Implementing the 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure

SGLT2 Inhibitors, Treatment Sequencing, and Value Statements
A BREAKTHROUGH FOR YOUR ADULT POPULATION WITH HFpEF

JARDIANCE is indicated to reduce the risk of CV death and hHF in adults with HF.

Not recommended in patients with T1D or for use to improve glycemic control in adults with T2D with eGFR <30 mL/min/1.73 m².

INDICATION AND LIMITATIONS OF USE

JARDIANCE is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.

JARDIANCE is not recommended in patients with type 1 diabetes mellitus. It may increase their risk of diabetic ketoacidosis.

JARDIANCE is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR <30 mL/min/1.73 m². JARDIANCE is likely to be ineffective in this setting based upon its mechanism of action.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: Hypersensitivity to empagliflozin or any of the excipients in JARDIANCE, reactions such as angioedema have occurred; patients on dialysis.
**JARDIANCE IS INDICATED in HFrEF and HFpEF**

**PROVEN SAFETY PROFILE**
Established across multiple trials and indications²

**SIMPLE TO START**
JARDIANCE has market-leading access†
No titration—target dose from day 1

**SUPPORTED BY GUIDELINES**
JARDIANCE,* as an SGLT2i, is recommended as part of the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure for adult patients with HF, regardless of LVEF³

**STRONG EFFICACY DATA**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RRR</th>
<th>ARR</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF‡</td>
<td>21%</td>
<td>3.3%</td>
<td>&lt;0.001</td>
<td>0.79 (0.69-0.90)⁴</td>
</tr>
<tr>
<td>HFrEF§</td>
<td>25%</td>
<td>5.3%</td>
<td>&lt;0.001</td>
<td>0.75 (0.65-0.86)⁵</td>
</tr>
</tbody>
</table>

*The SGLT2i class has gained a 1A recommendation for HFrEF and a 2a-B-R recommendation for HFmrEF and HFpEF.

**WARNINGS AND PRECAUTIONS**

**Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. Patients who present with signs and symptoms of metabolic acidosis should be assessed for ketoacidosis, even if blood glucose levels are less than 250 mg/dL. If suspected, discontinue JARDIANCE, evaluate, and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing JARDIANCE for at least 3 days prior to surgery.

**Volume Depletion:** Empagliflozin can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT2 inhibitors, including empagliflozin. Before initiating, assess volume status and renal function in patients with impaired renal function (eGFR <60 mL/min/1.73 m²), elderly patients or patients on loop diuretics. In patients with volume depletion, correct this condition. After initiating, monitor for signs and symptoms of volume depletion and renal function.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for JARDIANCE on adjacent pages.

Learn more at Jardiancehcp.com
IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Urosepsis and Pyelonephritis: Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been identified in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate for signs and symptoms of urinary tract infections and treat promptly.

Hypoglycemia: The use of Jardiance® (empagliflozin) tablets in combination with insulin or insulin secretagogues can increase the risk of hypoglycemia. A lower dose of insulin or the insulin secretagogue may be required.

Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene): Serious, life-threatening cases requiring urgent surgical intervention have occurred in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue JARDIANCE.

Genital Mycotic Infections: Empagliflozin increases the risk for genital mycotic infections, especially in patients with prior infections. Monitor and treat as appropriate.

Hypersensitivity Reactions: Serious hypersensitivity reactions have occurred with JARDIANCE (angioedema). If hypersensitivity reactions occur, discontinue JARDIANCE, treat promptly, and monitor until signs and symptoms resolve.

MOST COMMON ADVERSE REACTIONS (≥5%):
Urinary tract infections and female genital mycotic infections.

DRUG INTERACTIONS: Coadministration with diuretics may enhance the potential for volume depletion. Monitor for signs and symptoms.

USE IN SPECIAL POPULATIONS

Pregnancy: JARDIANCE is not recommended during the second and third trimesters.

Lactation: JARDIANCE is not recommended while breastfeeding.

Geriatric Use: JARDIANCE is expected to have diminished glycemic efficacy in elderly patients with renal impairment. Renal function should be assessed more frequently in elderly patients. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in T2D patients ≥75 years treated with empagliflozin.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information for JARDIANCE on adjacent pages.

ACCI=American College of Cardiology; ACEIs=angiotensin-converting enzyme inhibitors; AHA=American Heart Association; ARBs=angiotensin II receptor blockers; ARNs=angiotensin receptor-neprilysin inhibitors; ARR=absolute risk reduction; CI=confidence interval; CV=cardiovascular; HF=heart failure; HfPEF=heart failure with preserved ejection fraction; HfPEF=heart failure with reduced ejection fraction; HFSA=Heart Failure Society of America; hHF=hospitalization for heart failure; HR=hazard ratio; LVEF=left ventricular ejection fraction; MRAs=mineralocorticoid receptor antagonists; RRR=relative risk reduction; SGLT2i=sodium-glucose cotransporter-2 inhibitor.


1Based on Fingertip Formulary and/or data on file, Boehringer Ingelheim Pharmaceuticals, Inc. as of 3/20/2022.

A randomized, double-blind, placebo-controlled study examined the efficacy and safety of JARDIANCE 10 mg (n=2997) plus heart failure usual treatments (including ACEIs/ ARBs, ARNs, MRAs, beta blockers, and diuretics) vs placebo added to heart failure usual treatments (n=2991). The trial included 5988 patients who had chronic heart failure (New York Heart Association functional class II-IV) with preserved ejection fraction and a left ventricular ejection fraction of more than 40%. The median duration of follow-up was 26 months. The primary composite endpoint was time to first event of cardiovascular death or hospitalization. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(13):1413-1424.

A randomized, double-blind, placebo-controlled trial examined the efficacy and safety of JARDIANCE 10 mg (n=1863) plus heart failure standard-of-care treatments (including ACEIs/ ARBs, ARNs, MRAs, beta blockers, and diuretics) vs placebo added to heart failure standard-of-care treatments (n=1867). The trial included 3730 patients who had chronic heart failure (New York Heart Association functional class II-IV) with reduced ejection fraction and a left ventricular ejection fraction of 40% or less. The median duration of follow-up was 16 months. The primary composite endpoint was time to first occurrence of cardiovascular death or hospitalization. Kohler S, Zeller C, Illiev H, et al. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-II clinical trials. Adv Ther. 2017;34(7):1707-1726.

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ADVERSE REACTIONS: The following important adverse reactions are described below and elsewhere in the labeling: Ketoacidosis [see Warnings and Precautions]; Volume Depletion [see Warnings and Precautions]; Urinary tract infections [see Warnings and Precautions]; Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see Warnings and Precautions]; Necrotizing Fasciitis of the Perineum (Fourier’s Gangrene) [see Warnings and Precautions]; Genital Mycotic Infections [see Warnings and Precautions]; Hypersensitivity Reactions [see Warnings and Precautions]. Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JARDIANCE has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overall safety profile of JARDIANCE was generally consistent across the studied indications. Clinical Trials in Patients with Type 2 Diabetes Mellitus: The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin in patients with type 2 diabetes. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials [see Clinical Studies]. These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes for more than 5 years and had a mean hemoglobin A1C (HbA1C) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), and neuropathy (10%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 ml/min/1.73 m²). Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline and occurred more commonly in patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg than in patients treated with placebo.

Table 1: Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (%)</th>
<th>JARDIANCE 10 mg (%)</th>
<th>JARDIANCE 25 mg (%)</th>
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<tbody>
<tr>
<td>Urinary tract infection</td>
<td>7.6</td>
<td>9.3</td>
<td>7.6</td>
</tr>
<tr>
<td>Female genital mycotic infections</td>
<td>4.5</td>
<td>5.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.8</td>
<td>3.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Increased urination</td>
<td>1.7</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Dysuria</td>
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<td>3.9</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Male genital mycotic infections</td>
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<td>1.6</td>
</tr>
<tr>
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<td>0.4</td>
<td>0.3</td>
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*Premediated adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genitai candidiasis, genitai infection fungal, genitai trunct infection, vulvovaginitis, cervicitis, uterine infection fungal, vaginitis 8.5%, or Neutropenia (10%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 ml/min/1.73 m²). Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline and occurred more commonly in patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg than in patients treated with placebo.

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<td>0.3</td>
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</tbody>
</table>
Baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in hemocrit: In a pool of four placebo-controlled studies, median hemocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hemocrit clinically had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Postmarketing Experience: Additional adverse reactions have been identified during postapproval use of JARDIANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Gastrointestinal Disorders: Constipation; Infections; Necrotizing fasciitis of the perineum (Fourier’s gangrene), unspec and pylephlebitis; Metabolism and Nutrition Disorders: Ketoacidosis; Renal and Urinary Disorders: Acute kidney injury; Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria).

### DRUG INTERACTIONS:

#### Table 3: Clinically Relevant Interactions with JARDIANCE

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Clinical Impact</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.</td>
<td>Before initiating JARDIANCE, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.</td>
</tr>
<tr>
<td>Insulin or Sulfonyluregates</td>
<td>The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin</td>
<td>Coadministration of JARDIANCE with an insulin secretagogue (e.g., sulfonylureas) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.</td>
</tr>
<tr>
<td>Positive Urine Glucose Test</td>
<td>SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.</td>
<td>Monitoring glycomic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycomic control.</td>
</tr>
<tr>
<td>Interference with 1,5-anhydroglucitol (1,5-AG) Assay</td>
<td>Measurements of 1.5-AG are unreliable in assessing glycomic control in patients taking SGLT2 inhibitors.</td>
<td>Monitoring glycomic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycomic control.</td>
</tr>
</tbody>
</table>

### USE IN SPECIFIC POPULATIONS: Pregnancy

**Risk Summary:** Based on animal data showing adverse renal effects, JARDIANCE is not recommended during the second and third trimesters of pregnancy. The limited available data with JARDIANCE in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to maternal hyperglycemia and fetal and neonatal harm for poorly controlled diabetes in pregnancy (see Clinical Considerations). In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible (see Data). The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively (Clinical Considerations). Disease-associated maternal mortality and/or embryo death risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. Data: Animal Data: Empagliflozin administered directly to juvenile rats from postnatal day (PND) 2 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, while a dose of 30 mg/kg/day resulted in increased kidney weights at 30 and 100 mg/kg/day. Clinical Considerations: Disease-associated maternal and/or embryo death risk:

#### Table 2: Incidence of Overall and Severe Hypoglycemic Events in Placebo-Controlled Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy (24 weeks)</th>
<th>JARDIANCE 10 mg (n=226)</th>
<th>JARDIANCE 25 mg (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation and Related Events</td>
<td>Overall (%)</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Severe (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Study                                      | In Combination with Metformin (24 weeks) | JARDIANCE 10 mg + Metformin (n=266) | JARDIANCE 25 mg + Metformin (n=217) |
| Discontinuation and Related Events         | Overall (%)            | 0.5                     | 1.8                     | 1.4                     |
|                                             | Severe (%)             | 0                       | 0                       | 0                       |

Genital Mycotic Infections: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). Urinary Tract Infections: In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively (see Use in Specific Populations: Diabetics). Clinical Trials in Patients with Heart Failure: The EMPEROR-Preserved study included 3,570 patients with New York Heart Association class II-IV heart failure and left ventricular ejection fraction (LVEF) ≤40% followed for a median of 16 months, and EMPEROR-Preserved included 5,988 patients with heart failure and LVEF >40% followed for a median of 26 months. In both studies, patients were randomized to JARDIANCE 10 mg or placebo. The safety profile in patients with heart failure was generally consistent with that observed in patients with type 2 diabetes mellitus. Laboratory Tests: Increases in Serum Creatinine and Decreases in eGFR: Initiation of JARDIANCE causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy as patients these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m², respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with JARDIANCE. Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. The mean values were 90.3 to 90.6 mg/dL across treatment groups.
Lactation: maximum clinical dose). Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 154-times the 25 mg maximum clinical dose. In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose). Lactation: Risk Summary: There is limited information regarding the presence of JARDIANCE in human milk, the effects of JARDIANCE on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats [see Data]. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of JARDIANCE is not recommended while breastfeeding. Data: Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.63 to 0.8, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilations) during maturation. Pediatric Use: The safety and effectiveness of JARDIANCE have not been established in pediatric patients. Geriatric Use: In glycemic control studies in patients with type 2 diabetes mellitus, a total of 2721 (32%) patients treated with JARDIANCE were 65 years of age and older, and 491 (6%) were 75 years of age and older. EMPeror-Preserved included 2402 (80%) patients treated with JARDIANCE 25 mg, respectively [see Warnings and Precautions and Adverse Reactions]. In heart failure studies, EMPEROR-Reduced included 1188 (64%) patients treated with JARDIANCE 65 mg of age and older, and 503 (27%) patients 75 years of age and older. EMPeror-Preserved included 2402 (80%) patients treated with JARDIANCE 65 years of age and older, and 1281 (43%) patients 75 years of age and older. Safety and efficacy were similar for patients 65 years and younger and those older than 65 years. Renal Impairment: The efficacy and safety of JARDIANCE for glycemic control were evaluated in a study of patients with type 2 diabetes mellitus with mild and moderate renal impairment (eGFR 30 to less than 90 mL/min/1.73 m²) [see Clinical Studies]. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m², 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m², and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m². The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function [see Warnings and Precautions]. Use of JARDIANCE for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m². In a large cardiovascular outcomes study of patients with type 2 diabetes and established cardiovascular disease, there were 1819 patients with eGFR below 60 mL/min/1.73 m². The cardiovascular death findings in this subgroup were consistent with the overall findings [see Clinical Studies]. Studies of patients with heart failure [see Clinical Studies] enrolled patients with eGFR equal to or above 20 mL/min/1.73 m². No dose adjustment is recommended for these patients. There are insufficient data to support a dosing recommendation in patients with eGFR below 20 mL/min/1.73 m². Efficacy and safety studies with JARDIANCE did not enroll patients with an eGFR less than 20 mL/min/1.73 m². JARDIANCE is contraindicated in patients on dialysis [see Contraindications]. Hepatic Impairment: JARDIANCE may be used in patients with hepatic impairment [see Clinical Pharmacology]. OVERDOSAGE: In the event of an overdose with JARDIANCE, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied. Additional information can be found at www.jardiancehcp.com.
IMPLEMENTING THE 2022 HEART FAILURE GUIDELINE

Key Takeaways from the 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure

THE AMERICAN COLLEGE OF CARDIOLOGY (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) jointly published an updated clinical practice guideline for the management of heart failure (HF) in April 2022. This guideline consolidates and replaces the 2013 American College of Cardiology Foundation (ACCF)/AHA guideline for HF management and its subsequent 2017 focused update, which was developed by the ACC/AHA/HFSA. As it emphasizes both the importance of applying clinical judgement and a shared decision-making approach, the 2022 guideline outlines management recommendations based upon up-to-date evidence.

Focusing on HF prevention, management strategies, and implantable devices, the guideline addresses new recommendations for treatments (eg, for sodium-glucose cotransporter-2 [SGLT2] inhibitors, angiotensin receptor-neprilysin inhibitors [ARNIs]), atrial fibrillation (AF) management, management strategies specific to cardiac amyloidosis and cardio-oncology, and the use of left ventricular (LV) assist devices.

This article reviews key takeaways from the 2022 guideline and summarizes the guideline’s recommendations for SGLT2 inhibitor therapy.

Stages of HF Redefined

The 2022 HF guideline emphasizes the need for primary prevention, which may help mitigate the health and economic burden associated with HF; which is projected to spread to 2.97% of the US population by 2030. To address this need, guideline authors revised the stages of HF to emphasize those who are at risk, and highlighted the evolving role that structural cardiac changes and biomarkers play in identifying at-risk patients. These patients are potential candidates for preventive targeted treatment strategies.

The guideline describes persons with stage A disease as being “at risk for HF;” they lack HF symptoms, structural and/or functional heart disease, or abnormal cardiac biomarkers. Patients given a diagnosis of stage A HF may have such comorbidities as hypertension, cardiovascular disease (CVD), obesity, or diabetes; exposure to cardiotoxic agents; a genetic variant for cardiomyopathy; or a family history of cardiomyopathy. Stage B disease is described as “pre-HF;” although patients may not have symptoms or signs of the disease, they display evidence of 1 of the following: structural heart disease, increased filling pressures, or risk factors plus increased natriuretic peptide levels or persistently elevated cardiac troponin levels in the absence of competing diagnoses that could result in abnormal biomarkers. Stage C HF corresponds to symptomatic HF; this describes patients with structural heart disease and current or previous HF symptoms. Finally, stage D disease represents advanced HF; this includes individuals who have HF symptoms that interfere with their daily lives and who are admitted to the hospital recurrently despite attempts to optimize their guideline-directed medical therapy (GDMT).

Revised HF Classification

The classification of HF by LV ejection fraction (LVEF) has been modified. The guideline now defines HF with reduced ejection fraction (HFrEF) as involving an...
LVEF less than or equal to 40%. Patients who previously were in the HFrEF category and who have a follow-up measurement of LVEF greater than 40% are described as having HF with improved EF (HFimpEF). The use of the term “improved LVEF” for these patients is new in the 2022 guideline; the 2013 ACCF/AHA guideline had categorized these patients as having “HF with preserved EF-improved.” Authors of the updated guideline emphasized that this patient subgroup is more appropriately characterized by HFimpEF, since improvement in LVEF does not necessarily represent full myocardial recovery or normalization of LV function.\(^1\) The authors underscored the need for these patients to continue treatment—many patients with improvement in LVEF and biomarkers and resolution of symptoms relapse after 6 months following withdrawal of GDMT.\(^1,5\)

Patients with an LVEF of between 41% and 49% and evidence of increased LV filling pressures (either spontaneous or provokable) are described as having HF with mildly reduced EF (HFmrEF). HF with preserved EF (HFpEF), the final category, describes patients with an LVEF greater than or equal to 50% and evidence of spontaneous or provokable increased LV filling pressures. According to the guideline authors, establishing the diagnosis of HFmrEF and HFpEF can be challenging, because HF signs and symptoms often are nonspecific, and they can overlap with other conditions. Additionally, whereas elevated natriuretic peptide levels support the diagnosis, the presence of normal values do not exclude it. To address these challenges and improve diagnostic specificity, the guideline authors added the need to obtain evidence of increased filling pressures for the diagnosis of HF in the setting of LVEF greater than 40%. As described in the guideline, natriuretic peptide levels, echocardiographic diastolic parameters, or results from invasive hemodynamic measurement at rest or exercise can be used to fulfill the diagnostic criteria.\(^1\)

Additional Key Updates
The 2022 HF guideline authors modified treatment recommendations across the spectrum of HF; and the addition of SGLT2 inhibitors is a key update. The SGLT2 inhibitors are now part of the 4 medication classes recommended as GDMT for HFpEF; the others are β-blockers, mineralocorticoid receptor antagonists (MRAs), and renin-angiotensin system inhibitors that include ARNIs, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs). For the treatment of HFmrEF, SGLT2 inhibitors have a class 2a recommendation; the weaker class 2b recommendation is given to ARNIs, ACEIs, ARBs, MRAs, and β-blockers in this setting. New recommendations for the treatment of HFpEF include the use of SGLT2 inhibitors (class 2a recommendation) or MRAs or ARNIs (class 2b recommendation for both). Several prior recommendations for HFpEF have been renewed, including those for the treatment of hypertension and AF and the use of ARBs.\(^1\)

Other key updates include the addition of value statements, recommendations for amyloid heart disease, and the need for referral to HF specialty teams. Recognizing the importance of cost-value considerations, the authors developed and added value statements for select guideline recommendations related to published, high-quality cost-effectiveness studies. Among new recommendations for the treatment of amyloid heart disease are a diagnostic and therapeutic approach for cardiac amyloidosis that includes screening for monoclonal light chains and use of bone scintigraphy, genetic sequencing, anticoagulation therapy, and tetramer stabilizer therapy. Finally, guideline authors emphasized the importance of referring patients with advanced HF who wish to prolong survival to a HF specialty team, who would review the management of HF and assess patient suitability for advanced HF therapies. Additionally, the specialty team would use palliative care interventions including palliative inotropes according to the goals of the patient.\(^1\)

The New Role of SGLT2 Inhibitors Across the HF Spectrum
After initially demonstrating an improved rate of HF hospitalizations among patients with type 2 diabetes (T2D) who were at risk for HF; data on SGLT2 inhibitors also revealed benefits in patients with HF, irrespective of the presence of T2D.\(^6-10\) The updated HF guideline incorporates accumulating evidence on the beneficial CV effects of SGLT2 inhibitors.\(^1\) These agents are now recommended across the spectrum of HF (Table).\(^1\)

The Role of SGLT2 Inhibitors in Patients at Risk for HF
In patients with T2D who have or are at high risk for CVD, SGLT2 inhibitors have a class 1 recommendation to prevent HF-related hospitalizations.\(^1\) Such patients are at risk for HF (stage A). The recommendation is based on results from the randomized CANVAS program, DECLARE-TIMI 58, and EMPA-REG OUTCOME clinical trials, which examined the impact of SGLT2 inhibitor therapy on HF-related hospitalizations in this patient population.\(^1,4-8\)

The CANVAS program evaluated the impact of canagliflozin on CV, renal, and safety outcomes.\(^6\) This program consisted of 2 trials with identical inclusion criteria and enrolled patients with T2D who either were aged 30 years or older and had a history of symptomatic CVD or were aged 50 years or older and had 2 or more specific risk factors for CVD. After a mean follow-up of 188.2 weeks, treatment with canagliflozin was associated with a significantly reduced rate of hospitalization for HF.
The 2022 HF guideline notes that HF was present at baseline in approximately only 10% to 14% of participants in these trials.1,6-8 Thus, prevention of primary HF symptoms accounted for most of the reduction of HF-related hospitalizations following SGLT2 inhibitor therapy.1 The recommendation for the use of SGLT2 inhibitors in patients at risk for HF due to T2D and established or high risk of CVD also applies to patients with pre-HF, as management strategies instituted in stage A should be continued through stage B (pre-HF).

**SGLT2 Inhibitors in HFrEF**

SGLT2 inhibitors carry a class 1 recommendation for reducing HF hospitalization and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2D.1 Prior data suggested that use of SGLT2 inhibitors offered these benefits in patients without T2D.11 Results of the DEFINE-HF trial found that a greater proportion of patients with symptomatic HFrEF who were treated with dapagliflozin experienced clinically meaningful improvements in HF-related symptoms, functional status, and quality of life than did those given placebo. The observed benefits were consistent, regardless of T2D.

The new guideline recommendation is based on results of the DAPA-HF and EMPEROR-Reduced trials, which evaluated the efficacy of SGLT2 inhibitors (dapagliflozin and empagliflozin, respectively) in patients with symptomatic HFrEF irrespective of the presence of T2D.1,9,10 In the DAPA-HF trial, the primary composite outcome of worsening HF or CV death was 26% lower in patients treated with dapagliflozin compared with those treated with placebo (HR, 0.74; 95% CI, 0.65-0.85; P < .001), and consistent benefits were observed in patients without diabetes.9 In the EMPEROR-Reduced trial, empagliflozin therapy was associated with a 25% reduction in the primary composite outcome of CV death or HF hospitalization compared with placebo (HR, 0.75; 95% CI, 0.65-0.86; P < .001), with a consistent effect observed in patients with and without diabetes.10 The results of a meta-analysis of both trials found that SGLT2 inhibitor therapy was associated with a 13% reduction in all-cause mortality, a 14% reduction in CV death, and a 31% reduction in the risk of first HF hospitalization compared with use of placebo.12 Additionally, treatment with an SGLT2 inhibitor was associated with a significantly reduced risk of a composite renal end point (50% or higher sustained declines in estimated glomerular filtration rate, end-stage renal disease, or renal death) compared with placebo.

**Value Statement: SGLT2 Inhibitors in HFrEF**

A key addition to the updated guideline is the incorporation of value statements for select recommendations.1 The guideline includes a value statement for its class 1a recommendation for the use of SGLT2 inhibitors in patients with symptomatic chronic HFrEF that is based upon the results of 2 model-based economic evaluations of the use of dapagliflozin.1,13,14 Recognizing the wide range of costs currently associated with dapagliflozin, guideline authors indicate that treatment with SGLT2 inhibitors in this patient population provides “intermediate economic value.”1

**Incorporating SGLT2 Inhibitors as Part of GDMT in HFrEF**

The guideline authors emphasize the need to initiate GDMT for HFrEF at low-starting doses and to titrate up at specified intervals to achieve and maintain clinical trial–defined target doses, as tolerated by the patient.1 Initiation

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**TABLE. Recommendations for Use of SGLT2 inhibitors in HF**

<table>
<thead>
<tr>
<th>Stage of HF</th>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A, at risk for HF</td>
<td>To prevent HF hospitalization in patients with T2D who have CVD or are at high risk for CVD</td>
<td>1</td>
</tr>
<tr>
<td>Stage C, symptomatic HF</td>
<td>To reduce HF hospitalization and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2D</td>
<td>1</td>
</tr>
<tr>
<td>HFrEF</td>
<td>To reduce HF hospitalizations and CV mortality in patients with HFrEF</td>
<td>2a</td>
</tr>
<tr>
<td>HFrEF</td>
<td>To reduce HF hospitalizations and CV mortality in patients with HFrEF</td>
<td>2a</td>
</tr>
</tbody>
</table>

COR, class of recommendation; CVD, cardiovascular disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.
and titration of GDMT should be individualized and optimized as frequently as every 1 to 2 weeks based on patient-specific factors (eg, symptoms, vital signs, laboratory findings). For patients with HFrEF, decisions regarding simultaneous initiation or sequencing of GDMT usually are individualized, and they do not necessarily need to follow the sequence of trial publications. Based on a decision analytical model evaluating the impact of adding SGLT2 inhibitor therapy to GDMT, implementing quadruple therapy (ARNI, β-blocker, aldosterone antagonist, and SGLT2 inhibitor therapy) would, at the population level in patients with HFrEF eligible for SGLT2 inhibitor treatment, lead to an estimated relative risk reduction in all-cause mortality of 73%.15

SGLT2 Inhibitors in HfPef and HfMref

The guideline also includes a recommendation to use SGLT2 inhibitors in patients with HfPef or HfMref.1 In patients with HfPef, SGLT2 inhibitors carry a class 2a recommendation as a potentially beneficial treatment for reducing HF hospitalizations and CV mortality. This recommendation is based on results of the EMPEROR-Preserved trial, which evaluated empagliflozin in patients with chronic symptomatic HF, a LVEF greater than 40%, and elevated N-terminal pro-B-type natriuretic peptide levels.16 After a median follow-up of 26.2 months, treatment with empagliflozin was associated with a 21% lower risk of the primary composite outcome of HF hospitalization or CV death when compared with treatment with placebo (HR, 0.79; 95% CI, 0.69-0.90; P < .001). Study investigators stated that this benefit was mostly driven by a 29% reduction in HF hospitalization with empagliflozin treatment. Of note, these outcomes associated with empagliflozin therapy were similar, regardless of the presence of diabetes.

The guideline gives SGLT2 inhibitors a class 2a recommendation for the treatment of patients with HfMref, noting that use of these agents can be beneficial in reducing HF hospitalizations and CV mortality in this setting.2 The recommendation is based on data from the subgroup of patients enrolled in the EMPEROR-Preserved trial who had an LVEF of 40% to 50% at baseline.16 In this patient subgroup, empagliflozin therapy was associated with a reduced risk of the primary composite outcome of CV death or HF hospitalization by 29% compared with treatment with placebo (HR, 0.71; 95% CI, 0.57-0.88). The guideline notes the lack of prospective, randomized clinical trials designed specifically for patients within the HFmref category.1 Study results indicate that patients with an LVEF closer to 41% have shown a similar response to medical therapies to that of patients with HfReF. Therefore, as indicated in the guideline, it may be reasonable to treat patients on the lower end of the HFmref spectrum with the GDMT used to treat patients with HfReF.

Future Research Needs

Recommendations provided in the guideline are based on available evidence. However, though data and treatment strategies for patients with HF continue to evolve, significant evidence gaps remain. Providing clinicians with current, evidence-based recommendations would facilitate shared decision-making with patients and optimize outcomes.3 Many patients who would benefit from GDMT for HF remain undertreated in real-world settings.17 According to findings from the CHAMP-HF registry, only 22.1% of patients with HfReF who were eligible for all drug classes were prescribed some dose of an ACEI/ARB/ARNI, a β-blocker, and an MRA simultaneously, and just 1.1% of patients were prescribed target doses of medications in all 3 drug classes simultaneously. Other studies also highlighted the suboptimal implementation of GDMT for HF in routine practice, with many eligible patients failing to receive recommended treatments.18-19

Authors of the guideline call for future research, providing a list of selected issues that should be addressed. For instance, real-world evidence is needed to characterize the generalization of therapies in patient populations that may have been underrepresented in HF trials. Data are also needed on the impact of therapies in patient-reported outcomes and on optimal strategies for sequencing and titration of GDMT.1

The need for additional data on treatment strategies for patients with HfPef or HfMref, including additional efficacy and safety data concerning the use of SGLT2 inhibitor therapies in these populations, is also highlighted by the guideline.3 Recent clinical trial data have provided further understanding about the use of SGLT2 inhibitor therapy in this setting.20

The EMPULSE trial compared the clinical benefit of empagliflozin treatment with placebo among patients hospitalized with acute HF. At baseline, 28.7% of patients in the empagliflozin group and 35.1% of those in the placebo group had an LVEF greater than 40%. The primary outcome was clinical benefit, defined as a hierarchical composite of the time to all-cause death, the number of HF events, the time to first HF event, and a difference of 5 points or greater in the change from baseline on the Kansas City Cardiomyopathy Questionnaire Total Symptom Score. After 90 days, the results favored empagliflozin, with clinical benefit achieved by 53.9% of patients in the empagliflozin group compared with 39.7% of patients in the placebo group (stratified win ratio, 1.36; 95% CI, 1.09-1.68; P = .0054).

The DELIVER trial is evaluating the efficacy and safety of dapagliflozin therapy compared with placebo in patients with HfMref, HfPef, or improved LVEF.21 A total of 6263 patients fulfilled inclusion criteria; they have been...
randomly assigned to dapagliflozin treatment or placebo. The primary end point is CV death or either a hospitalization or an urgent visit for HF.

Trial data will further the understanding of SGLT2 inhibitor use in patients with HF and LVEF greater than 40% and will address some evidence gaps highlighted by the 2022 HF guideline.1,2

REFERENCES
IMPLEMENTING THE 2022 HEART FAILURE GUIDELINE

Insight From the Writing Committee Chair of the 2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure

A Q&A With Paul Heidenreich, MD

**AJMC®**: What stands out in the 2022 American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) Guideline for the Management of Heart Failure (HF) that was recently published?1

**HEIDENREICH**: One thing that the ACC/AHA is now doing with their guidelines, and we included a lot with the HF guideline, are value statements. And so, clinicians will see these value statements in the guideline, where we have taken the published data on cost-effectiveness and made a statement about whether this fits with the ACC/AHA’s definition for what is considered high, medium, or low value based on how much it costs to obtain a given outcome. These value statements are primarily aimed at policymakers, at payers, at industry. Although we think clinicians should also be aware of them, the primary guidance for clinicians is the clinical recommendations; this said, we do want clinicians to be aware that such value estimates have been made for many of the therapies. And, importantly, the vast majority of the HF treatments are of very high economic value. The clinicians can be confident that not only is this improving care, it’s also a wise use of resources.

**AJMC®**: The 2022 AHA/ACC/HFSA guideline consolidates and replaces both the 2013 American College of Cardiology Foundation (ACCF)/AHA guideline for HF management and the 2017 focused update developed by the ACC/AHA/HFSA.2,3 What are the 2 or 3 main advances in the management of HF since 2017 that the 2022 guideline reflects?

**HEIDENREICH**: There were several advances since our past update to the guideline in 2017. Primary among these are those focused around SGLT2 [sodium-glucose cotransporter-2] inhibitors, which were shown clearly to improve outcomes for those with reduced left ventricular ejection fraction (EF). But, also for the first time, SGLT2 inhibitors were shown to improve outcomes for those with preserved EF (EF > 40%). Those were 2 major milestones that are now reflected in the guideline. In addition, although it covers a smaller group, we now have treatment for cardiac amyloidosis with tafamidis that improves survival.

**AJMC®**: The guideline-writing committee proposed a set of terminologies for the stages of HF. Why was an update necessary?

**HEIDENREICH**: The guidelines have historically classified HF into stages A through D. In this guideline, we wanted to emphasize not so much the letter, but what that stood for. Rather than focusing on stage A, we wanted to say that these are patients at risk for HF. This is a group in which we want to prevent HF. Similarly, for stage B—which is patients who have cardiac dysfunction but do not yet have HF—we, again, wanted to emphasize that these are patients with pre-HF, where treatment is available. And then we left the term “HF” in the...
labels for stages C and D, where that term has been used in the past. We didn't get rid of the stages; we just wanted to emphasize and better describe which populations are in those stages.

**AJMC®**: What recommendations does the guideline have for the treatment of patients with HF with preserved ejection fraction (HFrEF)? How do those compare with the recommendations for those given a diagnosis of HF with reduced ejection fraction (HFrEF)?

**HEIDENREICH**: One of the major changes with the guideline is that we now have SGLT2 inhibitors recommended as the preferred drug for patients with an EF greater than 40%. We now split that population into those whose EFs are considered mildly reduced (HFmrEF; 41%-49%) and those whose EFs are considered preserved (HFpEF; ≥ 50%). For groups with HFmrEF or HFpEF, the SGLT2 inhibitors now have a class 2A recommendation. It’s not as strong as a class 1 recommendation, but it’s still strong.

For both HFmrEF and HFpEF, there are weaker recommendations for ACE [angiotensin-converting enzyme] inhibitors, ARNIs [angiotensin receptor-neprilysin inhibitors], angiotensin receptor blockers (ARBs) themselves, and MRAs [mineralocorticoid receptor antagonists]. For HFmrEF; there’s also a weaker recommendation for β-blockers.

The main difference between the recommendations for HFpEF and HFrEF is strength. All of these medications have class 1 recommendations for HFrEF but class 2A (for SGLT2 inhibitors) or class 2B recommendations if your EF is greater than 40%. These medications have demonstrated the most evidence for benefit in patients with HFrEF and are most strongly recommended for this population.

**AJMC®**: The first 3 of the guideline’s "Top 10 Take-Home Messages” address SGLT2 inhibitors. How have SGLT2 inhibitors impacted the management of HF since 2017, and how does the 2022 guideline reflect that impact?

**HEIDENREICH**: The SGLT2 inhibitors have clearly already impacted the management of HF. They are now 1 of 4 pillars of HF care for those with reduced EF; the other 3 being either ARNIs, ACE inhibitors, or ARBs as the second; MRAs as the third; and β-blockers as the fourth pillar. That was standard even before this guideline, that those are now the 4 pillars for treatment of HFrEF. The guideline now clearly states that for the first time in its recommendations.

And, again, SGLT2 inhibitors are probably the go-to medications for those with HFmrEF and HFpEF—if the EF is greater than 40%. As I mentioned previously, that’s reflected with a class 2A recommendation for SGLT2 inhibitors in those populations.

**AJMC®**: What is the evidence base for these recommendations for SGLT2 inhibitors in HFrEF and in HFpEF?

**HEIDENREICH**: We’ve had several trials of SGLT2 inhibitors in patients with HFrEF that were strongly positive. DAPA-HF [NCT03036124] used a combined end point that is traditional for all of these trials now: worsening HF (defined as unplanned hospitalization or intravenous therapy for HF) or CV [cardiovascular] death. In that trial, the SGLT2 inhibitor dapagliflozin demonstrated a strongly significant reduction in that combined primary outcome. Importantly, there was also a reduction in CV death alone and in all-cause mortality.

In the EMPEROR-Reduced trial [NCT03057977], use of the SGLT2 inhibitor empagliflozin was associated with a similar reduction in the primary combined outcome of CV death and hospitalization for HF. It didn’t have as strong of an impact on total mortality, but it was trending in the same direction. In the trial, empagliflozin therapy showed an improvement in kidney function or less decline in kidney function compared with placebo, and this was confirmed in other trials, specifically looking at those with kidney disease.

DAPA-HF and EMPEROR-Reduced were very strong trials. They established SGLT2 inhibitors as a fourth pillar for HFrEF.

For HFpEF, we’ve had multiple attempts at finding a drug to improve outcomes and many failures. It wasn’t until recently, when the EMPEROR-Preserved trial [NCT03057951] was published, that we saw a significant reduction in the combined primary end point of CV death or hospitalization for HF in patients with an EF over 40%. The trial did not show a death benefit associated with using empagliflozin, but, again, the trial was powered to look at that combined primary end point, and there was a clear reduction in CV death or HF hospitalizations. Of note, when investigators looked at the patients’ subgroups by EF, there seemed to be greater benefit as EF decreased.

**AJMC®**: How might the recommendations for SGLT2 inhibitors in HFrEF and HFpEF change treatment sequencing in HF?

**HEIDENREICH**: It is still challenging for the clinician to know exactly how to implement these 4 pillars of therapy for HFrEF. We have not had a large number of trials comparing drug sequencing strategies. Traditionally, the recommendations have been to start with an ARNi and a β-blocker and then to add on an SGLT2 inhibitor and an MRA. Also, the general recommendation is to start with a lower dose and titrate up, although, again, we don’t have a lot of randomized trial data to say that this is the best method.

There is reason to believe that having an SGLT2 inhibitor onboard may make it easier to add on an MRA,
or even an ARNi, because of potentially opposite effects on potassium loss. There are reasons to consider SGLT2s earlier rather than waiting and to definitely not wait for it to be the last of those 4 to start. It also seems to be fairly well tolerated, and, for patients who are hospitalized, it would, again, be reasonable to try to get patients on an SGLT2 inhibitor during hospitalization and not wait until after discharge, since there’s a lot of data to show that busy clinicians often do not change therapy for patients discharged from the hospital. And so, using that time as the opportunity to start an SGLT2 inhibitor is probably important.

“Clinicians will see... value statements in the guideline.... [W]e have taken the published data on cost-effectiveness and made a statement about whether this fits with the ACC/AHA’s definition for what is considered high, medium, or low value.”

—Paul Heidenreich, MD

AJMC®: How might adherence to this new guideline change clinical outcomes in HF? What tips do you have for clinicians as they adopt these new recommendations?

HEIDENREICH: Now, in addition to the device and interventional therapies that we recommend, there are 6 to 7 different pharmacotherapies for HF that have all been shown to reduce mortality. There have been estimates that if a patient were a candidate for all and were treated with all, we might reduce mortality and HF hospitalizations by up to 70% compared with how treatment used to be. If we were able to get all HF patients on the appropriate therapy, we would see a small, but real, improvement in both HF hospitalizations and mortality.

Now, it is a real challenge for clinicians to adopt all of these recommendations. For instance, as I mentioned, deciding on the order in which to implement all 4 pillars of HFrEF is hard. Even if you decided on an order, you would have a large number of interactions with the patient to up-titrate these.

Therefore, it is important to think of novel ways of implementing these recommendations. Some areas, facilities, and practices are now offering clinics designed just to get people on their HF therapy. Once patients are on their HF therapies, they go back to the main clinician. Advanced practice providers can offer these clinics, potentially under a protocol. Some places are experimenting with having pharmacists doing the up-titration. In addition, a health system dashboard that includes each patient with HF; the patient’s recommended therapies, and the patient’s current therapies can help a practice determine which patients should have their treatment adjusted and when. Using some of this technology and taking advantage of our advanced practice providers can help with what has become a very time-consuming, but very important, practice of getting patients on all of these recommended therapies.

AJMC®: Are there other important updates or recommendations in the guideline?

HEIDENREICH: We have a very nice algorithm for different cardiac resynchronization therapy indications for patients with HFrEF. In addition, we have an amyloidosis treatment algorithm that will describe which test to do and when, including when to do gene sequencing, and, of course, when to treat with tafamidis for those with cardiac amyloidosis.

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Rapid Sequencing of the Four Pillars of Heart Failure Treatment

A Q&A With Milton Packer, MD

AJMC®: Could you describe the conventional approach to combining all 4 “pillars” of therapy for heart failure with reduced ejection fraction [HFrEF]?

PACKER: For years, the conventional approach to implementing the 4 foundational drugs for HFrEF was based purely on the historical sequence in which these 4 classes of drugs were developed. Initially, in the early 1980s, ACE [angiotensin-converting enzyme] inhibitors were developed. Other inhibitors in the angiotensin system were developed thereafter. Then β-blockers were developed in the early 1990s, mineralocorticoid receptor antagonists (MRAs) were developed in the late 1990s, and neprilysin inhibitors were developed in about 2014. SGLT2 [sodium-glucose cotransporter-2] inhibitors were developed only in the past 2 or 3 years.

If you let history guide practice, then you start a renin-angiotensin-aldosterone system inhibitor first, titrate up to target dose, start a β-blocker, titrate up to target dose, and then start an MRA and titrate up to target dose. Then you start an SGLT2 inhibitor, which doesn’t require up-titration. If you do that according to a certain deliberate pathway, it takes 6 to 12 months to achieve treatment with the 4 foundational drugs. Six to 12 months! HFrEF progresses in 6 to 12 months. However, there’s a bigger problem: if you tell people this therapy will take 6 to 12 months, a very large proportion of people will not do it at all. Many people with HFrEF are on an ACE inhibitor and a β-blocker and that’s it. They’re not on any of the other foundational drugs. They’re not on MRAs. They’re not on a neprilysin inhibitor. They’re not on an SGLT2 inhibitor. Patients are not only getting delayed therapy; they’re not getting all the therapy they need. The result is that a large part of the benefit—mortality benefit, hospitalization benefit—of these drugs is lost.

The difference between being on an ACE inhibitor and β-blocker and being on all the foundational drugs is an incremental 50% to 60% reduction in the risk of death and the risk of hospitalization. We’re not talking a small, incremental treatment effect. We’re talking about a doubling or more of the benefit of some of the early drugs. If we follow a deliberate slow titration historical approach, we will have a lot of people with HFrEF who will have progression of disease, who will be hospitalized, and who will die. That will happen unnecessarily.

AJMC®: In a recent review article, you and coinvestigator John McMurray, MD, argue that all 4 pillars should be used in the first 4 weeks of treatment.1 What is the rationale for this recommendation?

PACKER: We think physicians should use all the foundational drugs. It’s 4 drugs interfering with 5 pathways. They should do it as rapidly as possible. How rapidly is that? We think that most patients can get to 4 drugs in 4 weeks. It’s a catchy phrase, but it’s a nice way of framing the goal. There are several reasons for this approach.

First, the clinical trial data show that so much of the benefit of these drugs is seen at the initial dose. β-blockers, which really do require up-titration,
are an exception. But for the other classes of drugs, the low starting dose gets you 70%, 80%, or more of the total treatment effect. It is much better to have all the foundational drugs at a starting dose than to have 1 drug at a maximal dose. You’re not covering all the systems you should be covering with 1 drug at a maximal dose. However, you’re covering almost everything you want to cover with low starting doses across the board.

Second, our approach is evidence-based. Most new drugs for HF were developed while patients were on background therapy with other drugs that were at low doses, not at target doses. We know, for example, that β-blockers work, because they were tested in patients getting low doses of an ACE inhibitor, not target doses. We know that spironolactone works in people getting low doses of ACE inhibitors and β-blockers. The same with neprilysin inhibitors and SGLT2 inhibitors. Almost none of the patients in the big major trials were getting target doses of all of the previous drugs before they got the new one. Our proposed framework is exactly the way that the clinical trials were conducted. The patients were already getting low doses, and they did not up titrate the background therapy during the trial. We’re closely mimicking how the trials were conducted.

Third, with this approach, we can determine in a reasonably short period of time whether a patient tolerates these drugs. You can pretty much know if someone tolerates a drug within a week.

AJMC®: In what order should these 4 drugs be introduced into HFrEF therapy?
PACKER: We think that certain drugs can be started on the same day, either because we know that they can be safely initiated at the same time, or because their actions mutually reinforce each other’s safety. For instance, we propose starting a β-blocker and an SGLT2 inhibitor on the same day, because β-blockers cause a little bit of fluid retention, and SGLT2 inhibitors counteract that fluid retention. When you combine the 2, you actually have a combination that is safer than if you had used only 1 drug. There are synergies across these 4 foundational drugs that allow them to be put into combined use much more rapidly.

We proposed a sequence that begins with a β-blocker and SGLT2 inhibitor, adds an angiotensin neprilysin inhibitor, and then adds an MRA. However, a different order would be fine; it really doesn’t matter which 2 to start. At the end of 4 weeks, everyone’s going to be at the same place. The sequence can be tailored to the personal preferences of the physician and the circumstances of the patient. The key is to get all 4 drugs on board in 4 weeks.

AJMC®: In the article, you recommend determining priority of treatment based upon relative efficacy, safety, and ease of use and emphasizes evidence-based treatment. Could you speak to the place of evidence-based medicine in HFrEF therapy?
PACKER: It seems axiomatic that all physicians should practice evidence-based medicine, but there are lots of reasons why they don’t. For one, other types of medicine compete for attention. For instance, there’s so-called “eminence-based medicine,” which is doing what experts say. There’s story-based medicine, which is giving drugs according to an idea of what the drugs are doing to the body rather than to evidence. And then there’s practical medicine: it can be difficult to prescribe certain drugs, because they’re expensive, or because they require authorization forms, or because a patient’s insurance doesn’t cover them.

Certain mistaken beliefs also hinder the practice of evidence-based medicine. For instance, there’s an idea that a patient can look okay and can have “stable HF.” Well, there’s no such thing as “stable HF.” Even if a patient says they feel the same as they did 3 months ago, their condition is not stable. HF inherently progresses, even if it is not noticeable to the patient or if the patient has adapted to that progression.

Finally, physicians have time constraints. Often, their exposure to a patient is less than 15, or even 10, minutes. Patients may have more than just HF. They may have 5, 6, 7 comorbid conditions. They all have to be managed in 10 minutes. All of these factors get in the way of practicing evidence-based medicine.

AJMC®: The aim is to get patients on all 4 of these pharmacotherapies in the first 4 weeks. However, you recommend getting HFrEF patients started on
both a β-blocker and an SGLT2 inhibitor. Why should treatment start there? **PACKER:** John McMurray and I thought that the combination of a β-blocker and an SGLT2 inhibitor was a good starting point for 2 reasons. One, β-blockers have dramatic effects on mortality; we’re talking a 35% reduction in risk of death. They reduce mortality more than any other class of drugs does, and they particularly reduce sudden death. You really want a β-blocker on board for someone with HF as early as possible. The earlier the better. β-blockers may require some up-titration so getting them on board early also gives you some time to then get them up to the right dose.

The biggest disadvantage of β-blockers is that, in some people, they cause fluid retention. So the first reason to add an SGLT2 inhibitor is that SGLT2 inhibitors counteract that fluid retention. The second reason is that SGLT2 inhibitors reduce hospitalization for HF: You can easily combine a β-blocker and an SGLT2 inhibitor. They mutually reinforce each other. They’re both given once daily. You can achieve an enormous amount of what you’re trying to achieve, because the effect size, the magnitude of benefit, is so large, and they reinforce each other’s safety, which is really nice.

**AJMC®:** In 2021, the European Society of Cardiology recommended SGLT2 inhibitors for frontline treatment in HFrEF based upon the EMPEROR-Reduced trials. In their April 2022 guideline, the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) recommended SGLT2 inhibitors to reduce hospitalization for HF and cardiovascular mortality in patients with symptomatic chronic HFrEF, citing the same trials. Can you describe how these trials have influenced the use of SGLT2 inhibitors in HFrEF?

**PACKER:** There have been 2 major trials of SGLT2 inhibitors in patients with HFrEF. The first of these was the DAPA-HF trial with dapagliflozin, and the second was the EMPEROR-Reduced trial with empagliflozin. We’ve been speaking of the 4 drugs in 4 weeks paper that John McMurray and I collaborated on. John McMurray led the DAPA-HF trial, and I led the EMPEROR-Reduced trial. The 2 trials came out with results that were almost superimposable on top of each other. It’s almost as if the numerical result in 1 trial was exactly replicated in the other trial. There were a few differences but amazingly similar results, both in terms of the nature of the benefit and the magnitude of the benefit. The biggest benefit of these drugs is to reduce hospitalizations for HF: It’s about a 35% reduction in risk of hospitalization of HF, which is a sizeable treatment effect. That was the reason that the addition of SGLT2 inhibitors to foundational drugs was supported both in the European guidelines and in the recent guidelines that were issued in the United States.

**AJMC®:** At the AHA Scientific Sessions 2021 in November, results of the EMPULSE trial were published; they demonstrated that SGLT2 inhibitors were beneficial in reducing adverse events among patients hospitalized with acute decompensated HF. How might the results of the EMPULSE trial influence future guidance regarding the use of SGLT2 inhibitors?

**PACKER:** No one was surprised by the results of EMPULSE. In EMPULSE, investigators initiated SGLT2 inhibitors in the hospital. Previously, we had had trials where we initiated ACE inhibitors in the hospital, β-blockers in the hospital, MRAs in the hospital. We knew that SGLT2 inhibitors should be initiated as early as possible.

The results of the EMPULSE trial jibe with our recommendations for rapid sequencing. When we say 4 drugs in 4 weeks, we don’t mean just outpatient 4 drugs in 4 weeks. We mean whenever you see the patient, and the patient is sufficiently out of their acute phase of their hospitalization—which is usually in the first 24 to 48 hours of therapy—after that, then it’s time to initiate 4 foundational drugs with the intent of achieving them in the next 4 weeks.

**AJMC®:** Recommendations in the ACC/AHA/HFSA guideline are in accord with points made by you and Dr. McMurray in your review, that simultaneous initiation or sequencing should not be delayed. What is the takeaway from this consensus?

**PACKER:** I was really impressed by the enthusiasm to get all 4 foundational drugs onboard as quickly as possible. Recommendations in the guideline give a sense that time is of the essence. That represents a meaningful change, because past guidelines took a slower approach. There is now a recognition that a slower approach doesn’t get people to where they need to be, either at all or rapidly enough. We now know where we need to be, and we have to get there as soon as possible.

The issuance of a guideline represents an opportunity for physicians to remember what is important. It reminds physicians, every physician who cares for patients with HF, what they should be thinking about, what their goals are, what they should be doing. We need reminders about that all the time, because, as of just a few years ago, the number of people getting evidence-based medicine with 4 foundational drugs for HFrEF in the United States was less than 5%. It’s a really disappointing number. If the guidelines serve as a reminder that we need to do better, that is exactly what their goal should be.
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Kaiser Permanente’s Clinical Pathway for the Use of SGLT2 Inhibitors in Heart Failure

A Q&A With Gary Besinque, PharmD

AJMC®: Kaiser has set up a clinical pathway for the use of SGLT2 [sodium-glucose cotransporter-2] inhibitors for patients with heart failure (HF). Could you describe this pathway?

BESINQUE: We update our HF management guidelines every 2 years. Well before our most recent update in April 2021, we recognized the impact of the various trials the FDA [United States Food and Drug Administration] had asked for that assessed the cardiovascular (CV) safety of SGLT2 inhibitors in patients with type 2 diabetes (T2D).1-4 Thereafter, a good number of studies examining SGLT2 inhibitors in patients with HF and with or without T2D demonstrated impressive results. Given all of this evidence, we began to consider where SGLT2 inhibitors would be placed in HF management.

We did an analogous exploration for the treatment of our patients with kidney failure. So both our kidney failure and HF guidelines were amended last year to include the institution of SGLT2-inhibitor therapies.

For HF guidance on whether to start SGLT2 inhibitors is based on where a patient is on the continuum of HF disease. We’re happy to recognize that presence or absence of T2D is not material to the decision to start an SGLT2 inhibitor.

AJMC®: When is the initiation of SGLT2-inhibitor therapy recommended?

BESINQUE: Generally, when we’re tweaking the HF guidelines, we make incremental moves, and that’s what happened when we introduced SGLT2 inhibitors. For early initiation—especially in patients with HF after a heart attack—we still rely heavily on the 3 β-blockers that have demonstrated good safety and efficacy in HF: carvedilol, bisoprolol, and metoprolol tartrate. After these have been initiated, we recommend then initiating ACE [angiotensin-converting enzyme] inhibitors or ARBs [angiotensin receptor blockers].

For HF patients—especially those with better ejection fraction and better New York Heart Association (NYHA) functional class—we think that SGLT2 inhibitors should be initiated third. We recommend initiating MRAs [mineralocorticoid receptor antagonists] and ARNIs [angiotensin receptor-neprilysin inhibitors] last.

AJMC®: Could you expand upon the evidence base that led to Kaiser’s recommendations for SGLT2 inhibitors in HF therapy?

BESINQUE: Some 15 years ago, the T2D medications thiazolidinedione, pioglitazone, and rosiglitazone got bad marks in some meta-analyses and the FDA-mandated CV safety trials for new T2D medications.5-6 This was the genesis of all of these remarkable trials assessing the CV safety of SGLT2 inhibitors in patients with T2D and trials examining SGLT2 inhibitors in patients with HF regardless of T2D.1-4,7-9

One of the first CV safety trials for SGLT2 inhibitors in patients with T2D left the biggest impression. The EMPA-REG OUTCOME trial [NCT01131676] involved use of empagliflozin in patients with established CV disease [CVD]...
and T2D. Remarkably, the 2 trial arms diverged almost immediately after initiation of therapy. At the end of 3 years, the placebo group demonstrated morbidity in the form of nonfatal MI, nonfatal stroke, and CV death. That composite primary outcome was reduced by 38% with the institution of the SGLT2 inhibitor empagliflozin.

It was a surprise that simply adding on an antidiabetic agent for patients with established CVD resulted in an improvement in CV status. Everybody sat on the edge of their chairs and said, “What’s going on here?” We’re still trying to figure that out.

Later, of the trials examining SGLT2 inhibitors in patients with or without T2D, EMPEROR-Reduced [NCT03057977] provided some of the most meaningful evidence for our recommendations. Most of the patients in that trial had NYHA functional class 2 HF; so our guidelines naturally pointed to these patients as having the most potential for improvement under SGLT2-inhibitor therapy.

AJMC: Was there an economic rationale for Kaiser including these agents earlier on in the spectrum of HF failure and earlier in the sequence of HF treatment?

BESINQUE: There’s an apocryphal tale from very early on. I was talking to 1 of the KOLs [key opinion leaders] in care management. This might have been 2016 or 2017. We spoke about the SGLT2 inhibitors, and he joked that maybe we’d replace our statins with SGLT2 inhibitors. I said, “I better look into this.” I don’t think he was being serious, of course, but that really meant a big deal, because we put statin use high on our list of needs. That impressed me greatly.

In brief, we expect that SGLT2 inhibitors will reduce hospitalization and that the savings from that reduction will outstrip the cost of the drug. In the EMPA-REG OUTCOMES trial, the heavy lifting in the outcomes was actually done by a reduction in HF hospitalizations. In HF, everybody has been struggling with 30-day readmission. A reduction in the number of hospitalizations over time would more than make up for the extra cost of instituting SGLT2 inhibitors early.

AJMC: What were the clinical and economic consequences of this decision to use SGLT2 inhibitors earlier in HF treatment?

BESINQUE: Time will tell. We just put in the endorsement of SGLT2-inhibitor use back in April 2021. So it’s been just over a year that we’ve offered the suggestion that SGLT2 inhibitors might be helpful in the management of patients with HF. We have some very capable people in our outcomes group who are watching this SGLT2-inhibitor deployment, and I eagerly anticipate some output from them.

AJMC: In their April 2022 guideline for the management of HF, the American College of Cardiology, American Heart Association, and Heart Failure Society of America now recommend the use of SGLT2 inhibitors in patients who are at risk for HF. What might be the value of bringing SGLT2 inhibitors to this early stage of treatment?

BESINQUE: Some great trials have demonstrated that SGLT2 inhibitors improve CV outcomes in not only HFrEF [HF with reduced ejection fraction], but also HFP EF [HF with preserved ejection fraction]. Indeed, the more myocardium there is to improve, the better. Myocardial energetics come into play. If you have better heart function, you’re preserving it longer. But the super fuel elements in SGLT2 inhibitors work at all stages of HF. Ultimately, the payoff of using SGLT2 inhibitors across all stages of HF might come in the form of lower health care utilization, lower morbidity and mortality, and improved quality of life, which are all great goals.

AJMC: Milton Packer, MD, and John McMurray, MD, recommend that patients with HFrEF should be started on a β-blocker and an SGLT2 inhibitor, and the remaining 2 pillars of HFrEF should be added to the treatment sequence within 4 weeks. This sequence is much more rapid than the conventional treatment approach, which takes 6 months or more. From an economic perspective, how compelling is this rapid approach?

BESINQUE: It definitely has merit. We certainly have struggled, especially with HFP EF; and it may be that introducing SGLT2 inhibitors very early in the care of these patients could make a strong impact on the quality of life and other dimensions of health care delivery.
Some early adopters in Kaiser are testing this out already on a small cohort of their patients to see if they can discern that.

But you do have to have numbers. We will have to await the arrival of good-sized number of patients who were treated in that way. As I said earlier, we really don’t know what SGLT2 inhibitors are doing. Once we do, we can find the people who need help in those areas. There’s an awful lot left to be explored in terms of where best to place this particular class of drugs in the treatment of HF:

AJMC®: Earlier this year, results were published from the EMPULSE trial, which demonstrated that beneficial effects of an SGLT2 inhibitor on health status persisted through 90 days in patients who were hospitalized for acute HF. From a payer perspective, how relevant are these results?

BESINQUE: EMPULSE trial participants were hospitalized with an HF exacerbation and started out on an SGLT2 inhibitor in-house. From the very beginning, once they were stabilized and off of inotropes, for example, and diuretics were stabilized, then investigators started the SGLT2 inhibitors and watched patients for 90 days. Payer perspective—wise, we really like to have a very large scale RCT [randomized controlled trial] to base our important guidance on. These results are going to contribute to our thinking, but you’ll have to treat a few more folks before we really take notice. This said, EMPULSE teases at the very thorny issue of 30-day hospital readmissions for patients with HF. We’re still wrestling with that issue and holding out hopes that SGLT2 inhibitors will contribute to solving that problem.

Interestingly, in addition to the main trial analyses, EMPULSE investigators also performed a post-hoc analysis of the KCCQ [Kansas City Cardiomyopathy Questionnaire] that was sent to patients. It has a 100-point scale, and the questionnaires were sent out every couple of weeks. It turns out that the difference between the SGLT2-inhibitor arm and the non-SGLT2–inhibitor arm averaged about 4 points. In the paper, it was called small, but we saw real improvement in KCCQ score and in the various dimensions. All the different facets of KCCQ showed that improvement.

AJMC®: You mention the rate of unplanned readmission within 30 days of discharge, which the National Committee for Quality Assurance monitors. As we consider the results of the EMPULSE trial, how hopeful should they be that the SGLT2 inhibitors might favorably impact this metric?

BESINQUE: We stumbled across the SGLT2 inhibitors serendipitously, simply because the FDA was concerned about the thiazolidinediones. And lo and behold, we came across some very spectacular results: SGLT2 inhibitors were not only not harmful, but actually helpful in improving the health status of patients with established CVD and T2D. Then we found out that it doesn’t matter whether patients with HF have T2D or not; you still get those improvements. It’s not the HbA₁c [glycated hemoglobin A₁c level] that’s doing this, but something else that is creating some remarkable results. We can be hopeful and should continue to explore what exactly the SGLT2 inhibitors can and cannot do.

AJMC®: What might be the approach to incorporating SGLT2 inhibitors into policy decisions?

BESINQUE: That’s definitely the question of the day. We wonder whether SGLT2 inhibitors can do their magic in other clinical arenas. For example, in CKD [chronic kidney disease], we are seeing post-hoc analyses of the original CV safety trials delving into whether renal function is improved. And, indeed, SGLT2 inhibitors do slow the loss of nephrons over time; as you age, your creatinine clearance continues to fall, but not as rapidly under the influence of SGLT2 inhibitors. So our nephrologists are likewise interested in finding that sweet spot in terms of preserving both kidney function and the piggy bank.

The economics are the elephant in the room when you’re talking about instituting newer therapies earlier, where earlier means among a much larger cohort. It does make waves in terms of the finance folks; they’re asking whether you can keep the enterprise afloat. Our purchasing and contracting team does a stellar job. Kaiser’s a large operation, so they can acquire some very favorable contracting. That was the case for our SGLT2 inhibitors. This has made it easier to explore the benefits and dimensions of SGLT2-inhibitor use in our program.

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