Cardiometabolic Risk Reduction: A Review of Clinical Guidelines and the Role of SGLT-2 Inhibitors

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doi: 10.12788/jfp.0216

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- Identify how heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) and associated cardiovascular (CV) risks are interconnected.
- Initiate guideline-recommended therapy to reduce CV risk in patients with HF, CKD, and/or T2DM.
- Apply evidence for sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) to clinical practice, based on recent and emerging trials.
- Review evidence suggesting increased incidence and severity of COVID-19 infection in patients with diabetes.

KEY TAKEAWAYS

- Current guideline-directed treatment algorithms for HF and diabetes both recommend SGLT-2 inhibitors based on patient-specific characteristics and comorbidities.
- In patients with HF, the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin reduced rates of cardiovascular death and hospitalization for worsening heart failure.
- The SGLT-2 inhibitors canagliflozin and dapagliflozin are associated with a lower risk of worsening kidney function and cardiovascular or renal death. A phase 3 trial evaluating kidney outcomes for empagliflozin is currently ongoing.

TARGET AUDIENCE

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

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SPONSORSHIP

This article is sponsored by Primary Care Education Consortium, in collaboration with the Primary Care Metabolic Group.

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ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, of the Primary Care Education Consortium.

SUPPORTER

This article is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company.

CASE SCENARIO

RW is a 56-year-old woman whose last primary care visit was more than 7 years ago. When RW was lost to follow-up, she had a history of type 2 diabetes mellitus (T2DM), obesity, and hypertension (HTN). She reports not taking any medications during this time but did quit smoking 3 years ago. She now seeks medical care because she reports feeling unwell. A thorough diagnostic evaluation confirms T2DM, obesity, and hypertension (HTN). RW

also has heart failure with reduced ejection fraction (HFrEF) and stage 2 chronic kidney disease (CKD) with moderate albuminuria.

Lab work: Glycated hemoglobin (A1c) 9.0%, estimated glomerular filtration rate (eGFR) 62 mL/min/1.73 m^2, urinary albumin-to-creatinine ratio (UACR) 120 mg/g, and left ventricular ejection fraction (LVEF) 35%

Vitals: Body mass index (BMI) 36.0 kg/m2, blood pressure 144/92 mm Hg in clinic today

Current medications: None; historically was prescribed metformin 500 mg 1 tablet twice daily, atorvastatin 10 mg daily, and lisinopril 5 mg daily

CARDIOVASCULAR DISEASE

The patient in the case scenario above is at risk for multiple medical issues, including cardiovascular (CV) complications, given her comorbidities and history. Cardiovascular diseases (CVDs) include those affecting the heart or blood vessels. Physiologically, the CV system is highly interconnected with the renal and metabolic systems.[1] The integration of the cardio-renal-metabolic system is responsible for a variety of homeostatic processes including blood pressure regulation, volume status, and glucose reabsorption and transportation.[1] Thus, CV and renal risk exist along an interconnected pathophysiologic continuum.[2,3]

Chronic heart failure. HF is a complex clinical syndrome in which structural or functional impairment of ventricular filling or ejection of blood interferes with the heart's ability to pump effectively.[4] Chronic HF can be broadly grouped into 2 categories: systolic heart failure, or heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure, or heart failure with preserved ejection fraction (HFpEF). HFrEF is defined as an LVEF ≤40%, while HFpEF is an LVEF ≥50%.[4] Presence and severity of HF is further classified by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) stages of HF and the New York Heart Association (NYHA) functional classification.[4]

Chronic kidney disease. CKD is defined as abnormalities of kidney structure or function, present for at least 3 months, with known health implications.[5,6] Staging of CKD is classified based upon cause, glomerular filtration rate (GFR) category, and albuminuria category.[5,6] GFR categories (G1-G5) are assigned along a spectrum of GFR measurements, from ≥90 mL/min/1.73 m^2 (normal) to <15 mL/min/1.73 m^2 (which is end-stage kidney disease [ESKD]).[7] Albuminuria is categorized from normal to severe as A1 (UACR <30 mg/g), A2 (UACR 30-300 mg/g), or A3 (UACR >300 mg/g).[7]

Epidemiology. The prevalence of HF in the United States is estimated at 6.5 million individuals; this number is projected to surpass 8 million by 2030.[7] Despite advances in surgical and medical therapy, HF remains a major cause of healthcare utilization and diminished health-related quality of life (HRQoL).[8,9] In 2014 alone, there were more than 1 million emergency department visits, approximately 980,000 hospitalizations, and 83,705 deaths with HF as the primary diagnosis.[10] Comparatively, the prevalence of CKD is more than 38 million individuals in the United States.[11,12]

Risk factors. Several comorbid conditions serve as independent risk factors for developing HF. Coronary artery disease, HTN, diabetes mellitus, metabolic syndrome, smoking, and obesity are among those most frequently implicated.[4,13] According to the ACCF/AHA, HTN may be the single most important modifiable risk factor for HF in the United States.[4,14] Higher levels of blood pressure and longer duration of HTN, particularly in individuals of advanced age, are associated with a greater incidence of HF.[4] Clinical trials suggest patients with T2DM are at nearly 2 times the risk of developing HF as those without diabetes.[15,16] Similarly, uncontrolled diabetes and HTN are the most common causes of CKD in adults.[12] The relationships between CKD, diabetes mellitus, and HF are bidirectional, with each disease independently increasing the risk for the others.[12,17]

GUIDELINE-RECOMMENDED MEDICAL THERAPY

Nonpharmacologic therapy for HF. Guideline-directed nonpharmacologic interventions for HF management include daily weight checks, regular physical activity, and sodium restriction. All patients with HF are encouraged to participate in regular physical activity as functional status permits.[4] Cardiac rehabilitation in the HF population has been shown to improve functional capacity, exercise duration, and HRQoL while reducing hospitalizations and mortality.[4] Due to the association between sodium intake and HTN, left ventricular hypertrophy (LVH), and CVD, the AHA recommends restricting sodium intake to ≤1500 mg/d in patients with stage A or B HFrEF.[4] While evidence for limiting dietary sodium in stage C and D HFrEF is less clear, some degree of sodium restriction (eg, <3 g/d) is likely warranted.[4]

HFrEF pharmacologic therapy. Guideline-directed medical therapy (GDMT) is the mainstay of pharmacologic therapy for HFrEF.[4] For individuals at risk of HF, or those in stage A, HTN and lipid disorders should be managed concordant with published guidelines.[4] Thus, optimal blood pressure for individuals with HFrEF is <130/80 mm Hg.[18-21] In addition to appropriate blood pressure control and statin therapy, angiotensin-converting enzyme inhibitors (ACEIs) and evidence-based beta blockers should be used in all patients with stage B HFrEF.[4] Treatment with 1 of 3 evidence-based beta blockers—bisoprolol, carvedilol, or metoprolol succinate—should be initiated at low doses in stable patients and gradually titrated up as tolerated to target doses of 10 mg/d, 50 mg/d

in 2 divided doses, and 200 mg/d, respectively.[4] In patients with HFrEF NYHA class II-IV who tolerate an ACEI or angiotensin II receptor blocker (ARB), replacement with an angiotensin receptor neprilysin inhibitor (ARNI) is recommended to further reduce morbidity and mortality.[18,21] Additionally, diuretics should be prescribed as needed for volume overload in stage C HFrEF.[4] The 2021 Update to the 2017 American College of Cardiology Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment describes the treatment algorithm for GDMT in stage C HFrEF **(FIGURE 1)**.[22] The inclusion of dapagliflozin and empagliflozin as GDMT for symptomatic HF highlights the emerging role for sodium-glucose cotransporter-2 (SGLT-2) inhibitors in HFrEF management.[22]

HFpEF pharmacologic therapy. Whereas GDMT is the standard of care for HFrEF, HFpEF pharmacotherapy is more limited and is aimed at controlling symptoms and managing comorbid conditions. Blood pressure control in accordance with existing HTN guidelines remains the most important recommendation for patients with HFpEF. Renin-angiotensin-aldosterone system (RAAS) inhibition with an ACEI, ARB, or possibly ARNI represents preferred antihypertensive therapies to attain systolic blood pressure <130 mm Hg in the setting of HFpEF.[18,20] Diuretics should be prescribed to all patients with HTN and HFpEF who have evidence of fluid retention.[4,20]

Pharmacologic approaches to glycemic treatment. The American Diabetes Association's (ADA) *Standards of Medical Care in Diabetes–2021* maintain that metformin and comprehensive lifestyle modifications, including weight management and physical activity, are first-line interventions in the management of T2DM.[23] Based on the results of CV outcomes trials (CVOTs), the ADA now recommends considering indicators of high-risk or established atherosclerotic CVD (ASCVD), CKD, or HF for all patients to help guide therapy independent of baseline A1c, A1c goals, or metformin use **(FIGURE 2)**.[23]

For patients with T2DM and HF, guidelines recommend initiation of an SGLT-2 inhibitor with proven benefit.[23,24] While empagliflozin, canagliflozin, and dapagliflozin have all shown a reduction in HF in CVOTs, empagliflozin and dapagliflozin are the 2 SGLT-2 inhibitors with primary HF outcome data.[23,25,26] For patients with diabetic kidney disease (DKD) and albuminuria, an SGLT-2 inhibitor with primary evidence supporting slowed CKD progression is preferred.[23] In the absence of albuminuria, patients with T2DM and CKD (eGFR <60 mL/min/1.73 m^2) may consider a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or SGLT-2 inhibitor with proven CVD benefit.[27-33] When established ASCVD or indicators of high ASCVD risk are present, a GLP-1 RA or SGLT-2 inhibitor with proven CVD benefit is preferred.[23,24]

For T2DM patients without high-risk or established ASCVD, CKD, or HF, medication selection is based upon efficacy, side effect avoidance, cost, and patient preference.[23] If there is a compelling need to minimize hypoglycemia, such as patients who experience frequent hypoglycemic episodes or hypoglycemia unawareness, an SGLT-2 inhibitor, GLP-1 RA, dipeptidyl peptidase-4 inhibitor (DPP-4i), or thiazolidinedione (TZD) is preferred.[23] To minimize weight gain or to promote weight loss, an SGLT-2 inhibitor or GLP-1 RA is recommended.[23] Finally, if cost is a major issue, TZDs or sulfonylureas should be considered.[23]

Management of diabetes in CKD. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 Clinical Practice Guidelines for Diabetes Management in CKD recommend a comprehensive approach to kidney-heart risk factor management.[5] Treatment with an ACEI or ARB should be initiated in patients with diabetes, HTN, and albuminuria, and these medications should be titrated to the highest approved dose that is tolerated.[5] Metformin and SGLT-2 inhibitors are the preferred, first-line antihyperglycemic therapies for patients with T2DM, CKD, and an eGFR ≥30 mL/min/1.73 m^2.[5]

EMERGING ROLE OF SGLT-2 INHIBITORS

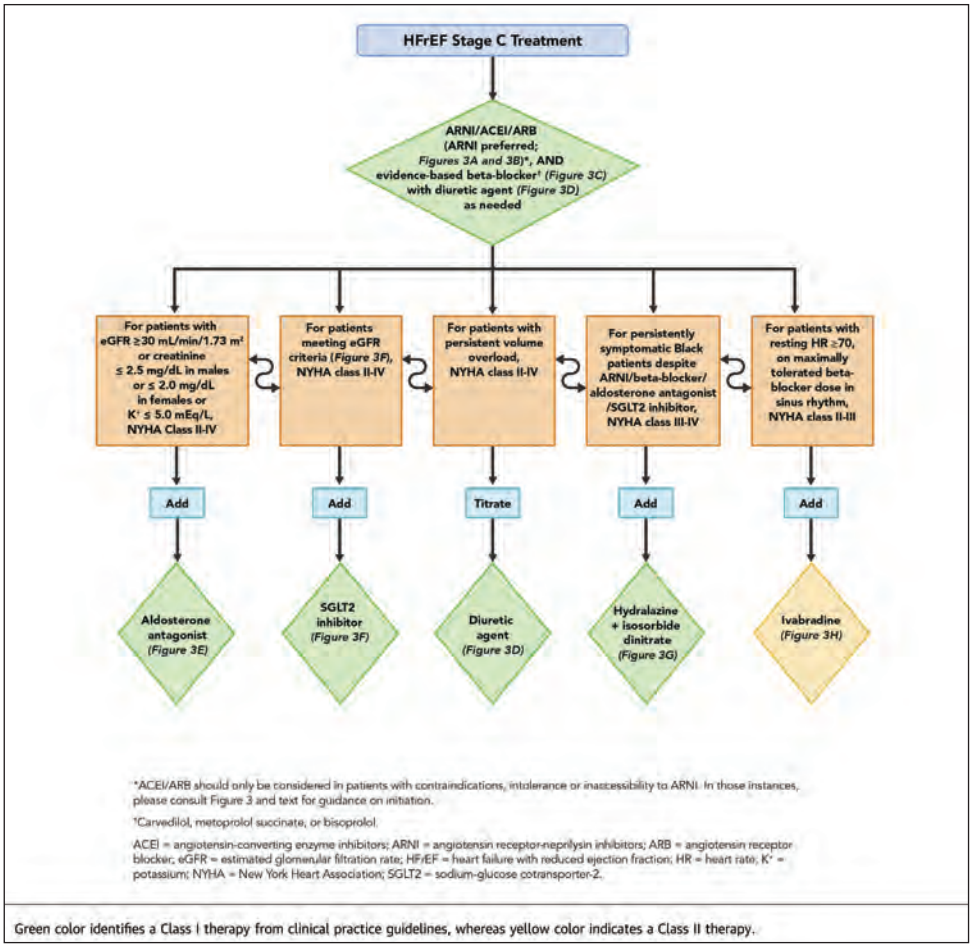
Cardiovascular outcomes trials. In 2008, the FDA issued guidance for industry requiring CVOTs for all new T2DM medications.[33] A composite of CV death, myocardial infarction, or ischemic stroke, referred to as 3-point major adverse cardiac events (MACE), often serves as the primary outcome of CVOTs. The 4 SGLT-2 inhibitors currently available in the United States have each demonstrated noninferiority to placebo as part of standard therapy with respect to CV safety.[34-40] Reduced rates of hospitalizations for HF have been observed across the class of SGLT-2 inhibitors in CVOTs.[35-37,40]

Empagliflozin was the first drug in this class to not only demonstrate CV safety but also benefit in patients with T2DM at high CV risk compared to placebo, based on results of the EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) in 2015.[36] The hazard ratio for reduction in MACE with empagliflozin was 0.86 (95% confidence interval (CI): 0.74-0.99; P=0.04). Canagliflozin was studied in patients with T2DM and high CV risk, demonstrating a reduced rate of 3-point MACE compared to placebo.[35] Dapagliflozin was noninferior to placebo for reducing CV risk in patients with T2DM and ASCVD or at high CV risk.[37] Ertugliflozin was non-inferior to placebo for 3-point MACE in patients with T2DM and ASCVD.[40]

SGLT-2 inhibitors in chronic HF

Canagliflozin. In patients with T2DM and high CV risk, canagliflozin reduced HF-related fatalities and hospitalizations by 30% compared to placebo (HR 0.70; 95% CI: 0.55-0.89).[40] In subgroup analyses, the hazard ratios for HFrEF, HFpEF, and HF

FIGURE 1. **Treatment algorithm for guideline-directed medical therapy in HFrEF**[22]



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unknown EF (HFuEF) were 0.69 (95% CI: 0.48-1.00), 0.83 (95% CI: 0.55-1.25), and 0.54 (95% CI: 0.32-0.89), respectively.[40] When HFuEF events were assumed to be HFpEF, the updated HR for HFpEF was 0.71 (95% CI: 0.52-0.97), and when HFuEF events were assumed to be HFrEF, the updated HR for HFrEF was 0.64 (95% CI: 0.48-0.86).[40] Thus, further studies will be required to clarify the benefit of canagliflozin in HFrEF vs HFpEF.

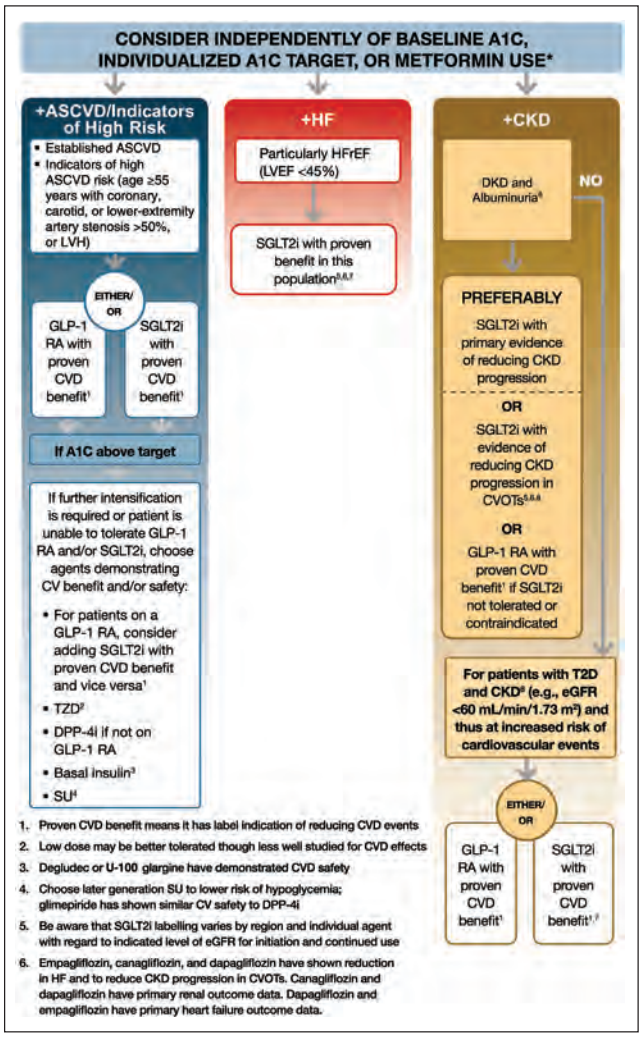
Dapagliflozin. The DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) trial compared dapagliflozin 10 mg/d to placebo, in addition to standard therapy, in patients with NYHA class II-IV HF and an LVEF ≤40% with or without T2DM. During the 18.2-month follow-up period, the composite outcome of worsening HF or CV death occurred in 16.3% of patients receiving dapagliflozin vs 21.2% of patients in the placebo group (P<0.001).[41] Additionally, individuals in the dapagliflozin group were less likely to experience CV death or hospitalization due to HF (16.1% vs 20.9%; P<0.001).[41] The use of dapagliflozin also resulted in fewer symptoms of HF, as quantified by the Kansas City Cardiomyopathy Questionnaire (P<0.001).[41] Findings of DAPA-HF were consistent in patients regardless of the presence or absence of T2DM.

DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) is an ongoing, phase 3 trial evaluating the effect of dapagliflozin in reducing the composite of CV death or HF events in patients with HFpEF NYHA class II-IV with or without T2DM.[42] Dapagliflozin 10 mg/d will be compared to placebo, in addition to the standard of care.

DETERMINE-preserved (Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction) is a phase 3 trial evaluating the effect of once-daily dapagliflozin on exercise capacity in patients with HFpEF NYHA class II-IV with or without T2DM.[43] The trial was completed in July 2020; however, results are not yet available.

Empagliflozin. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial, patients with NYHA class II-IV HF and an LVEF ≤40% were randomized to empagliflozin 10 mg/d or placebo, in addition to standard therapy. Treatment with empagliflozin reduced rates of the primary composite outcome of CV death or hospitalization for worsening heart failure (19.4% vs 24.7%; P<0.001).[44] The effect of empagliflozin on the primary outcome was consistent in patients with and without T2DM. Moreover, a total of 553 patients were hospitalized for HF in the placebo group whereas only 388 patients were hospitalized for HF in the empagliflozin group (P<0.001). Uncomplicated genital tract

FIGURE 2. **2021 ADA diabetes treatment algorithm**[23]



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infections were reported more frequently with empagliflozin.

EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) is an ongoing phase 3 trial evaluating the safety and efficacy of once-daily empagliflozin compared to placebo in patients with HFpEF with or without T2DM.[45]

SGLT-2 inhibitors in CKD

Canagliflozin. In the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) trial, patients with T2DM and albuminuric CKD were assigned to canagliflozin 100 mg/d or placebo. Eligible patients had an eGFR of 30 to <90 mL/min/1.73 m^2, a UACR of >300 to 5000 mg/g, and were treated with RAAS blockade.[46] The trial was stopped early due to the efficacy benefit of canagliflozin; this resulted in a median follow-up period of 2.62 years. The primary outcome, a composite of serum creatinine doubling, ESKD, renal death, or CV death, occurred in 11.1% of patients in the canagliflozin group and 15.5% of patients in the placebo group (P<0.001).[46] The relative risk of the renal-specific composite of ESKD, serum creatinine doubling, or renal death was 34% lower in the canagliflozin group (HR 0.66; P<0.001), while the relative risk of ESKD alone was 32% lower in the canagliflozin group (HR 0.68; P=0.002).[46] There were no differences in the rates of amputation or fracture between groups.

Dapagliflozin. DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) compared dapagliflozin 10 mg/d to placebo in patients with an eGFR of 25 to 75 mL/min/1.73 m^2 and a UACR of 200 to 5000 mg/g with or without T2DM. The trial was stopped early due to efficacy, resulting in a median follow-up of 2.4 years.[47] The rate of the primary outcome, a composite of a sustained decline in eGFR of 50%, ESKD, or death from renal or CV causes, was lower in the dapagliflozin group (9.2%) vs the placebo group (14.5%; P<0.001).[47] Death from any cause also occurred less frequently in the dapagliflozin group (4.7% vs 6.8%; P=0.004).[47] The effects of dapagliflozin were similar in patients with and without T2DM, and the incidence of adverse events and serious adverse events were similar between groups.

Empagliflozin. EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) is an ongoing, phase 3 trial evaluating the effect of empagliflozin on kidney disease progression and CV death in patients with preexisting CKD with or without T2DM.[48]

CASE SCENARIO *(CONT'D)*

Patient RW, a 56-year-old woman seeking medical care after 7 years of minimal healthcare contact.

Pertinent medical conditions: T2DM, obesity, HTN, stage B HFrEF, and stage 2 CKD with moderate albuminuria

Though there are many issues that would need to be addressed, medical management would include prescribing medications for T2DM, HTN, HF, and CKD. Based on current evidence, a suggested approach might be to restart metformin, add an SGLT-2 inhibitor, restart an ACEI, add a GDMT beta blocker for HF (carvedilol, bisoprolol, or metoprolol succinate), and restart a moderate-intensity statin. Symptomatic treatment for fluid overload related to HF might also be indicated, which would include the use of diuretics. Her eGFR should be closely monitored with initiation of these medications.

COVID-19 AND T2DM

Diabetes is one of the most important comorbidities linked to severity of COVID-19 infection.[49] The risk of a fatal outcome from

COVID-19 is up to 50% higher in patients with diabetes than in those without diabetes.[49,50] Several hypotheses exist to explain the increased incidence and severity of COVID-19 infection in this population; in general, individuals with diabetes are at an increased risk of infection due to hyperglycemia-associated immune dysfunction.[49,51] Regardless of the exact mechanism, the risk of mortality in patients with T2DM appears significantly and independently related to hyperglycemia.[50] The relationship between improved glycemic control and improved outcomes in patients with COVID-19 and preexisting T2DM serves as a guiding principle for the provision of care.[52]

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