SD, McMurray JJ, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *Diabetes Res Clin Pract*. 2022 [crossref].
16. Spertus JA, Birmingham MC, Nassif M, et al. (2022) The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med*. [crossref].
17. U.S. Food and Drug Administration. Sotagliflozin (Inpefa®) prescribing information. 2023
18. U.S. Food and Drug Administration. Empagliflozin (Jardiance®) prescribing information. 2023
19. U.S. Food and Drug Administration. Dapagliflozin (Farxiga®) prescribing information. 2023
20. Heerspink HJ, Stefánsson BV, Correa-Rotter R, et al. (2020) Dapagliflozin in patients with chronic kidney disease. *Diabetes Res Clin Pract*. [crossref].
21. Group E-KC (2023) Empagliflozin in patients with chronic kidney disease. *Diabetes Res Clin Pract*. [crossref].
22. Heidenreich PA, Bozkurt B, Aguilar D, et al. (2022) 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. *J Am Coll Cardiol*. [crossref].
23. Stevens PE, Ahmed SB, Carrero JJ, et al. (2024) KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. [crossref].
24. Committee ADAPP (2023) Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. *Diabetes Care*. [crossref].
25. Arnold SV, Kosiborod M, Wang J, et al. (2018) Burden of cardio-renal-metabolic conditions in adults with type 2 diabetes within the diabetes collaborative registry. *Diabetes Obes Metab*. [crossref].
26. Rossing P, Caramori ML, Chan JCN, et al. (2022) Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int*. [crossref].
27. Neuen BL, Oshima M, Agarwal R, et al. (2022) Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of randomized controlled trials. *Circulation*. [crossref].
28. Agarwal R, Joseph A, Anker SD, et al. (2022) Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol*. [crossref].
29. Butler J, Jones WS, Udell JA, et al. (2024) Empagliflozin after Acute Myocardial Infarction. *N Engl J Med*. [crossref].
30. Hernandez AF, Udell JA, Jones WS, et al. (2024) Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction. *Circulation*. [crossref].
31. Petrie MC, Udell JA, Anker SD, et al. (2024) Empagliflozin in acute myocardial infarction in patients with and without type 2 diabetes. *Eur J Heart Fail*. [crossref].
32. Marilly E, Cottin J, Cabrera N, et al. (2022) SGLT2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. *Diabetologia*.
33. Halimi S, Verges B (2014) Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab*. [crossref].
34. Stollberger C, Finsterer J, Schneider B (2023) Adverse events and drug-drug interactions of SGLT2 inhibitors in heart failure. *Expert Rev Cardiovasc Ther*.
35. Talha KM, Butler J, Greene SJ, et al. (2023) Population-level implications of SGLT2 inhibitors. *JAMA Cardiol*.
36. Ahmad T, Desai NR (2022) Reimagining evidence generation for heart failure. *Circ Cardiovasc Qual Outcomes*.
37. Bhatt AS, Varshney AS, Moscone A, et al. (2023) Virtual care team guided management. *J Am Coll Cardiol*.
38. Ghazi L, Yamamoto Y, Riello RJ, et al. (2022) Electronic alerts to improve therapy. *J Am Coll Cardiol*.
39. Blood AJ, Chang L-S, Hassan S, et al. (2024) Remote management program. *Circulation*.
40. Epping-Jordan J, Pruitt S, Bengoa R, et al. (2004) Improving quality of care. *BMJ Qual Saf*.
41. Desai AS, Maclean T, Blood AJ, et al. (2020) Remote optimization of therapy. *JAMA Cardiol*.

Citation:

West L, Chapman B, Patolia H, Stulock R, Carroll R, et al. (2025), Beyond Diabetes Care, Sodium-Glucose Co-transporter-2 (SGLT2) Inhibitors in Cardiovascular and Renal Health: Evidence and Implementation. *Endocrinol Diabetes Metab J* Volume 9(2): 1-7.