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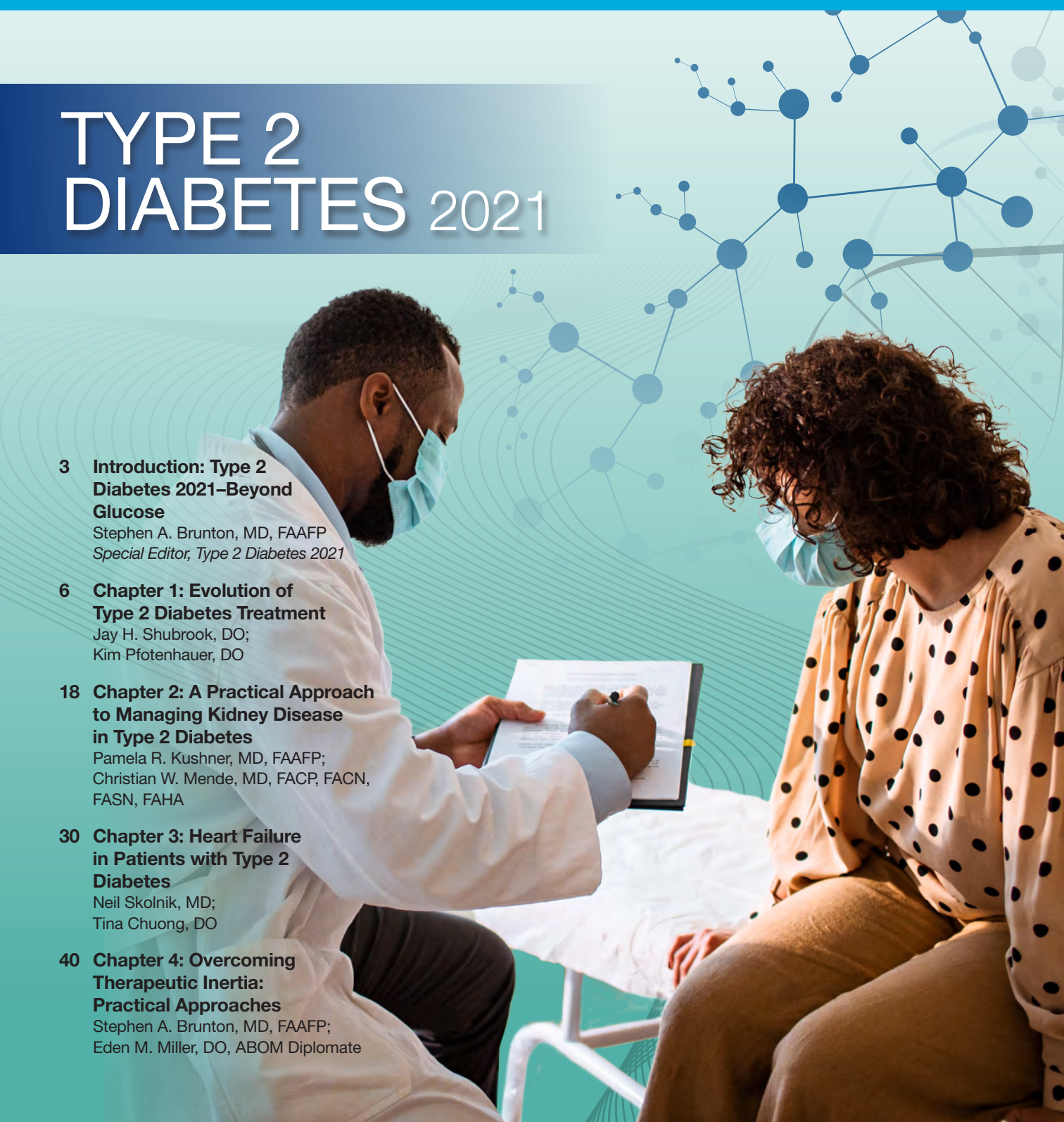
TYPE 2 DIABETES 2021



INTRODUCTION

Type 2 Diabetes 2021–Beyond Glucose

Stephen A. Brunton, MD, FAAFP
Special Editor, Type 2 Diabetes 2021

The management of type 2 diabetes (T2D) has changed substantially since the first American Diabetes Association (ADA) Standards of Care were published in 1989,[1] and metformin was introduced in the United States in 1995.[2] Further changes occurred after completion of cardiovascular (CV) outcomes trials (CVOTs) that were required for new diabetes therapies.[3] Although metformin remains the foundation for T2D treatment in 2021, results from CVOTs have transformed our understanding of optimal patient care in T2D.[4,5] We have moved away from the glucocentric approach of T2D management into an era in which the interplay among T2D, obesity, atherosclerotic CV disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD) is increasingly recognized. This supplement brings together key updates in the field of T2D to help you care for your patients who have not only T2D, but also other interconnected diseases.

In the first article of this supplement, Drs. Shubrook and Pfotenhauer reflect on the increasing complexity of treating individuals with T2D. For example, the ADA Standards of Care has evolved from a short document to more than 200 pages in length.[5] This transformation is due in part to our increased understanding of T2D, the availability of new treatments, and the beneficial effects of some T2D medications on cardiorenal outcomes. Of note, the ADA Standards of Care is now a "living document" with updates occurring shortly after new studies are published.[6] Improving glycemic control in adults with T2D is still important, and ADA guidance recommends consideration of ASCVD, CKD, and HF to aid therapy selection after metformin.[5] Importantly, for patients with T2D who have established ASCVD, indicators of high CV risk, or established CKD or HF, a sodium-glucose co-transporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with demonstrated cardiac and renal benefits is recommended as treatment independent of a patient's glycated hemoglobin (HbA1c), with consideration of patient-specific factors.[5]

As primary care clinicians, we have to think beyond a single diagnosis, and provide holistic care to our patients with T2D, including identifying and managing cardiac, renal, and metabolic risk factors. This includes early screening for diabetic kidney disease (DKD). Drs. Kushner and Mende provide practical pointers for diagnosing, managing, and monitoring DKD in the second article of this supplement. This includes recognition of changing phenotype based on data showing a decrease in the prevalence of albuminuria and an increase in the prevalence of reduced estimated glomerular filtration rate (eGFR) in patients with T2D.[7] We have to remember

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to monitor both eGFR and urinary albumin excretion at least annually.

When it comes to treatment, optimizing glycemic control and blood pressure are still paramount in preventing and slowing progression of DKD. However, we now have treatment options beyond renin-angiotensin-aldosterone system inhibitors to reduce end-stage kidney disease (ESKD) and improve morbidity and mortality. The CREDENCE (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) trial demonstrated a 30% risk reduction in the composite kidney endpoint (doubling creatinine, ESKD, renal or CV death) in patients with DKD.[8,9] More recently, the DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) trial extended the kidney benefit of dapagliflozin to patients with CKD with or without diabetes. This trial reported a 39% relative risk reduction in the primary outcome (sustained ≥50% eGFR decline, ESKD, or death from renal or CV causes) in patients with CKD with or without diabetes.[10] Trials of other SGLT2 inhibitors in patients with CKD are ongoing. Importantly, the newly released Kidney Disease Improving Global Outcomes (KDIGO) guidelines for management of CKD in T2D now recommend combination therapy with metformin and an SGLT2 inhibitor if eGFR is adequate, and GLP-1 RAs may also be added or used.[11]

The focus shifts to the importance of HF as a clinical outcome in patients with T2D in the third article by Drs. Skolnik and Chuong. It has been 5 years since EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removal of Excess Glucose) was the first CVOT to show that a glucose-lowering medication, empagliflozin, reduced the risk of CV events and, unexpectedly, reduced the risk of hospitalization for HF (HHF) in patients with T2D.[12] Since then, additional evidence has supported SGLT2 inhibitor-associated decreases in the occurrence of HHF in patients with T2D.[13-15] Subsequently, 2 trials have examined whether SGLT2 inhibitors reduce the risk of HHF in patients with established HF receiving recommended HF therapies, regardless of the presence or absence of diabetes. Findings from DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) demonstrated that dapagliflozin reduced the risk of HHF, improved survival, and reduced symptoms in patients with HF with reduced ejection fraction (HFrEF) with or without T2D. More recently, EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) showed that treatment with empagliflozin reduced the risk of CV death or HHF compared with placebo; this effect was consistent among patients with and without diabetes.[16] In addition, empagliflozin slowed progression of loss of kidney function and improved quality of life (secondary endpoints). In summary, the strong association between T2D and HF, and recent findings on the benefits of SGLT2 inhibition on HF outcomes, provide impetus for primary care clinicians to consider CV complications, including HF, when developing treatment plans for patients with T2D.

Finally, Dr. Miller and I conclude the supplement with our chapter on overcoming therapeutic inertia. Large landmark trials have established the importance of early intensive glycemic control for reducing microvascular complications in T2D, and recent CVOTs demonstrate that we have therapies that can further modify the course of kidney, HF, and CV event outcomes. We need to be diligent, and consider creating a T2D-only focused appointment with our patients in which we review the "ABCs" of diabetes that we teach our patients—A1c, blood pressure, and cholesterol—and commit to changing the therapy at every visit in which an improvement in HbA1c goals is not achieved. When you have a patient with T2D and possible comorbid cardiac and/or renal disease, the worst thing that you can do is nothing at all!

Given today's digital environment, many of our patients search for information on the internet and social media, challenging us to stay current about treatment options. We hope that this supplement on the management of T2D helps you to integrate up-to-date information on emerging research with regard to T2D and common comorbidities to assist you and your patients in making informed decisions. ●

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CHAPTER 1

Evolution of Type 2 Diabetes Treatment

Jay H. Shubrook, DO; Kim Pfotenhauer, DO

INTRODUCTION

Primary care professionals deal with many patients with many diseases, including individual patients who may have multiple chronic diseases. One such chronic disease is type 2 diabetes (T2D), the most common form of diabetes, affecting an estimated 34 million people in the United States.[1] Primary care professionals are responsible for managing the care of the majority of patients with T2D in the United States, and so face the potentially daunting task of selecting a treatment plan drawn from a wide range of options, which must account for any other coexisting conditions. Once agreed and established, the treatment plan will need to be reviewed on an ongoing basis, and within the limited time allocated to assess and discuss treatment options with each patient.

Diabetes management is much more difficult now than even just 10 years ago, and this challenge is clearly reflected in the guidance given to physicians. The first American Diabetes Association (ADA) Standards of Care for the treatment of T2D published in 1988 were just 4 pages long,[2] but have since evolved into the 224-page 2020 update.[3] Similarly, the abridged version of the Standards of Care has grown from 6 pages when first published in 2014, to 29 pages in the most recent iteration.[4] This expansion has been driven in part by our increased understanding of the disease, but also by the corresponding increase in the number of medications available for the many subindications that have been identified **(FIGURE 1)**.[3,5-8]

The progressive nature of diabetes itself typically requires intensification of therapy to maintain adequate glucose control. Metformin is the preferred initial treatment for T2D in most cases owing to its glucose- and non-glucose-related benefits, and in general it should be continued as long as the agent is tolerated and not contraindicated.[3] As T2D progresses, treatment may need to be escalated to maintain glycemic control through the addition of new glucose-lowering agents, resulting in double- and triple-therapy combinations. However, there is no one-size-fits-all solution for which agents to add and in what sequence, adding to the complexity. Consequentially, the sheer volume of information and guidance regarding T2D can be overwhelming for primary care professionals who have to try to address T2D management within the limits of relatively short appointments. Although treatment was previously driven by glucose management above everything else, we are now realizing that one also has to consider the effects and potential risks or benefits of any medications on common comorbidities that contribute significantly to patient morbidity and mortality, such as obesity, cardiovascular disease (CVD), chronic kidney disease (CKD), and heart failure (HF). The average patient with T2D may be receiving 6 or more medications for diabetes and related conditions.[9] Each additional treatment adds to the complexity of the

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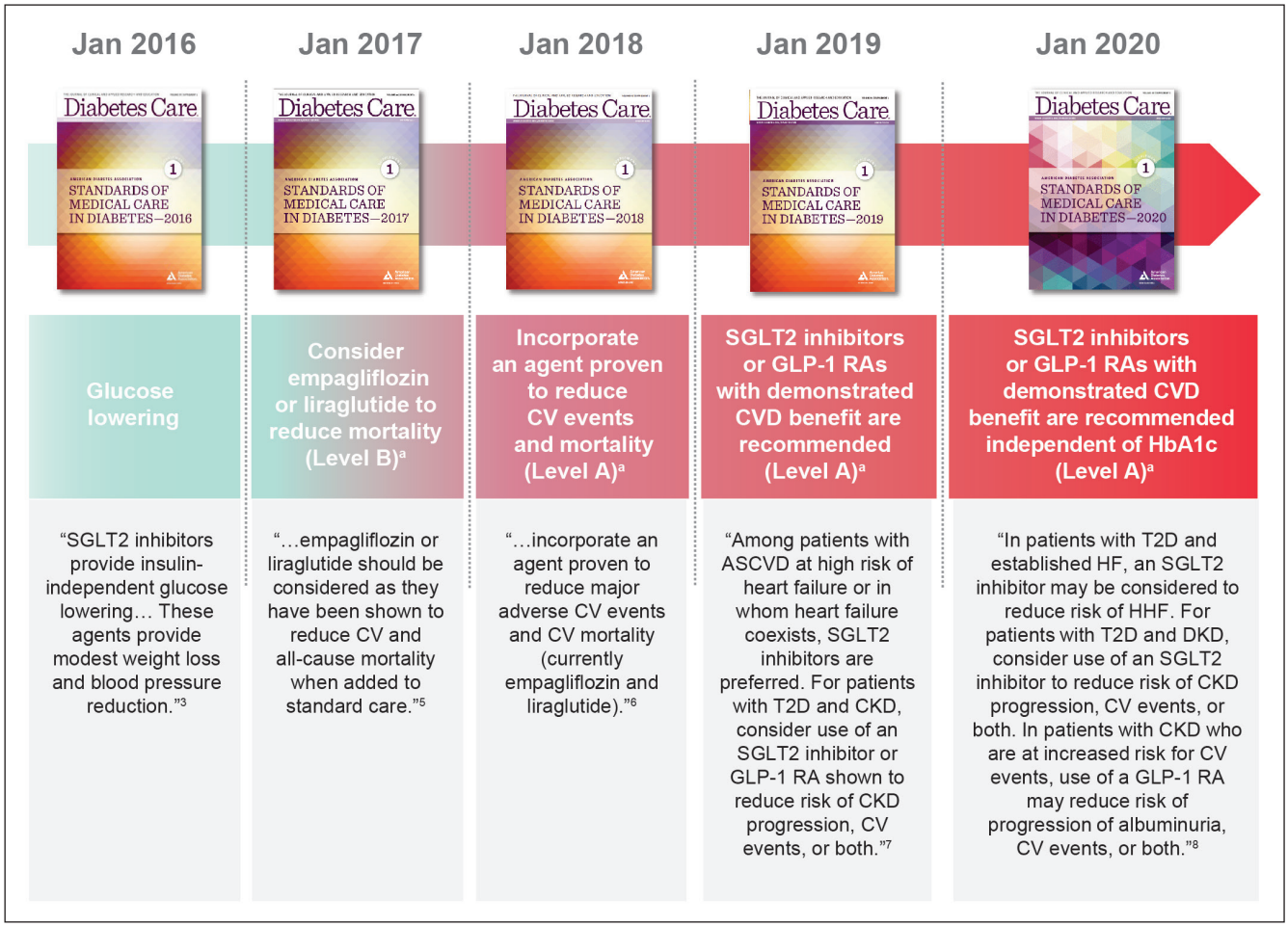
FIGURE 1 **Evolution of the ADA Standards of Care in Diabetes 2016–present**



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DKD, diabetic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; HHF, hospitalization for heart failure; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes.

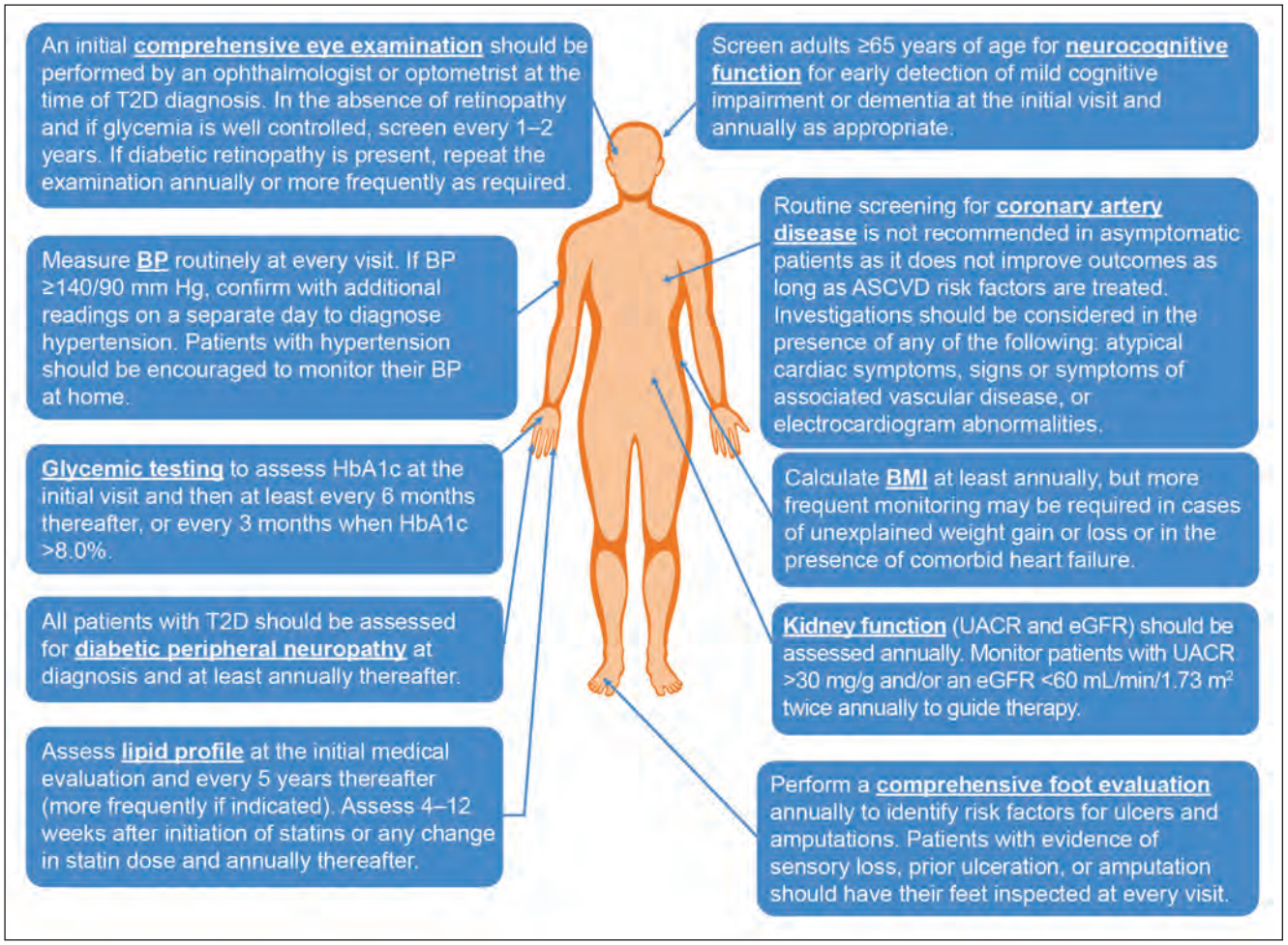
[a] ADA recommendations with A level evidence are based on large well-designed clinical trials or well-done meta-analyses. Recommendations with lower levels of evidence may be equally important but are not as well supported.

regimen for the patient and increases the potential for medication interactions. For this reason, a holistic approach is required to address all the needs of a patient when developing a treatment plan, rather than a strict focus on glucose control, CVD, or CKD in isolation. In this chapter, we provide a summary of the available treatment options for patients with T2D and obesity, CKD, and CVD. Although not intended as a comprehensive guide, this chapter will help primary care professionals to navigate the ever-changing landscape of the treatment of T2D.

TREATMENT STRATEGIES BEYOND GLUCOSE CONTROL

For many years treatment was focused on blood glucose control, with a "lower is better" mindset dominating treatment paradigms. Treatment focused on glycated hemoglobin (HbA1c) levels, sometimes based on only a single reading, with little understanding of the balance of risks and benefits associated with intensive glucose control. As the understanding of diabetes and its progressive nature grew, a drive toward earlier intervention and more rapid intensification of treatment in order to achieve and maintain HbA1c targets ensued. However, increasing evidence has shown that this approach is not always associated with clear benefit, and may even be directly associated with an increased risk of harm, typically related to hypoglycemia episodes.[10-13] More recently, factors other than glycemic control have risen in prominence combined with growing evidence that addressing comorbidities alongside glycemic control can translate into significant benefits in patient morbidity and mortality.[3]

FIGURE 2 **ADA-recommended screening and evaluations of patients with T2D**[3,14]



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio.

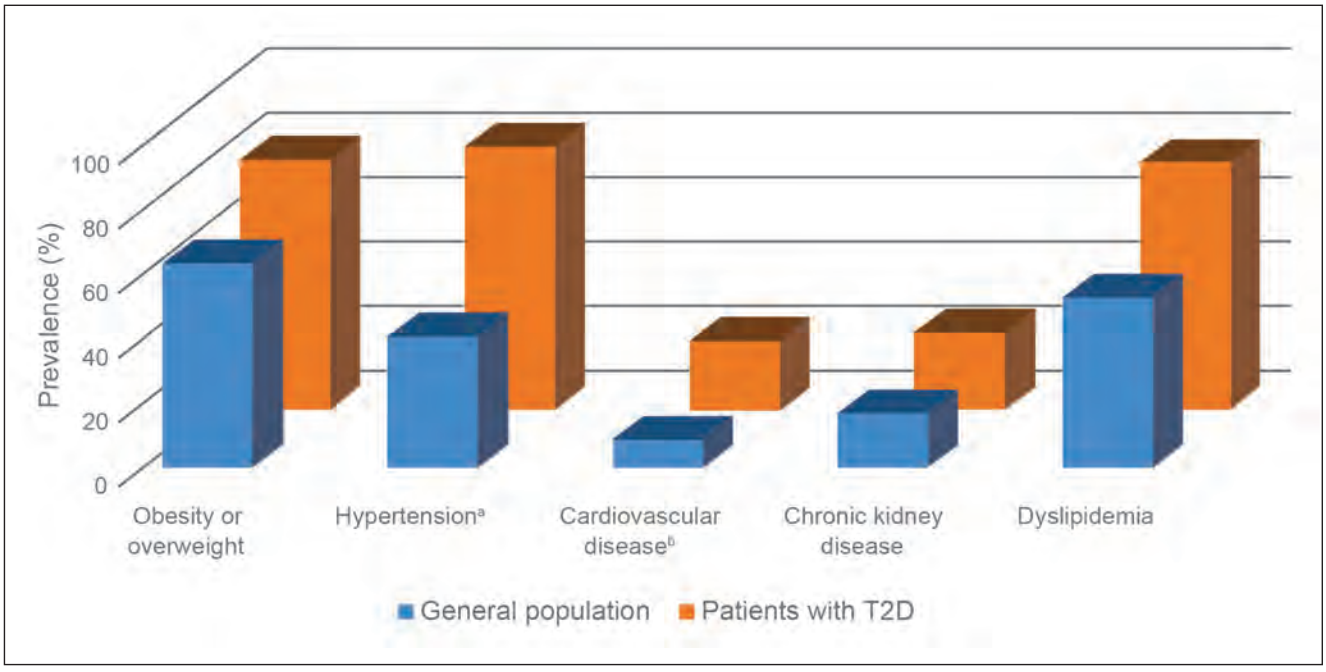
Current ADA Standards of Care

Current ADA Standards of Care recommend a complete medical evaluation at the initial diabetes-related visit, including an evaluation for diabetes complications and potential comorbid conditions such as obesity, atherosclerotic CVD (ASCVD), CKD, and HF **(FIGURE 2)**.[3,14] These comorbidities are not only more prevalent in patients with T2D than in the general population **(FIGURE 3)**,[15-17] but the progression of T2D and risk of any adverse outcomes may be increased by the presence of the comorbidity.[14] Conversely, T2D is associated with an increased risk of developing HF and CVD, and the presence of T2D may also impact their progression and associated outcomes.[23] Treatment plans still center around an individualized target HbA1c for the patient as they did previously, but the need to give greater consideration to the effect of these comorbidities is now recognized. A target HbA1c of <7% may be appropriate for non-pregnant adults, whereas targets of <6.5% may be useful in some patients if this can be safely achieved without excessive risk of hypoglycemia.[18] Conversely, a target HbA1c <8% may be more appropriate in patients with a high risk of hypoglycemia, significant comorbidities, or limited life expectancy **(FIGURE 4)**.[4,18] However, the complexity of the regimen and treatment burden should also be considered, as these factors can affect patient adherence and persistence, and thus the long-term efficacy of any treatment plan.

Modifiable risk factors and lifestyle changes

The current ADA Standards of Care recommend that modifiable risk factors, such as obesity, a sedentary

FIGURE 3 **Prevalence of key comorbidities in the US general population and in patients with T2D**



Abbreviation: T2D, type 2 diabetes.

Data from Iglay et al (2016),[15] Toth et al (2012),[16] and Benjamin et al (2019).[17]

[a]Hypertension defined as ≥130/80 mm Hg.

[b]Excluding hypertension.

lifestyle, or smoking, should be addressed simultaneously when present.[4] These are also known risk factors for some of the key morbidities associated with T2D, and thus addressing them is a cornerstone of therapy for patients with all stages of T2D. Management may involve increased exercise, dietary modification, or other simple changes to patient lifestyle, but in some cases pharmacological intervention may also be beneficial. However, relatively inexpensive lifestyle changes can result in significantly reduced progression of both T2D and related comorbidities.

Nonpharmacologic interventions and education

Early intervention can maximize the long-term benefits and reduce complications. Therefore, patients diagnosed as having prediabetes should be referred to an intensive behavioral lifestyle intervention program, with the aim of achieving and maintaining a 7% loss of body weight and increasing moderate-intensity physical activity (such as brisk walking) to at least 150 minutes per week.[19] These intervention programs have proven to be very cost-effective for diabetes prevention and reducing progression,[20,21] and so should be covered by third-party payers. All patients with T2D should participate in diabetes self-management education (DSME) and be provided support to help them achieve appropriate goals as required.[19]

Smoking

Smoking is a known CV risk factor, and all patients with T2D or prediabetes are advised to stop smoking cigarettes or using other tobacco products (including e-cigarettes) as a matter of routine. Patients using tobacco should be offered counseling or other pharmacologic treatments to help them stop.

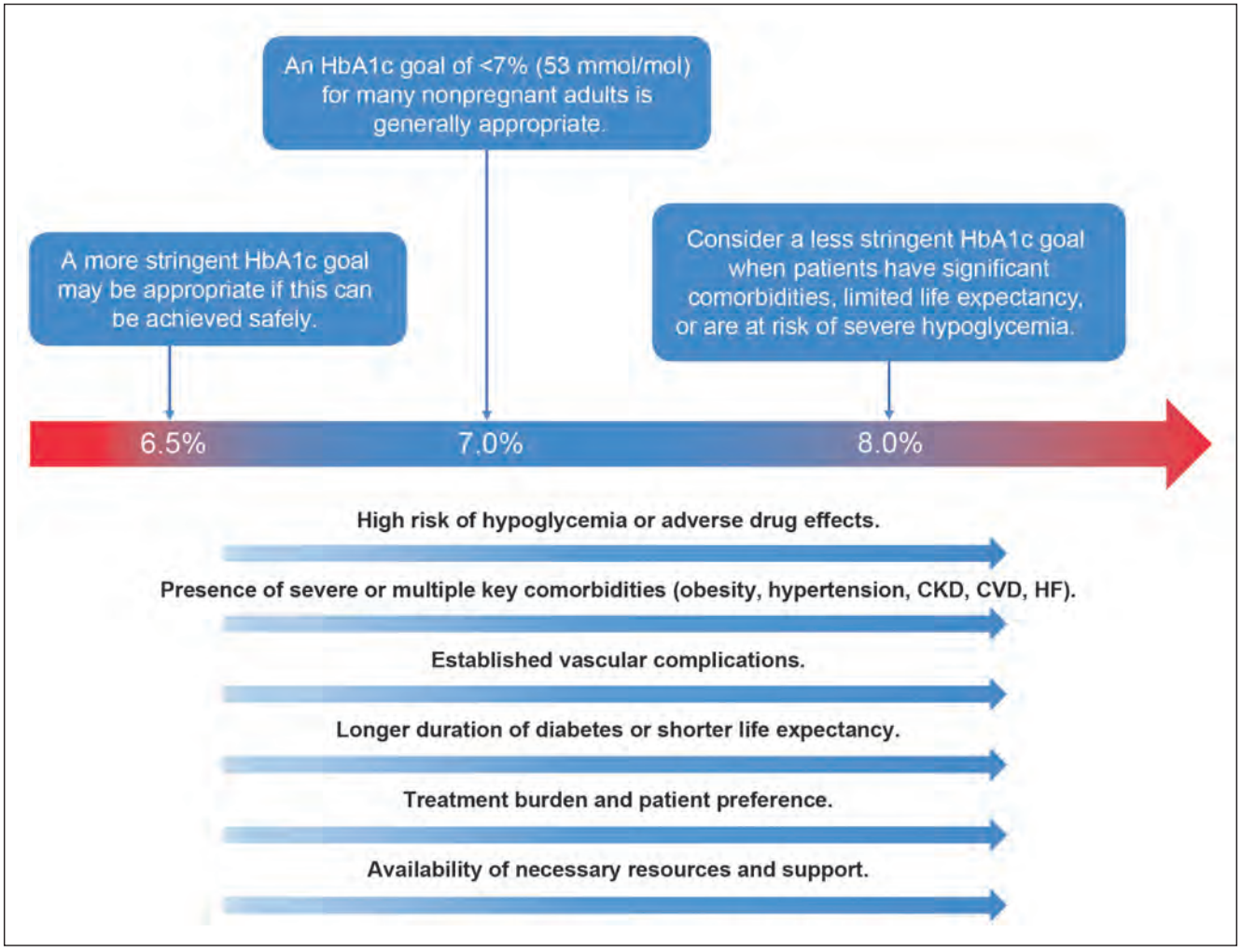
Physical exercise

All adults are recommended to reduce sedentary behavior where possible. Adults with T2D are recommended to engage in 150 minutes or more of moderate- to vigorous-intensity aerobic exercise in addition to 2 to 3 sessions per week of resistance exercise on nonconsecutive days.[22]

Diet

There is no one-size-fits-all guide to calorie intake and macronutritional or micronutritional requirements for patients with T2D. Any dietary changes would need to account for patient preferences including tradition, culture, religion, and cost. The current ADA Standards of

FIGURE 4 **Factors affecting selection of target HbA1c**[4]



Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HF, heart failure.

Care recommend referral to a registered dietitian nutritionist (RD/RDN) to assess overall nutrition, and to create a personalized meal plan for the patient that aligns with the overall treatment plan, including physical activity and medication use.[4]

MANAGEMENT OF COMORBIDITIES

Hypertension

For patients with blood pressure >120/80 mm Hg, recommended lifestyle interventions include weight loss if they are overweight or obese, and a Dietary Approaches to Stop Hypertension (DASH)-style eating pattern incorporating whole grains, fat-free or low-fat dairy products, fruits, vegetables, poultry, fish, and nuts (red meat and sweets can be included in small amounts).[23] The aim of this diet is to reduce sodium intake and increase potassium intake, and ideally should be coupled with moderation of alcohol intake and increased physical activity as appropriate. For patients with blood pressure ≥140/90 mm Hg, pharmacologic intervention (ie, angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], thiazide-like diuretics, or dihydropyridine calcium channel blockers) is considered appropriate; for patients with blood pressure ≥160/100 mm Hg, initiation of 2 antihypertensive agents or a single-pill combination of drugs should be considered to reduce the risk of CV events.[24] Multiple-drug therapy is often required to achieve blood pressure targets. However, while ACE inhibitors and ARBs are generally considered the first-line treatment for hypertension, combinations of ACE inhibitors and ARBs should be avoided due to increased risk of adverse events.[23]

Dyslipidemia

In patients with T2D, general lifestyle changes including weight loss, dietary modification to increase intake of n-3 fatty acids, viscous fiber, and plant stanols, while reducing the intake of trans fat, are recommended to help normalize the patient's lipid profile and reduce the risk of developing ASCVD. These measures should be intensified in patients with elevated triglyceride levels (≥150 mg/dL) or low high-density lipoprotein (HDL) cholesterol (<40 mg/dL for male and <50 mg/dL for female patients).[23] For patients with dyslipidemia but without ASCVD, moderate-intensity statin therapy should be considered unless contraindicated, and high-intensity statin therapy should be considered in patients with multiple ASCVD risk factors or older than 50 years of age unless contraindicated.[23] For patients with T2D and ASCVD, high-intensity statin therapy should be added alongside lifestyle modifications.[23]

Obesity

In the United States, obesity (defined as a body mass index [BMI] ≥30 kg/m^2) is more than twice as prevalent in patients with T2D than in the overall adult population.[25,26] Treating obesity can delay the progression of prediabetes to T2D, and is also beneficial in patients with T2D; a modest sustained weight loss of 3% to 5% is associated with improved glycemic control and tangible clinical benefit.[27,28]

Many glucose-lowering agents are known to affect body weight, and this factor should be considered when selecting a treatment plan in these patients. Metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with varying degrees of weight loss. Dipeptidyl peptidase-4 (DPP-4) inhibitors are weight neutral, and insulin secretagogues (sulfonylureas and meglitinides), thiazolidinediones, and insulin are associated with weight gain.[3] Primary care professionals should review patient medications with respect to comorbidities and wherever possible replace agents that are associated with weight gain with a suitable alternative.

Treatment of patients with obesity and T2D

Increased exercise or physical activity and reduced calorie intake, coupled with behavioral therapy, is recommended for patients with obesity and T2D, with the aim of achieving and maintaining a body weight reduction of ≥5%.[27] The primary goal is to achieve an energy deficit of 500 to 750 kcal/day, but plans should be tailored to account for the patient's other nutritional needs, and cultural or religious preferences. Once short-term weight loss goals have been achieved, ongoing monitoring of body weight should be encouraged. Long-term (≥1 year) weight maintenance programs are recommended when available, along with support and counseling, to prevent the patient from regaining weight after an initial success.

Four weight loss medications are currently approved by the US Food and Drug Administration (FDA) and can be considered as adjuncts to diet, physical activity, and behavioral counseling in patients with a BMI ≥27 kg/m^2.[27] Weight loss medication should be discontinued if weight loss is <5% after 3 months or if there are significant safety or tolerability issues at any time.[4]

Cardiovascular disease

Guidance from the ADA recognizes that both prediabetes and T2D are associated with a heightened risk of CVD.[23] A systematic review including more than 4.5 million adults with T2D showed that CVD and related complications are the leading cause of morbidity and mortality in patients with T2D, accounting for approximately half of all deaths.[29] Although intensive glucose-lowering has demonstrated benefits with regard to microvascular complications,[30] historically there has been little evidence of direct benefits with regard to macrovascular complications.[31] Position statements from the ADA have long emphasized the importance of prevention of CV complications while managing patients with T2D. In 2008, the FDA mandate required companies to rule out excess CV risk through meta-analyses of preregistration studies and prospective cardiovascular outcomes trials (CVOTs) statistically powered to evaluate CV risk in patients with T2D on all new glucose-lowering medications.[32] Several of these CVOTs subsequently identified unexpected cardioprotective benefits, as first demonstrated by the SGLT2 inhibitor empagliflozin in the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose) trial.[33] Since then, SGLT2 inhibitors have demonstrated beneficial effects on multiple key CV risk factors including HbA1c, body weight, blood pressure, blood lipids, renal function, and microalbuminuria.[34-36] Similarly, CVOTs with some GLP-1 RAs including liraglutide, semaglutide, and dulaglutide, have confirmed a reduction in major heart and vascular events,[37-39] but this effect was not seen in CVOTs with other GLP-1 RAs, such as exenatide and lixisenatide.[40,41] An umbrella review of glucose-lowering agents found that several agents, including glimepiride, rosiglitazone, and pioglitazone, were associated with increased risk of negative CV outcomes.[42]

Conversely, SGLT2 inhibitors and GLP-1 RAs as a class were both found to reduce the risk of adverse CV outcomes. In a network meta-analysis of 74,874 patients across 64 trials, empagliflozin and canagliflozin improved survival in patients with T2D, with empagliflozin being superior to the other SGLT2 inhibitors for all-cause and CV mortality reduction; dapagliflozin only reduced the risk of worsening HF, with an effect similar to that of canagliflozin and empagliflozin.[43] Consistent with these findings, a recent systematic review and network meta-analysis identified a 20% reduction in deaths with SGLT2 inhibitors compared with placebo or no treatment; GLP-1 RAs were associated with a 12% lower mortality, but no effect was observed for DPP-4 inhibitors.[44]

Treatment of patients with CVD

The ADA Standards of Care recommend that in patients with known ASCVD, ACE inhibitor or ARB therapy should be considered to reduce the risk of CV events. In patients with T2D in whom ASCVD predominates or who have multiple risk factors for ASCVD, an SGLT2 inhibitor or GLP-1 RA with a label indication for reducing CV events should be selected as part of their glucose-lowering treatment regimen unless contraindicated.[3] These recommendations are in line with those of the American College of Cardiology, which recommends SGLT2 inhibitors with proven cardiac benefit for the treatment of patients with ASCVD who are not suitable for treatment with metformin.[45]

Heart failure

Patients with T2D have up to a 74% increased risk of developing HF, and patients with T2D and HF are twice as likely to be hospitalized for HF and 4 times more likely to die than those without HF.[46] SGLT2 inhibitors have been associated with reduced rates of HF hospitalization in several recent CVOTs that included patients with T2D (most of whom also had ASCVD).[47] This reduction in the risk of HF hospitalization in patients with T2D receiving SGLT2 inhibitors has since been confirmed across a broader range of patients in real-world clinical practice.[48,49] Further, dedicated trials of dapagliflozin and empagliflozin in patients with HF and a reduced ejection fraction have also now demonstrated both kidney and mortality benefits, and these benefits are seen regardless of the presence or absence of diabetes.[50-52]

Treatment of patients with HF

Current ADA Standards of Care recommend that in patients with T2D and stable HF, metformin may be continued if estimated glomerular filtration rate (eGFR) remains >30 mL/min/1.73 m^2 but should be avoided in unstable or hospitalized patients.[23] In patients with T2D and established HF, an SGLT2 inhibitor may be considered to reduce risk of HF hospitalization as part of their glucose-lowering regimen, independent of their baseline HbA1C or target HbA1C.[23] Conversely, thiazolidinediones are associated with an increased risk of HF and should be avoided in patients with symptomatic HF.[23]

Chronic kidney disease

CKD is associated with a significantly increased risk of CV events, HF, and CV-related mortality, even in the absence of other comorbidities,[53] and is the leading cause of end-stage kidney disease (ESKD)[54] in the United States, with patients eventually requiring ongoing dialysis or a kidney transplant. An estimated 37% of patients with T2D will develop CKD secondary to T2D, known as diabetic kidney disease (DKD)[25]; more than half of these patients will go on to CKD stage 3 and 4, yet many are unaware of their kidney disease.[25] Glycemic control is beneficial in preventing CKD, and in established DKD can help to delay loss of kidney function in the long term.[3] However, the risk of hypoglycemia is also increased in this population[55,56] and therefore continuous glucose monitoring may be beneficial. Ideally, urinary albumin-to-creatinine ratio (UACR) and eGFR values should be obtained in a stable patient at the time of diagnosis of T2D and repeated at least yearly, regardless of treatment.[57] If the UACR is >30 mg/g and/or eGFR <60 mL/min/1.73 m^2, repeat testing in the following 2 months and subsequently at least twice a year should be performed to guide therapy.[4]

Some glucose-lowering drugs may require a dose reduction or are contraindicated in patients with impaired kidney function, and it is important to consider this when selecting a treatment plan for patients with T2D and CKD. In CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), a dedicated renal study, canagliflozin reduced the risk of renal events, with the most benefit seen in the lowest eGFR groups.[58] On the strength of these findings, the FDA has approved canagliflozin to slow the development of CKD in patients with T2D. Similarly, findings from another dedicated renal study, DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease), showed that dapagliflozin reduced the risk of worsening kidney function in patients with CKD with and without T2D.[59] Although there is evidence of similar renal benefits with empagliflozin based on analysis of EMPA-REG OUTCOME,[35] a dedicated renal study for this agent is still

underway (EMPA-KIDNEY, Empagliflozin Once Daily to Assess Cardio-Renal Outcomes in Patients with Chronic Kidney Disease; [NCT03594110]).

Treatment of patients with T2D and CKD

Current guidance from the ADA recommends that dyslipidemia and blood pressure control is optimized in patients with T2D to reduce the risk or slow the progression of CKD, in line with the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[60,61] If possible, UACR and eGFR values should be assessed at the time of diagnosis of T2D and repeated annually, regardless of treatment.[57] In patients in whom eGFR is <60 mL/min/1.73 m^2 or UACR is <30 mg/g, renal function should be assessed every 6 months, and their treatment plan revised as necessary.[57]

Metformin should not be initiated in patients with an eGFR <45 mL/min/1.73 m^2, and guidance from KDIGO recommends to reduce the dose of metformin in patients with an eGFR <45 mL/min/1.73 m^2;[62] metformin is contraindicated for use in patients with an eGFR <30 mL/min/1.73 m^2 and should be discontinued. Patients who are already on metformin and have an eGFR <45 mL/min/1.73 m^2 should be reassessed regularly in case eGFR declines. The ADA recommends that canagliflozin, empagliflozin, or dapagliflozin should be considered as part of the glucose-lowering regimen in patients with indicators of high risk or established CKD, independent of their HbA1c or target HbA1c, to reduce the risk of CKD progression and CV events.[4,57] SGLT2 inhibitors and GLP-1 RAs should be strongly considered for patients with T2D and CKD who require another drug added to metformin to attain target HbA1c or who cannot use or tolerate metformin.[4] Again, this guidance is in line with the current guidance from KDIGO,[62] which recommends that glycemic management for patients with T2D and CKD should include first-line treatment with metformin and an SGLT2 inhibitor in addition to lifestyle therapy, with additional drug therapy as needed for glycemic control.

Giving patients a voice

As with any chronic condition that requires ongoing treatment, patient adherence is vital to the success of any treatment plan; any treatment can work only for as long as the patient continues to take it. Asking for the patient's input during the selection of treatment can help meet their goals, which may not always exactly align with those of the provider, and thus increase treatment adherence and persistence. Further, as T2D is a condition in which failure to regularly take medication may not result in any immediately obvious effect, patient education is also an important step to encourage patients to take any medications as directed. This education may include what the patient might expect from the medication in terms of glucose reductions, nonglycemic effects, and side effects so that they are aware and know what to look for.

CONCLUSIONS

With the ever-increasing number of treatment options available, primary care professionals may find the sheer volume of information overwhelming, but the only incorrect action is doing nothing. T2D is a progressive disease, and it is important to stay on top of T2D early and adjust treatment often; good glycemic control can result in long-term beneficial effects on T2D complications that persist even during periods of subsequent poorer metabolic control, often described as a legacy effect.[13,63] The goal should be to identify relevant comorbidities early in the patient journey, and monitor for progression of existing comorbidities at regular intervals thereafter as recommended. Any treatment plan for patients with T2D should include treatment of comorbidities when present, and the choice of treatments for glycemic control and selection of treatment targets should consider the presence of such comorbidities. ●

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A Whole-Patient Approach

to medication selection for patients with T2D

Review previous/existing treatments and risk factor control

7.0% A generally appropriate target A1c for nonpregnant adults

6.5% A more stringent target may be preferred when it can be achieved safely

8.0% Consider less stringent targets when patients have significant comorbidities, limited life expectancy, or are at risk of severe hypoglycemia

Ⓜ **Metformin** is the preferred initial agent for the treatment of T2D; continue for as long as tolerated

Additional agents should be added as required to maintain glycemic control, and should be selected based on a **patient-centered approach**

- **Comorbidities**
- **Hypoglycemia**
- **Body weight**
- **Side effects**
- **Cost**
- **Patient preference**

Does your patient have CVD?

PATIENTS WITH KNOWN ASCVD

Ⓐ Consider **ACE inhibitor or ARB** therapy for patients with hypertension to reduce the risk of CV events

PATIENTS WITH ESTABLISHED ASCVD OR MULTIPLE ASCVD RISK FACTORS

Ⓢ Ⓖ An **SGLT2 inhibitor or GLP-1 RA** with demonstrated CV benefit is recommended

Does your patient have HF?

Ⓜ Avoid **metformin** in unstable HF or hospitalized patients

Ⓢ In established HF, an **SGLT2 inhibitor** may reduce risk of HF hospitalization as part of the patient's glucose-lowering regimen

Ⓣ Avoid **thiazolidinediones** for patients with symptomatic HF

Treatments by drug class

Ⓜ **Metformin** ($4/mo)

Ⓘ **Insulin** ($25+/mo)

Ⓢ **SGLT2 inhibitors***
- Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

Ⓖ **GLP-1 RA***
- For weight loss, semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- Dulaglutide, liraglutide, and semaglutide have associated CV benefits

Ⓢu **SUs**
- Later generation SUs are recommended to reduce the risk of hypoglycemia
- Glimepiride, glipizide ($4/mo)

Ⓣ **Thiazolidinediones**
- Pioglitazone ($11/mo)

ⓐ **α-Glucosidase inhibitor**
- Acarbose ($19/mo)

*Drug costs for all GLP-1RAs and SGLT2 inhibitors are estimated at more than $100/mo and in some cases may be more than $1000/mo

Does your patient have CKD?

- Optimize blood pressure and glycemic control to reduce the risk or slow the progression of CKD

eGFR (mL/min/1.73 m²)

75

60 — **ACE inhibitor or ARB** is recommended for patients with hypertension

45 — Ⓜ Reassess treatment with **metformin**

Ⓢ Consider **SGLT2 inhibitors** to reduce risk of CKD progression, CV events, or both

30 — Ⓜ **Metformin** is contraindicated

Refer patients to a nephrologist if eGFR <30 mL/min/1.73 m², if there are difficult management issues, or rapidly progressing kidney disease

15

Ⓖ In patients at increased risk for CV events, a **GLP-1 RA** may reduce risk of progression of albuminuria, CV events, or both

Does your patient have a high BMI?

- High-intensity interventions (diet/physical activity/behavioral therapy) to achieve and maintain **7% weight loss** are recommended, with long-term weight maintenance support for patients who achieve weight loss goals

Patient BMI	Patient BMI cut-off for Asian Americans
40 kg/m²	37.5 kg/m²

Metabolic surgery recommended when patients cannot achieve durable weight loss and improvement in comorbidities with nonsurgical methods

35 kg/m²	32.5 kg/m²

Consider metabolic surgery when patients do not achieve durable weight loss/improvement in comorbidities with nonsurgical methods

30 kg/m²	27.5 kg/m²

Consider weight loss medications, but evaluate potential benefits vs potential risks

27 kg/m²

- Consider the effect on weight when selecting glucose-lowering medications

WEIGHT LOSS Ⓜ Ⓢ Ⓖ ⓐ → Metformin, SGLT2 inhibitors, GLP-1 RA, α-glucosidase inhibitors

WEIGHT NEUTRAL Ⓓ → DPP-4 inhibitors

WEIGHT GAIN Ⓘ Ⓣ Ⓢu → Insulin secretagogues, thiazolidinediones, SUs, insulin

ABBREVIATIONS
A1c, glycated hemoglobin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium-glucose co-transporter 2; SU, sulfonylurea; T2D, type 2 diabetes

Guidance based on the *Standards of Medical Care in Diabetes*—2020 Abridged for Primary Care Providers. American Diabetes Association. *Clin Diabetes*. 2020;38:10-38.

All drug prices were taken from GoodRx. Available at: https://www.goodrx.com/

CHAPTER 2

A Practical Approach to Managing Kidney Disease in Type 2 Diabetes

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INTRODUCTION

Chronic kidney disease (CKD) is a common comorbidity that will develop in about 40% of patients with type 2 diabetes (T2D).[1] In fact, diabetes is the leading cause of dialysis or kidney transplantation in the United States.[2] Furthermore, for all patients with CKD, the mortality risk in CKD from cardiovascular (CV) complications is 10-fold greater than reaching end-stage kidney disease (ESKD).[3] CKD is defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or urine albumin excretion of >30 mg/24 hours or a urinary albumin-to-creatinine ratio (UACR) >30 mg/g that is present for >3 months.[4,5] The standard classification of CKD stages by KDIGO (Kidney Disease: Improving Global Outcomes) is based on eGFR level and degree of albuminuria (**FIGURE**).[4] However, CKD is frequently unrecognized, and patients with CKD are often unaware of their condition.[2] Among patients with CKD stages 3 and 4 between 2013-2014, reported awareness of disease was only 12.4%, and varied by eGFR (5.9%, 21.4%, and 57.3% for eGFR 45-59, 30-44, and 15-29 mL/min/1.73 m^2, respectively). In patients with diabetes and moderate to severe CKD (stage 3 or 4), awareness is also low; 24.9% are aware of their kidney disease.[6]

During the course of CKD, the eGFR loss per year ranges from 2 to 5 mL/min/1.73 m^2, depending on the CKD stage, degree of albuminuria, as well as control of glycemia, hypertension, and other factors (such as cigarette smoking and obesity).[4] This is an important consideration in view of the much slower decline of up to 0.8 mL/min/1.73 m^2 associated with normal aging.[7] The main driving forces in the development and progression of CKD are hyperfiltration and glomerular hypertension secondary to multiple factors: metabolic (hyperglycemia, hyperinsulinemia), hemodynamic (hypertension, renin-angiotensin-aldosterone system [RAAS] activation) and subsequently albuminuria, inflammation, and fibrosis.[8,9] Importantly, treatment to reduce albuminuria has been shown to be associated with subsequent renoprotection, irrespective of the drug class used. A meta-analysis of clinical trials of drug effects on albuminuria and ESKD showed that each 30% reduction in albuminuria was associated with a 23.7% reduction in ESKD risk.[10]

CKD secondary to microvascular changes associated with diabetes is referred to as diabetic kidney disease (DKD). Also, patients with T2D can have concurrent CKD caused by other conditions, such as hypertension, heart failure (HF), obesity, polycystic kidney disease, and glomerulopathies, as well as systemic conditions, such as systemic lupus erythematosus. Patients with DKD generally present with long-standing T2D, retinopathy, albuminuria

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FIGURE **Albuminuria and eGFR categories used to define CKD[4]**

eGFR categories (mL/min/1.73 m²)				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g (<3 mg/mmol)	30-300 mg/g (3-30 mg/mmol)	>300 mg/g (>30 mg/mmol)
	G1	Normal to high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Risk for progression, morbidity, and mortality

Low risk | Moderately increased risk | High risk | Very high risk

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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without gross hematuria, and gradually progressive eGFR loss.[5] The presence of albuminuria >30 mg/g is a sign of endothelial dysfunction and a risk factor for (1) CV events, doubling the risk of CV death and (2) CKD progression and macroalbuminuria (>300 mg/g), especially when hypertension, hyperglycemia, obesity, and dyslipidemia are not well controlled.[11]

The clinical course of CKD in patients with diabetes has changed over recent decades, and GFR decline can be observed before the development of albuminuria, or can occur in the absence of albuminuria.[12] Reduced GFR in the absence of albuminuria in T2D is associated with a lower but still significant risk of ESKD, CKD progression, or rapid decline in GFR compared with patients with albuminuria.[13] More than one-third of patients with T2D and eGFR <60 mL/min/1.73 m² have been reported to have no albuminuria, and this prevalence is growing.[14] Data from the National Health and Nutrition Examination Surveys (1988–2014) showed that the prevalence of albuminuria has decreased over time in parallel with an increase in the prevalence of reduced eGFR.[12] This change in phenotype may be attributable to higher proportions of adults taking glucose-lowering medications, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs), and statins.

RISK FACTORS FOR DKD

The 2 most important risk factors for DKD are uncontrolled hyperglycemia and hypertension.[8] In addition, the risk can be increased by modifiable factors such as obesity, smoking, physical inactivity, and a high-protein diet (>1.2 g/kg per day), in addition to nonmodifiable factors including age, race, and family history of CKD/ESKD.[15]

Hyperglycemia

In the absence of hyperglycemia, DKD will not develop.[9] The presence of hyperglycemia causes hyperfiltration (defined as eGFR >125 mL/min/1.73 m²), glomerular hypertension, and secondary structural renal abnormalities, including basement membrane thickening, podocyte injury, glomerular sclerosis, and interstitial fibrosis.[15] In addition, several cellular mechanisms contribute to renal injury, including the accumulation of advanced glycation products, profibrotic cytokines such as transforming growth factor-beta, and the production of reactive oxidative species.[9,16]

It is often not recognized that thickening of the glomerular basement membrane occurs shortly after the onset of T2D.[16] Therefore, early attainment of glycemic control is important, and the general goal for glycated hemoglobin (HbA1c) is from <6.5% to <8.0%.[4] If tolerated without hypoglycemia, an HbA1c target of <6.5% is

preferred in DKD to reduce the risk of further progression. These goals need to be individualized for life expectancy, extent of comorbidities, duration of diabetes, and other clinical considerations.[5] In some studies in which tight glycemic control (HbA1c ≤6.0%) in T2D was compared with a standard of ~7.3%, no differences in eGFR decline were shown between groups, although an increase in hypoglycemia and mortality was noted among patients with CKD.[17,18] Subsequent long-term studies (such as Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE]-ON[19]) showed glycemic control (HbA1c target ≤6.5%; median trial HbA1c 7.2%) was associated with a reduced risk of ESKD. However, in T2D a slowing of eGFR decline with intensive glycemic control is not seen for at least 2 years.[5] For patients with DKD, the risk of hypoglycemia is increased as a result of reduced renal gluconeogenesis, decreased renal and peripheral metabolism of insulin (up to 40%), and often reduced caloric intake.[20,21] This highlights the role of continuous glucose monitoring in this population for detecting hypoglycemia unawareness, as well as the importance of selecting glucose-lowering therapies with a low risk of hypoglycemia.

Hypertension

After diabetes, hypertension is the second most common cause of CKD and ESKD.[22] ACE inhibitors or ARBs are drugs of choice for patients with hypertension and albuminuric DKD.[5] In addition to the reduction of CV events,[5] the renal risk reduction (defined as a doubling of creatinine, ESKD, or renal death) is between 16% and 20% for these agents.[23,24] Importantly, both drug classes potently lower albuminuria and the associated risk of ESKD.[5] However, treatment with a combination of ACE inhibitors and ARBs should be avoided due to the increased risk of adverse events.[25] Guidelines from the American Diabetes Association (ADA) recommend a target of <130/80 mm Hg for patients with DKD with albuminuria >300 mg/g and <140/90 mm Hg for all other patients, with individual goals guided by the tolerability of therapy.[5,26]

For patients who require treatment with an ACE inhibitor or ARB, creatinine and potassium levels should be monitored for 2 to 4 weeks after initiation.[5] However, these drugs should **not** be discontinued due to a rise in creatinine levels, unless the increase exceeds 30%.[5] The increase in creatinine is secondary to a renal hemodynamic effect and does **not** signify renal toxicity. Stopping RAAS blockade in CKD increases vascular events and the risk of ESKD. Volume depletion should be corrected before initiation of ACE inhibitors or ARBs, especially with concomitant diuretic therapy.[5] Because ACE inhibitors are excreted renally, dose reduction is required in patients with an eGFR <30 mL/min/1.73 m^2. In contrast, ARBs are excreted hepatically and do not require dose adjustment in patients with CKD. Importantly, concomitant use of nonsteroidal anti-inflammatory drug (NSAID) therapy reduces the effectiveness of all antihypertensive drugs except for calcium channel blockers (CCBs). Furthermore, NSAIDs are not recommended for chronic therapy in patients with CKD due to their potential nephrotoxicity.[27] Nonetheless, in the United States, the reported use of both prescribed and over-the-counter NSAIDs is common in patients with CKD.[28]

More than 80% of patients with CKD require combination therapy to achieve blood pressure control.[29] CKD is associated with sodium retention and volume expansion which, depending on severity, may be reduced by diuresis associated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, thiazides, or loop diuretics. The efficacy of thiazides declines greatly when eGFR is <30 mL/min/1.73 m^2, requiring the use of loop diuretics (such as furosemide).[30] CCBs (such as amlodipine) are suitable for administration with ACE inhibitors and ARBs, with no need for dose adjustment based on kidney function due to their hepatic metabolism.[31] Mineralocorticoid antagonists—spironolactone and eplerenone—are indicated in HF treatment; they are potent antihypertensive drugs, especially in resistant hypertension, and they reduce albuminuria.[32] The risk of hyperkalemia is high when these agents are used in combination with an ACE inhibitor/ARB or NSAID in patients with CKD. NSAID use is not recommended for patients with eGFR levels <60 mL/min/1.73 m^2 because of a risk of acute kidney injury and CKD progression.[4]

Obesity

In the United States, the prevalence of obesity (body mass index [BMI] ≥30 kg/m^2) has increased to 42.5% in the adult population.[33] In individuals with T2D, the prevalence of overweight and obesity (BMI ≥25 kg/m^2) is almost twice as high, at about 89%.[34] Increased BMI has a substantial impact on the risk of CKD, which is increased by 3.5-fold in obese patients.[35] Mechanisms underlying the association of obesity and increased risk of CKD include hyperfiltration, insulin resistance, the presence of a chronic inflammatory state, activation of the RAAS and sympathetic nervous system, and increased sodium reabsorption, which can counteract the effects of antihypertensive drug therapy and thus contribute to refractory hypertension.[36,37] Obesity also causes glomerular hypertrophy, and extra- and intrarenal fat deposition (fatty kidney disease).

The importance of weight loss in patients with obesity (defined in this study as BMI >30 kg/m^2) is underlined by the observation that this can reduce albuminuria, improve hypertension, and slow CKD progression.[36]

Dyslipidemia

Although treatment of elevated levels of low-density lipoprotein (LDL) and triglycerides has not been shown to slow the progression of CKD,[38] it is an important consideration for lowering the risk of CV events in a high-risk population in which CKD, diabetes, hypertension, dyslipidemia, and obesity frequently coexist.[39] Statins reduce the risk of CV events, including in patients with CKD, although the stage of CKD modifies treatment efficacy; statins have not been shown to be effective in patients on dialysis or among kidney transplant recipients.[40] KDIGO Clinical Practice Guidelines recommend statin therapy for patients with CKD (eGFR <60 mL/min/1.73 m^2) and diabetes aged 18-49 years, with the addition of ezetimibe for patients aged ≥50 years.[41] Similarly, the ADA guidelines recommend a combination of statin/ezetimibe therapy for adults with a 10-year CV risk of ≥20%.[42] Hypertriglyceridemia (defined as levels >150 mg/dL) is common in insulin resistance states such as obesity, metabolic syndrome, diabetes, and CKD.[43] In patients with DKD and triglyceride levels ≥135 mg/dL, icosapent ethyl therapy in addition to weight loss should be considered when LDL levels are controlled with statin therapy.[42]

Age

Individuals older than 40 years have a linear decline in eGFR of 0.8 mL/min/1.73 m^2 per year in the absence of any disease secondary to senescence of nephrons and nephrosclerosis.[7]

Smoking

Smoking is a well-established major CV risk factor. Cessation is strongly advised for patients with T2D, with or without CKD. Population studies have shown a higher incidence of albuminuria and CKD among smokers[44] (and individuals exposed to second-hand smoke).

CARDIOVASCULAR RISK OF CKD

Declining eGFR and albuminuria are independent risk factors for CV events and HF, even in the absence of other comorbidities,[45,46] and importantly DKD represents an even greater risk than CKD per se due to coexisting macrovascular arterial disease in T2D. The greatly increased risk of CV disease among patients with CKD can be seen in data from 5% of the Medicare population (CV disease prevalence was 64.5% among patients aged ≥66 years with CKD vs 32.4% among those without CKD), this increased CV risk persists across the spectrum of CV disease.[45] CKD is also associated with an increased risk of all-cause mortality. Albuminuria is also associated with a risk of HF, with a doubling of the risk of HF events with microalbuminuria, and triple the risk with macroalbuminuria.[47] Data from 10,640 patients with T2D in the ADVANCE study showed the risk of CV events was increased 2.2-fold among patients with a 50% loss of eGFR, and 3.2-fold among patients with both eGFR <60 mL/min/1.73 m^2 and UACR >300 mg/g.[48] The reason that CKD per se represents such a strong risk for CV events, including HF, is not fully understood.

In addition to the traditional risk factors of declining eGFR and albuminuria, the list of nontraditional risk factors for CV disease in CKD is extensive, and includes oxidative stress (including LDL oxidation), endothelial dysfunction, chronic inflammatory state, activation of RAAS and the sympathetic nervous system, accumulation of "uremic" toxins, and many others.[49]

In summary, the combination of a reduced eGFR and albuminuria is a multiplier of increased risk of CKD progression, CV events, and HF, albeit each is an independent risk factor. Managing the multiple comorbidities associated with CKD is an ideal role for primary care clinicians who are experienced in looking at the patient as a whole. Using medications that address multiple risk factors simplifies the CKD treatment regimen, and patients would likely benefit from this multifaceted approach.

THERAPEUTIC CONSIDERATIONS IN DKD

Selection of glucose-lowering drugs

Many glucose-lowering drugs require dose reduction or are contraindicated in patients with CKD, depending on the disease stage. It is beyond the scope of this review to discuss all glucose-lowering therapies, though the most commonly prescribed drugs are considered in **TABLE 1**.

When choosing a glucose-lowering agent, clinicians should consider evidence-based benefits reflected in clinical management guidelines from the ADA 2020,[26] American Association of Clinical Endocrinologists (AACE),[51] and KDIGO guidelines[4,52] that specify therapy that addresses multiple comorbidities. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and SGLT2 inhibitors, when added to standard-of-care therapy with ACE inhibitors or ARBs, have shown substantial benefits in CV outcomes in CKD (as described below) that are independent of glucose lowering, with a low risk of hypoglycemia, and have now changed the paradigm of diabetes care. The 2020 ADA recommendation states that SGLT2 inhibitors (canagliflozin, empagliflozin,

TABLE 1 **Use of glucose-lowering therapies in CKD**

Metformin

- Not to be initiated at eGFR level <45 mL/min/1.73 m^2.[5]
- In long-term therapy, dose should be reduced to 1000 mg/d.
- Benefits and risks should be reassessed frequently.
- Treatment should be discontinued if eGFR <30 mL/min/1.73 m^2.

Sulfonylureas

- Except for glipizide, all other drugs in this class accumulate with eGFR <45 mL/min/1.73 m^2.
- Dose reduction or discontinuation is required at eGFR levels <30 mL/min/1.73 m^2.[50]

DPP-4 inhibitors

- Dose adjustments are required in patients with eGFR <45 mL/min/1.73 m^2 for all DPP-4 inhibitors, except linagliptin.[a]
- Linagliptin is largely excreted hepatically; no dose modification is required.[51]

SGLT2 inhibitors

- In DKD, SGLT2 inhibitors are the drugs of choice after (or potentially before) metformin in patients with eGFR ≥30 mL/min/1.73 m^2.[26]
- Risk of CKD progression and albuminuria reduced with SGLT2 inhibitor therapy.[5]
- Dose adjustment required in CKD (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin).[26]

GLP-1 RAs

- GLP-1 RAs have direct positive renal effects, compared with placebo, with a reduction of albuminuria shown in large clinical trials.[5]
- No hard outcome data in DKD exist (pending outcome of ongoing trial with semaglutide, NCT03819153).
- Exenatide should not be used at eGFR levels <30 mL/min/1.73 m^2.
- All other agents may be used with dose reductions at eGFR <30 mL/min/1.73 m^2 (limited published data).

Insulin

- Patients may require a reduced dose depending on kidney function.

Abbreviations: CKD, chronic kidney disease; DKD, diabetic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter 2.

[a]Please consult prescribing information of individual drugs for additional details on dosing in CKD.

dapagliflozin) have been shown to reduce the risk of CKD progression and CV events, and should be strongly considered in patients with DKD who have not met their individual glycemic goals.[26] Specifically the use of an SGLT2 inhibitor should be considered in patients with eGFR ≥30 mL/min/1.73 m^2 and urinary albumin >30 mg/g, particularly in patients with urinary albumin >300 mg/g (evidence level A, ie, based on evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered). In patients with CKD who are at increased risk for CV events, use of a GLP-1 RA may reduce risk of progression of albuminuria, CV events, or both (evidence level C, ie, based on poorly controlled/uncontrolled studies).[5] In this context, the newly released KDIGO guidelines for the management of CKD in T2D now recommend combination therapy with metformin and an SGLT2 inhibitor if eGFR is ≥30 mL/min (regardless of albuminuria); GLP-1 RAs may also be used.[52]

Although recent research on the long-term outcomes of glucose-lowering therapies has largely focused on CV outcomes, 2 dedicated renal outcomes trials have been completed. These trials have further evaluated the findings of 3 cardiovascular outcomes trials (CVOTs) in which secondary and exploratory analyses showed an association with SGLT2 inhibition and improved renal outcomes, although these CVOTs generally included participants at low risk for ESKD.[53-55] The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial evaluated participants with T2D and albuminuria >300 mg/g and DKD (average eGFR was 57 mL/min/1.73 m^2 [range 30-90] and UACR ~900 mg/g). The composite endpoint (doubling creatinine, ESKD, or

TABLE 2 **Nonpharmacologic management of DKD and its complications**[4,41]

- KDIGO states "Patients with Diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts, and lower in processed meats, refined carbohydrates, and sweetened beverages"[52]
  - Protein intake of 0.8 g/kg per day is recommended for patients with DKD
  - Sodium intake of <2 g (<5 g salt) is advised to reduce risks of hypertension and CV events
  - Use of potassium-containing salt substitutes should be avoided due to risk of hyperkalemia (usually when eGFR <30 mL/min/1.73 m^2 and with RAAS blockade)
- All patients with T2D and renal disease should meet with a diabetes educator to review diet recommendations
- Moderate-intensity physical activity (brisk walking, swimming, biking, yoga) is encouraged for a minimum of 150 minutes per week

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RAAS, renin-angiotensin-aldosterone system; T2D, type 2 diabetes.

CV death) was reduced by 30%. Among 1000 patients in the trial treated for 2.5 years, the primary composite outcome would occur in 47 fewer patients in the canagliflozin group than in the placebo group; number needed to treat (NNT), 22; 95% CI, 15-38. In addition, the composites of CV death or HF admission were reduced by 31% (canagliflozin would prevent 25 composite events of CV death, myocardial infarction, or stroke; NNT, 40; 95% CI, 23-165; and 22 HF admissions; NNT, 46; 95% CI, 29-124).[56] These effects were independent of glucose lowering, and below an eGFR of 45 mL/min/1.73 m^2 there is declining effectiveness of SGLT2 inhibitors in reducing HbA1c while effects on cardiac and renal outcomes are preserved. As a result of these findings, canagliflozin has been approved in DKD to reduce the risk of ESKD and worsening of kidney function, CV death, and HF admission for patients with an eGFR as low as 30 mL/min/1.73 m^2 and albuminuria ≥300 mg/g. More recently, the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) in patients with and without T2D and CKD (eGFR ≥25 to <75 mL/min/1.73 m^2 and UACR 200–5000 mg/g) has shown that dapagliflozin reduces the risk of kidney failure and death regardless of the presence of T2D.[57] This international trial of 4304 participants with CKD, with or without T2D, showed a 39% reduction in the primary endpoint of a composite of worsening of renal function or risk of death (defined as ≥50% sustained decline in eGFR, onset of ESKD, or CV or renal death) in patients who received dapagliflozin vs placebo. The DAPA-CKD trial also showed a significant reduction in the risk of hospitalization for HF, CV death, or death from any cause in this patient population.

The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) has investigated the long-term effects of empagliflozin on CV and kidney outcomes in patients with HF, with or without diabetes.[58] The composite renal outcome (chronic dialysis or renal transplantation or a sustained reduction of ≥40% in eGFR or a profound sustained reduction in eGFR) was reduced by 50% in patients who received empagliflozin vs placebo in addition to standard of care. Another trial of empagliflozin, the ongoing Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY, NCT03594110) is evaluating the effects of empagliflozin on kidney disease progression or CV death in participants with CKD irrespective of albuminuria levels following the observation of a slowing of kidney disease progression in a prespecified secondary analysis of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removal of Excess Glucose (EMPA-REG OUTCOME) trial.[59] EMPA-KIDNEY will enroll around 6000 participants with CKD, with or without diabetes, (eGFR ≥45 to <75 mL/min/1.73 m^2 and UACR ≥200 mg/g or eGFR ≥20 to <45 mL/min/1.73 m^2).

At the start of all SGLT2 inhibitor therapy, an eGFR decline of about 5 mL/min should be expected. This decrease occurs in patients with or without T2D and is secondary to hemodynamic reduction of intraglomerular pressure, and over the following 3 months the eGFR tends to return to baseline.

Complications and treatment of CKD

In addition to selecting glucose-lowering therapies for management of hyperglycemia and improvement of cardiorenal outcomes in DKD, the other complications associated with CKD, such as anemia, mineral and bone disorders, and fluid and electrolyte abnormalities, need to be addressed. The development of complications can be reduced by pharmacotherapy as well as dietary interventions (**TABLE 2**).[60] The management of the complications

TABLE 3 **When to refer to a nephrologist**[4]

- Acute kidney injury (loss of >50% eGFR over 2 days)
- Albuminuria >300 mg/g (UACR)
- CKD progression
  - >5-mL loss per year or change in stage
  - eGFR <30 mL/min/1.73 m^2
- Active sediment: red cell cast, white blood cells in urine due to infection
- Resistant hypertension: not at goal on 3 drugs (CCB, RAAS inhibitor, diuretic)
- Recurrent nephrolithiasis (≥2 episodes)
- Hyperkalemia (persistent serum potassium >5.6 mEq/L)
- Hereditary kidney disease (polycystic kidney disease)

Abbreviations: CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-to-creatinine ratio.

of CKD can be complex and should occur in consultation with or by referral to a nephrologist (**TABLE 3**).

Metabolic acidosis, defined as a serum bicarbonate level of <22 mEq/L (with normal lung function) is common in CKD, especially in patients with an eGFR of <45 mL/min/1.73 m^2, and can lead to adverse effects including accelerated renal function loss, bone disease, decreased albumin and muscle protein synthesis, insulin resistance, and RAAS activation.[61] Chronic metabolic acidosis has also been shown to contribute to chronic inflammation, the progression of CKD, and the development of CV disease.[61] To reduce the development of complications, therapeutic options include sodium bicarbonate (650 mg tablets twice daily) initially. The extra sodium load needs to be considered, but sodium bicarbonate causes less salt retention and hypertension than sodium chloride (the mechanism is unclear).[61] In addition, the consumption of fresh fruit and vegetables is an underutilized approach that will raise bicarbonate levels provided potassium levels remain controlled (<5.0 mEq/L).

Anemia (defined by the World Health Organization as a hemoglobin level of <13.0 g/dL in adults and <12.0 g/dL in premenopausal women) occurs earlier and is more severe in DKD compared with other CKD (alone).[62] Among patients with diabetes, the prevalence of anemia (hemoglobin <12.0 g/dL) has been estimated to be 22.2% in patients with eGFR <60 mL/min/1.73 m^2 and 52.4% for an eGFR <30 to 60 mL/min/1.73 m^2.[63] Although the pathogenesis of anemia in CKD is complex, it centers on a relative deficit of erythropoietin and on iron deficiency.[62] The evaluation of anemia includes a complete blood count, reticulocyte count, serum iron levels, ferritin, transferrin saturation, vitamin B12 and folate levels, and assessment of thyroid function. B12 levels can be lowered by both metformin and proton pump inhibitors,[64] which are commonly used in patients with T2D who have multiple comorbidities. Depending on the severity of iron deficiency, oral or intravenous therapy can be initiated. Iron therapy should be reassessed at a ferritin level of >500 µg/L and stopped at 800 µg/L.[65] Referral to a nephrologist might be required for intravenous iron therapy and initiation of erythropoiesis-stimulating agents, although this can frequently be managed in the primary care setting.[66]

Hyperphosphatemia (phosphate levels >4.5 mg/dL) typically occurs in patients with an eGFR <45 mL/min/1.73 m^2 and represents an imbalance between oral phosphate intake and reduced renal excretory capacity. Hyperphosphatemia is associated with increased all-cause mortality, thus treatment is advised.[67] Before starting phosphate-binding medications, patients should be advised to reduce their intake of phosphate-rich foods, such as dairy products and animal proteins (chicken, turkey, processed foods). Although many drugs contain phosphate, they seldom need to be stopped. Phosphate-lowering therapy should not be initiated to prevent elevated phosphate levels, and should be started only when hyperphosphatemia is persistent. Multiple oral phosphate binders are available; of these options, ferric citrate is not only an effective phosphate binder but also improves iron status.

Like hyperphosphatemia, hypercalcemia (calcium levels >10.5 mg/dL) is associated with increased mortality in CKD.[68] Hypercalcemia can occur in patients with CKD due to vitamin D excess, use of calcium-containing phosphate binders, or elevated parathyroid hormone (PTH) levels.[60] Although there is no agreed ideal PTH level in CKD, mild elevations are considered appropriate in CKD. Complex interactions between vitamin D, serum calcium, phosphate, and PTH require attention, and the

involvement of a nephrologist or endocrinologist in the evaluation is recommended.

THE ROLE OF PRIMARY CARE CLINICIANS IN MANAGING DKD

Because CKD is frequently unrecognized,[1] primary care clinicians have a key role in the identification of CKD among their patients. While the US Preventive Services Task Force[69] has concluded that the evidence is insufficient for CKD screening in asymptomatic individuals, multiple guidelines recommend that clinicians should screen patients with risk factors such as diabetes, hypertension, age >60 years, obesity, low birth weight, CV disease, or other CKD risk factors (eg, family history of kidney failure).[52,70,71] When the diagnosis of T2D is established, serum creatinine, eGFR, and spot UACR should be measured (for patients on ACE inhibitors/ARBs or diuretics, serum potassium should also be monitored).[5] The ADA recommends monitoring of eGFR and UACR levels at least annually; patients with urinary albumin >30 mg/g and/or eGFR <60 mL/min/1.73 m^2 should be monitored at least twice annually.[5]

Primary care clinicians manage most patients with T2D in the United States and can play a substantial role in decreasing the morbidity and mortality of DKD. By considering the whole patient, primary care clinicians are uniquely placed to manage the CV, metabolic, and kidney risk factors in their patients with T2D.

As a result of the paradigm shift in T2D management in recent years, treatment options for reducing the morbidity, mortality, and expense associated with ESKD have finally broadened beyond ACE inhibitor and ARB therapy. Selection of glucose-lowering therapies and organ protective treatments that address multiple comorbidities is advised, in particular SGLT2 inhibitors, shown to slow the progression of DKD CV events. GLP-1 RAs have so far been shown to only reduce albuminuria; importantly, both GLP-1 RAs and SGLT2 inhibitors improve CV outcomes for patients with DKD.[5] The time has come for primary care to work with patients upstream to help stem the flood of DKD-related morbidity and mortality. ●

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CKD Evaluation and Management in patients with T2D

Identify risk factors for development and progression of CKD in T2D[1]

Non-modifiable

DEMOGRAPHIC
- Older age
- Race/ethnicity (Black, American Indian, Hispanic, Asian/Pacific Islanders)

HEREDITARY
- Family history of CKD
- Genetic kidney disease

Modifiable

SYSTEMIC FACTORS
- Hyperglycemia
- Hypertension
- Obesity

KIDNEY INJURIES
- Acute kidney injury
- Smoking
- Toxins (including potential nephrotoxins, eg, NSAIDs)

When to screen?[2]

- At diagnosis of T2D
- Annually thereafter

Identify CKD in patients with T2D[2]

Present for >3 months

- eGFR <60 mL/min/1.73 m^2

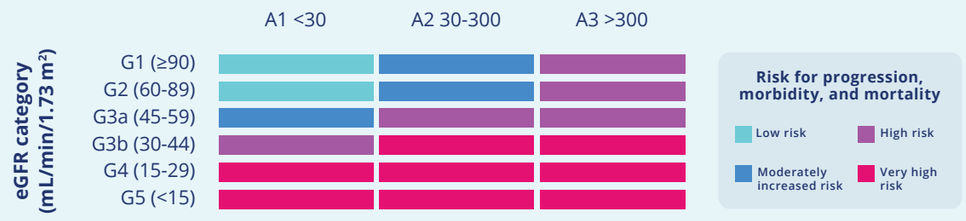
and/or

- Urine albumin excretion of >30 mg/24 hours

or

- UACR >30 mg/g

Determine CKD stage[3]



Monitor CKD in T2D[2]

- Monitor eGFR and urine albumin excretion at least annually
- Monitor twice annually if UACR >30 mg/g and/or eGFR <60 mL/min/1.73 m^2

Manage risk factors for progression[4,5]

- Lifestyle: smoking cessation, dietary modification, weight management
- Consider statins for lipid management (additional lipid-lowering therapy if LDL ≥70 mg/dL)
- BP <130/80 mm Hg; if appropriate ACEIs and ARBs are drugs of choice
- Hyperglycemia: A1c <6.5% to <8.0% (general goal); <8.0% (advanced CKD)

Select appropriate glucose-lowering therapies[5-7]

Metformin

- eGFR ≥45 mL/min/1.73 m^2 — *Continue treatment*
- eGFR 30–44 mL/min/1.73 m^2 — *Reduce dose*
- eGFR <30 mL/min/1.73 m^2 — *Discontinue*

Consider independently of A1c if CKD predominates + SGLT2 inhibitor (preferred*)

- eGFR 30–60 mL/min/1.73 m^2 or UACR >30 mg/g, particularly UACR >300 mg/g — *Initiate treatment*
- eGFR <30 mL/min/1.73 m^2 — *Discontinue or do not initiate*

+/- GLP-1 RA†

- If SGLT2 inhibitor not tolerated or contraindicated, or if eGFR not adequate
  If A1c above target, and patient on SGLT2 inhibitor, consider adding
- eGFR <60 mL/min/1.73 m^2 — *No adjustment required (dulaglutide, liraglutide, or semaglutide)*
- ESKD — *Limited experience with use*

*SGLT2 inhibitor with evidence of reducing CKD progression
†GLP-1 RA with proven CVD benefit[6]

Manage complications in consultation with nephrologist[8]

- Hyperkalemia
- Metabolic acidosis
- Vitamin D deficiency
- Hyperphosphatemia
- Secondary hyperparathyroidism
- Anemia

When to consider nephrologist referral

- Uncertainty about CKD etiology
- Management challenges (eg, anemia, secondary hyperparathyroidism, metabolic bone disease, resistant hypertension, electrolyte disturbances)
- Advanced CKD (eGFR <30 mL/min/1.73 m^2) with possibility of renal replacement therapy[2]

ABBREVIATIONS

A1c, glycated hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GI, gastrointes tinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio

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CHAPTER 3

Heart Failure in Patients with Type 2 Diabetes

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INTRODUCTION

In people with type 2 diabetes (T2D), heart failure (HF) has a prevalence of approximately 10% to 15%.[1,2] The continued growth in the prevalence of diabetes, combined with an aging population, is resulting in an epidemic of diabetes-associated HF. Overall, an estimated 34.1 million (13%) adults in the United States have diabetes,[3] 90% to 95% of whom have T2D.[4,5] Not only does the presence of T2D increase the risk of developing HF compared to those without T2D, which we detail below, but patients with concurrent HF and diabetes experience worse cardiovascular (CV) outcomes, higher risk of hospitalization, and a poorer prognosis than patients with HF but without diabetes.[2]

The increased risk of HF associated with T2D has been identified in numerous observational studies. For example, in the late 1970s, the Framingham Heart Study identified a link between diabetes and the risk of HF.[6] The presence of diabetes was associated with an approximately 2- to 5-fold increase in the incidence of HF, and was particularly marked among women (average annual age-adjusted incidence of HF per 1000 patients: 7.6 among men with diabetes vs 3.5 for men without diabetes; corresponding figures for women were 11.4 and 2.2, respectively). The Reykjavik study recruited a population-based cohort between 1967 and 1997 that was followed until 2002, and demonstrated a strong association between any glucometabolic abnormality and the occurrence of HF.[7] The prevalence of HF was doubled in people with abnormalities of glucose metabolism, compared to those without, and again doubled in the presence of T2D (odds ratio [OR] 1.7; 95% confidence interval [CI], 1.4-2.1 for abnormalities of glucose metabolism and HF; OR 2.8; 95% CI, 2.2-3.6 for T2D and HF).[7]

The risk of hospitalization for heart failure (HHF) is also increased in patients with HF and diabetes, who have twice the risk compared with those without diabetes.[8] A Swedish observational study showed that T2D was an independent predictor of mortality across all HF groups, with mortality increased by 30% to 50% among patients with T2D vs those without T2D.[9] The Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) program has shown that diabetes is an independent predictor of CV morbidity and mortality in HF regardless of ejection fraction.[10] Diabetes was also associated with a greater relative risk of CV death or HHF among patients with preserved ejection fraction (pEF) vs reduced ejection fraction (rEF). This finding was largely driven by an increase in HHF, and might reflect the longer survival of patients with pEF who thus have a longer time at risk from HHF compared to those with rEF with a shorter life expectancy.

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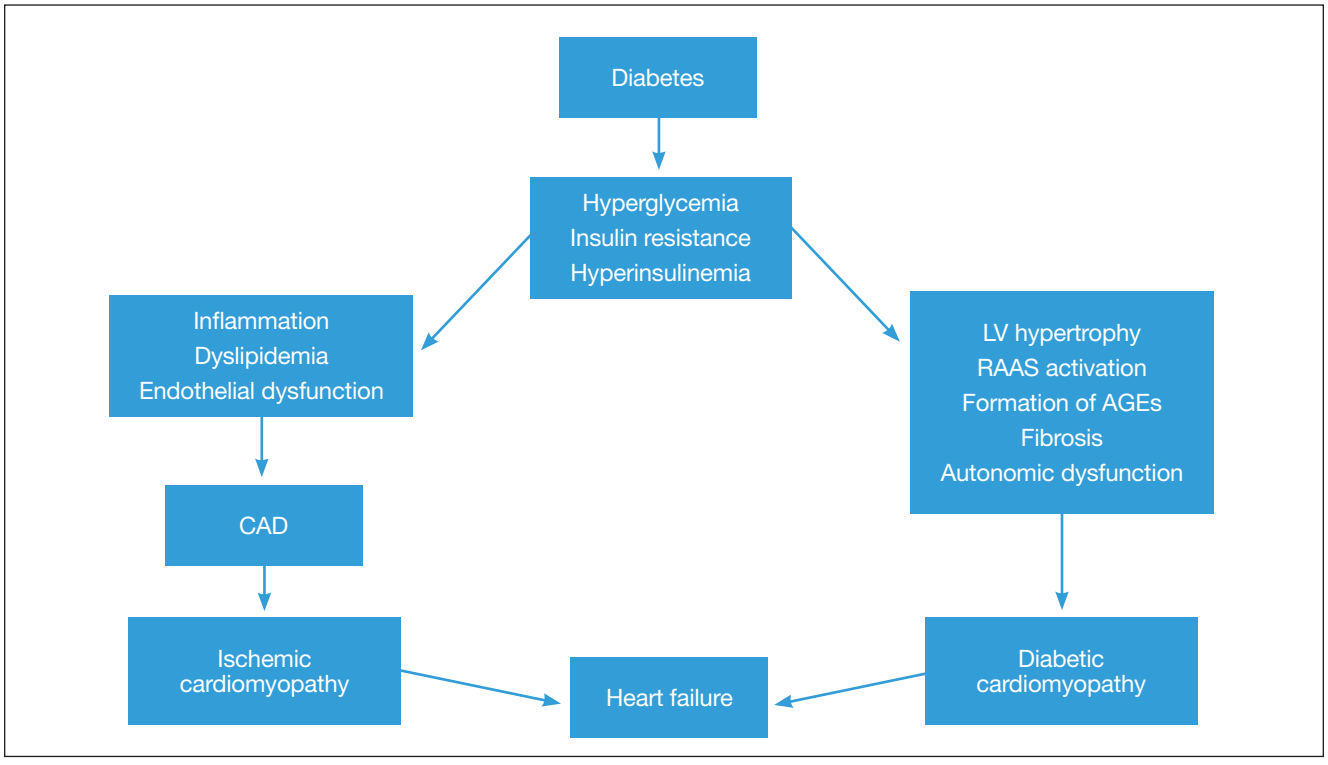
FIGURE **Pathophysiology of HF in diabetes**[12]



Abbreviations: AGEs, advanced glycation end products; CAD, coronary artery disease; HF, heart failure; LV, left ventricular; RAAS, renin-angiotensin-aldosterone system.
Source: American Heart Association, Inc. Dunlay SM, Givertz MM, Aguilar D, et al. *Circulation*. 2019;140(7):e294-e324.

Patients with diabetes and HF also show worse outcomes after hospitalization. In a study of patients with rEF (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan [EVEREST]), diabetes was associated with higher post-discharge CV mortality and HHF, compared with patients without diabetes.[11] Patients with diabetes also had a 20% increased rate of HHF compared with those without diabetes. These findings underline the importance of developing postdischarge strategies aimed at reducing rehospitalization rates in patients with diabetes and HF.

The pathophysiology of HF in T2D is multifactorial. Structural heart disease and HF can result from a range of systemic, myocardial, and cellular mechanisms.[12] The presence of hyperglycemia, insulin resistance, and hyperinsulinemia in T2D trigger a cascade of deleterious effects that contribute to the development of HF (**FIGURE**).[12] HF in T2D can be a result of coronary artery disease, which leads to ischemic cardiomyopathy and the development of HF. Alternatively, primary HF may develop in the absence of significant epicardial coronary artery disease as a consequence of diabetic cardiomyopathy (DCM). DCM is a distinct condition caused by structural, functional, and metabolic abnormalities of the myocardium, and is independent of the macrovascular complications of T2D.[13] Evidence also suggests that hyperglycemia can have a deleterious effect on the myocardium even before diabetes is diagnosed,[14] which underscores the importance of early assessment of CV risk factors and control of hyperglycemia. Furthermore, the persistence of a high prevalence of HF despite improvements in glycemic control suggests that factors other than glycemia can also contribute to the high risk of HF in people with diabetes.[2]

CARDIOVASCULAR OUTCOMES TRIALS

Background and rationale

Concern that there might not be a direct link between glycemic outcomes and the development of CV disease came to a head in 2007 when an analysis of trials with rosiglitazone suggested that rosiglitazone may increase CV events.[15] It was in this context that the US Food and Drug Administration (FDA) issued guidance to industry in 2008, advising the routine evaluation of CV risk for

TABLE 1 **HF data from CVOTs: DPP-4 inhibitors**

	SAVOR-TIMI 53[20]	EXAMINE[21, 22]	TECOS[23]	CARMELINA[24]
Drug	Saxagliptin	Alogliptin	Sitagliptin	Linagliptin
Participants, N	16,492	5380	14,671	6979
Median study duration, years	2.1	1.5	3.0	2.2
Baseline prevalence of HF, %	13	28	18	27
HHF, drug vs placebo, %	3.5 vs 2.8	3.1 vs 2.9	3.1 vs 3.1	6.0 vs 6.5
HR (95% CI)	1.27 (1.07-1.51)	1.07 (0.79-1.46)	1.00 (0.83-1.20)	0.90 (0.74-1.08)

Abbreviations: CI, confidence interval; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase-4; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio.

all new therapies for T2D. The FDA guidance recommended that such trials of new glucose-lowering drugs prospectively adjudicate all CV events occurring in the clinical trial program, and should include major adverse CV events (MACE), including CV death, nonfatal myocardial infarction (MI), and nonfatal stroke. Additional endpoints for consideration included hospitalization for acute coronary syndrome and urgent revascularization procedures. HF was not specifically mentioned as a trial endpoint. In response to the FDA guidance, several large CV outcomes trials (CVOTs) were undertaken in patients with T2D. The finding that specific agents in the sodium-glucose co-transporter 2 (SGLT2) inhibitor and glucagon-like peptide-1 receptor agonist (GLP-1 RA) classes markedly reduce the risk of MACE and HHF led to a major change in treatment recommendations for patients with T2D.[8] Based on the results of the CVOTs, the Standards of Medical Care in Diabetes published by the American Diabetes Association (ADA) now emphasize assessment of the presence of atherosclerotic cardiovascular disease (ASCVD), HF, renal disease, and CV risk as the initial step in a patient-centered risk-based approach to selecting glucose-lowering therapies.[16] In March 2020, the original FDA guidance was withdrawn in light of the findings from subsequent CVOTs, none of which demonstrated an increased risk of CV events with glucose-lowering therapies.[17]

CVOTs: Glucose-lowering therapies in patients with CV disease/increased CV risk

The ADA recommends that CV risk factors should be systematically assessed at least annually in all patients with T2D.[8] These risk factors include obesity/overweight, hypertension, dyslipidemia, smoking, a family history of premature coronary disease, chronic kidney disease, and the presence of albuminuria. For patients with T2D, the goals of treatment are to prevent or delay complications and to maintain quality of life. This involves measures aimed at controlling glycemia and the management of CV risk factors. Thiazolidinediones can increase the risk of HHF and are contraindicated in class III and IV heart failure.[2,18] These agents are not recommended for use in patients with symptomatic HF.[8] The effects of glucose-lowering agents on HF outcomes in patients with T2D have been shown to be neutral for α-glucosidase inhibitors, sulfonylureas, and GLP-1 RAs and most dipeptidyl peptidase-4 (DPP-4) inhibitors.[19] Two DPP-4 inhibitors, saxagliptin[20] and alogliptin,[21] have been shown to increase HHF. Positive effects on HF outcomes have been reported with metformin, although these findings are based on data from observational studies in which an effect of confounding factors, such as disease severity, cannot be excluded.[18] CV protective effects have been demonstrated in large CVOTs of SGLT2 inhibitor agents vs placebo.[8]

DPP-4 inhibitors

The DPP-4 inhibitors are increasingly used for the management of T2D, and several CVOTs have evaluated these agents (**TABLE 1**). These CVOTs evaluated DPP-4 inhibitor therapy when added to standard care, which allowed physicians to adjust therapies as needed to maintain glycemic targets in line with national or regional guidelines. Although the initial CVOTs did not include HF outcomes as primary outcome measures, uncertainties about the long-term effect of DPP-4 inhibitors on the risk of HHF were raised following publication of the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trial.[20] The results showed that HHF was more likely for patients who received saxagliptin than those allocated to placebo (3.5% vs 2.8%, respectively). Furthermore, the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial showed that HHF was the first event in 3.1% of patients taking alogliptin vs 2.9% taking placebo.[21]

TABLE 2 **HF data from CVOTs: GLP-1 RAs**

	ELIXA[29]	LEADER[30]	SUSTAIN-6[31]	EXSCEL[32]	REWIND[28,33]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Dulaglutide
Participants, N	6068	9340	3297	10,782	9901
Median study duration, years	2.1	3.8	2.1	3.2	5.4[a]
Baseline prevalence of HF, %	22	14	24	16	8.6
HHF, drug vs placebo, %	4.0 vs 4.2	4.7 vs 5.3	3.6 vs 3.3	3.0 vs 3.1	4.3 vs 4.6
HR (95% CI)	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	0.93 (0.77-1.12)

Abbreviations: CI, confidence interval; CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio.

[a]Median study duration.

In response to these studies, a safety review by the FDA advised that HF warnings be added to the drug labels of saxagliptin and alogliptin as they may increase the risk of HF, particularly among patients with existing heart or kidney disease.[25] In contrast, 2 other CVOTs of DPP-4 inhibitors in patients with T2D and increased CV risk, the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin)[23] and the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study with Linagliptin) trials[24] found no significant increase in the risk of HHF. Although possible mechanisms for a deleterious CV effect of DPP-4 inhibitors have been proposed to explain the findings of SAVOR-TIMI 53, the benefits and risks of DPP-4 inhibitors in patients with T2D and established left ventricular dysfunction require further evaluation.[26]

GLP-1 RAs

Four GLP-1 RAs (liraglutide, semaglutide, albiglutide, dulaglutide) have been shown to reduce the risk of MACE, particularly among patients with existing CV disease.[27] However, in contrast to the SGLT2 inhibitors, CVOTs with the GLP-1 RAs lixisenatide (ELIXA), liraglutide (LEADER), semaglutide (SUSTAIN-6), exenatide once weekly (EXSCEL), dulaglutide (REWIND),[28] and albiglutide (HARMONY) have shown no significant effect on HF risk (**TABLE 2**).[34] The ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial in patients with T2D and a recent history of angina or hospitalization due to unstable angina, showed a neutral effect of lixisenatide on 4-point MACE (CV death, MI, stroke, or hospitalization for unstable angina) vs placebo (13.4% vs 13.2%; hazard ratio [HR] 1.02; 95% CI, 0.89-1.17; *P*<0.001 for noninferiority and *P*=0.81 for superiority), and no significant between-group differences for HHF (4.0% vs 4.2%; HR 0.96; 95% CI, 0.75-1.23).[29] In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, while there was a decreased risk of the 3-point MACE for liraglutide compared with placebo (13% vs 14.9%; HR 0.87; 95% CI, 0.78-0.97; *P*<0.001 for noninferiority; *P*=0.01 for superiority), HHF was not significantly reduced (4.7% vs 5.3%; HR 0.87; 95% CI, 0.73-1.05; *P*=0.14) among patients with T2D and high CV risk who received liraglutide vs placebo.[30] A further noninferiority trial, SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), showed a reduced occurrence of 3-point MACE among patients with T2D and high CV risk who received semaglutide vs placebo (6.6% vs 8.9%; HR 0.74; 95% CI, 0.58-0.95; *P*<0.001 for noninferiority; *P*=0.02 for superiority), in addition to standard care. However, semaglutide showed a neutral effect on HHF (3.6% vs 3.3%; HR 1.11; 95% CI, 0.77-1.61; *P*=0.57).[31] Another CVOT of patients with T2D, with or without previous CVD, the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial, showed no significant difference in incidence of MACE among patients who received exenatide vs placebo (11.4% vs 12.2%; HR 0.91; 95% CI, 0.83-1.00; *P*<0.001 for inferiority; *P*=0.06 for superiority), with a neutral effect on HHF (3.0% vs 3.1%; HR 0.94; 95% CI, 0.78-1.13).[32] Subsequently, in the HARMONY (Albiglutide and CV Outcomes in Patients with T2D and CVD) trial, there was a reduced risk of 3-point MACE vs placebo (7.0% vs 9.0%; HR 0.78; 95% CI, 0.68-0.90; *P*<0.0001 for noninferiority; *P*=0.0006 for superiority), although the composite of death from CV causes or HHF did not differ significantly between patients who received albiglutide vs placebo (HR 0.85; 95% CI, 0.70-1.04; *P*=0.113).[35] Similar findings were reported from the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial, in which the addition of dulaglutide to standard care in patients with T2D and high CV risk was associated with a reduction in 3-point MACE (12.0% vs 13.4%; HR 0.88; 95% CI, 0.79-0.99; *P*=0.026) but no significant reduction in HHF (4.3% vs 4.6%; HR 0.93; 95% CI, 0.77-1.12; *P*=0.46).[28]

TABLE 3 **HF data from CVOTs: SGLT2 inhibitors**

	EMPA-REG OUTCOME[36]	CANVAS[37]	CREDENCE[38]	DECLARE-TIMI 58[39]	VERTIS CV[40]
Drug	Empagliflozin	Canagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Participants, N	7020	10,142	4401	17,160	8246
Median study duration, years	3.1	2.4	2.6	4.2	3.5 (mean)
Baseline prevalence of HF, %	10	14	15	10	24
HHF, drug vs placebo, %	2.7 vs 4.1	5.5 vs 8.7[a]	4.0 vs 6.4	2.5 vs 3.3	2.5 vs 3.6
HR (95% CI)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.61 (0.47-0.80)	0.73 (0.61-0.88)	0.70 (0.54-0.90)

Abbreviations: CI, confidence interval; CVOT, cardiovascular outcomes trial; HF, heart failure; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2, sodium-glucose co-transporter 2.

[a]Data given per 1000 patient-years.

SGLT2 inhibitors

The first trial to demonstrate the CV benefits of SGLT2 inhibitor therapy was the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removal of Excess Glucose).[36] This randomized, double-blind, placebo-controlled trial of 7020 patients with T2D and high CV risk showed that, after a median follow-up of 3.1 years, empagliflozin added to standard care was associated with lower rates of the composite 3-point MACE outcome of CV death, nonfatal MI, or nonfatal stroke (14% relative risk reduction [RRR]); death from CV causes (38% RRR); death from any cause (32% RRR); and HHF (35% RRR), compared with placebo (**TABLE 3**).

In the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program, a reduction in the primary composite 3-point MACE outcome (26.9 vs 31.5 per 1000 patient-years; HR 0.86; 95% CI, 0.75-0.97; *P*<0.001 for noninferiority; *P*=0.02 for superiority) was shown for canagliflozin vs placebo added to standard care in patients with T2D and high CV risk. However, while no statistically significant difference in CV mortality was observed (11.6 vs 12.8 per 1000 patient-years; HR 0.87; 95% CI, 0.72-1.06), canagliflozin was shown to reduce the risk of HHF by 33% (5.5% vs 8.7%; HR 0.67; 95% CI, 0.52-0.87).[37] Data from the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed that canagliflozin was associated with a 39% reduction in HHF (4.0% vs 6.4%; HR 0.61; 95% CI, 0.47-0.80) and a 31% reduction in the composite of CV death or HHF (8.1% vs 11.5%; HR 0.69; 95% CI, 0.57-0.83) when used in a population with diabetic kidney disease with albuminuria >300 mg/24 hours.[38]

DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) was the largest CVOT of an SGLT2 inhibitor; it showed dapagliflozin to be associated with a lower rate of CV death or HHF vs placebo (4.9% vs 5.8%; HR 0.83; 95% CI, 0.73-0.95; *P*=0.005), primarily driven by a 27% reduction in HHF (2.5% vs 3.3%; HR 0.73; 95% CI, 0.61-0.88).[39] In addition, dapagliflozin was noninferior but not statistically superior compared with placebo for 3-point MACE (8.8% vs 9.4%; HR 0.93; 95% CI, 0.84-1.03; *P*=0.17). The observation of CV benefits in patients without diabetes is consistent with previous suggestions that SGLT2 inhibitors may provide benefits that extend beyond glucose lowering.

In a further SGLT2 inhibitor trial in patients with T2D and established ASCVD, the VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety–Cardiovascular) trial, results showed that ertugliflozin was noninferior to placebo for the primary endpoint of 3-point MACE (11.9% vs 11.9%; HR 0.97; 95% CI, 0.85-1.11; *P*<0.001). The trial did not meet secondary endpoints for superiority; a 30% reduction in HHF was observed (2.5% vs 3.6%; HR 0.70; 95% CI, 0.54-0.90).[40]

Analyses of HF data from CVOTs

Following the detection of a possible HF signal with some DPP-4 inhibitors, further analyses of data from existing CVOTs were performed. HF outcomes were evaluated in the overall population and subgroups in the EMPA-REG OUTCOME trial, including patients with investigator-reported HF at baseline.[41] The analyses identified a 35% reduction in HHF (4.1% vs 2.7% for placebo vs empagliflozin; HR 0.65; 95% CI, 0.50-0.85; *P*=0.002) and a similar reduction in the composite outcome of HHF or

Key points for primary care

- HF is twice as common in patients with T2D vs patients without T2D. Assessment of CV status, CV risk, and HF is an important part of the patient-centered approach to management of patients with T2D.
- Robust evidence shows a benefit of SGLT2 inhibitors in decreasing the occurrence of hospitalization for HF in patients with or without T2D. In contrast, GLP-1 RAs improve MACE but do not significantly improve hospitalization for HF.
- The association of T2D and HF underlines the importance of identifying and treating hyperglycemia, with the aim of reducing the development and progression of CV complications including HF.

CV death (8.5% vs 5.7%; HR 0.66; 95% CI, 0.55-0.79), with a consistent benefit in patients with or without baseline HF. Empagliflozin also reduced all-cause hospitalization, with both HHF and hospitalization for other causes contributing to the reduction. Additional endpoints of investigator-reported HF (6.1% vs 4.4%; HR 0.70; 95% CI, 0.56-0.87) and first introduction of loop diuretics showed reductions with empagliflozin (8.6% vs 13.3%; HR 0.62; 95% CI, 0.53-0.73).

New trials were also initiated that evaluated HF outcomes with SGLT2 inhibitors, both in patients with and without T2D. While the results of these trials are awaited, surrogate endpoints have been evaluated in patients with HF. The recently completed EMPERIAL (Effect of Empagliflozin on Exercise Ability and Heart Failure Symptoms in Patients with Chronic Heart Failure)-Preserved (NCT03448406) and EMPERIAL-Reduced trials (NCT03448419) (with pEF and rEF, respectively) evaluated the effect of empagliflozin on exercise capacity using the 6-minute walk test.[42]

DEDICATED TRIALS IN PATIENTS WITH HF, WITH OR WITHOUT T2D

The first dedicated outcome study in patients with HF, the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial of patients with HFrEF (DAPA-HF), showed that the risk of worsening HF or CV death was reduced among patients who received dapagliflozin vs placebo, irrespective of whether patients also had diabetes.[43] The primary outcome of a composite of worsening HF or CV death occurred in 16.3% of patients in the dapagliflozin group compared with 21.2% in the placebo group (HR 0.74; 95% CI, 0.65-0.85), and a first worsening HF event was reported in 10.0% and 13.7% of patients, respectively (HR 0.70; 95% CI, 0.59-0.83). Death from CV causes occurred in 9.6% and 11.5%, respectively (HR 0.82; 95% CI, 0.69-0.98). In contrast to several previous CVOTs, the patient population of DAPA-HF was at greater baseline risk from HHF and death from CV causes, and most of the patients in this trial were already being treated with a loop diuretic and a mineralocorticoid receptor antagonist. Nonetheless, the occurrence of volume depletion and worsening of kidney function was infrequent (<8%, with no between-group differences).

Two trials have also evaluated SGLT2 inhibitor therapy in patients with acute or chronic HF, with or without T2D. The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction, NCT03057951)[44] and the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction, NCT03057977)[45] have investigated the long-term effects of empagliflozin on CV death and HHF in patients with HF (both with HFpEF and HFrEF), with or without diabetes. Results from EMPEROR-Reduced have shown a 25% reduction in risk of the primary composite outcome of CV death or HHF, with empagliflozin vs placebo, when added to standard care (19.4% vs 24.7% patients respectively; HR 0.75; 95% CI, 0.65-0.86).[45] The effect of empagliflozin on the primary outcome was consistent regardless of the presence or absence of T2D. In addition, the risk of first and recurrent HHF was reduced by 30% for patients in the empagliflozin group compared with placebo (HR 0.70; 95% CI, 0.58-0.85). Results from EMPEROR-Preserved are expected in 2021.

Two further ongoing trials, the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure, NCT03619213) and the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure study, NCT03521934) are evaluating dapagliflozin in patients with HFpEF and sotagliflozin in patients with worsening HF, respectively.

In response to findings from recent clinical trials, the recommendation from the ADA was updated in August 2020 to state that in patients with T2D and established HF with rEF, an SGLT2 inhibitor with proven benefit in this patient population should be considered to reduce the risk of worsening HF (Grade A level of evidence).[46]

Outside the clinical trial setting, real-world data are being collected in the ongoing Empagliflozin Comparative Effectiveness and Safety (EMPRISE) study, which is evaluating the CV effects of empagliflozin that can be

observed in routine clinical practice.[47,48] Using 2 commercial and 1 federal (Medicare) claims data sources in the United States, outcomes for patients using empagliflozin or sitagliptin are being compared. A planned interim analysis from EMPRISE showed that, compared with sitagliptin, the initiation of empagliflozin was associated with an approximately 50% reduced risk of HHF among patients with T2D receiving standard care in clinical practice, across a wide spectrum of patients with or without a history of CV disease.[47] These findings are consistent with the results of EMPA-REG OUTCOME[36] and indicate that a reduction in HHF can be achieved with empagliflozin in routine clinical practice where the range of CV risk among patients is broader than the more limited populations enrolled in CVOTs.[47] Additional results from EMPRISE will provide important new perspectives on the CV death reductions with empagliflozin in a population that includes a broad range of CV risk.

CONCLUSIONS

Choosing the correct glucose-lowering therapy for T2D includes first assessing for the presence of ASCVD, HF, renal disease, and CV risk. Based on multiple trials, if an individual has ASCVD, the ADA management algorithm recommends that in addition to metformin, a patient should receive either an SGLT2 inhibitor or a GLP-1 RA that has evidence of CV outcome benefit.[8] If a patient has established HF, then treatment with an SGLT2 inhibitor with proven benefit in this patient population should be strongly considered. ●

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HF Evaluation and Management in patients with T2D

HF in patients with T2D

People with **T2D** have a 2-fold greater risk of **HF** vs those without **T2D**[1]

Up to 3 in 10 people with **T2D** have **HF**[2]

Monitor patients with T2D to reduce HF risk[3]

Assess CV risk factors at least annually for prevention and management of ASCVD and HF

- Dyslipidemia
- Obesity/overweight
- Hypertension
- Smoking
- Chronic kidney disease
- Family history of premature coronary disease
- Presence of albuminuria

Management of patients with T2D and HF[3]

- Lifestyle modifications, including exercise and balanced caloric intake
- Lipid management
- BP management
- Glycemic control
- Standard treatment, (eg, β-blockers, mineralocorticoid inhibitor, and consideration of ACEIs and ARBs)

Select appropriate glucose-lowering therapies for patients with T2D and HF[3-5]

METFORMIN

- **First-line** therapy for T2D, **including those with HF**
- Reduces mortality and CV morbidity in patients with diabetes, with or without HF[6]
- **Continue** for glucose-lowering as long as it is **tolerated and not contraindicated**
  - Avoid in unstable/hospitalized with HF
  - Avoid if eGFR <30 mL/min/1.73 m^2

SGLT2 INHIBITORS

- Consider **independently of baseline or target A1c** to reduce risk of HHF
- Prefer agent with **evidence of reducing HF risk**
  - Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin reduce risk of HHF[7,8]
  - Canagliflozin and empagliflozin reduce risk of MACE; empagliflozin reduces risk of CV death[3]
- Consider **SGLT2 inhibitor with proven benefit** in patients with **T2D and established HFrEF** to reduce risk of **worsening HF and CV death**[9,10]; may be a class effect[4]
- Avoid if eGFR <45 mL/min/1.73 m^2 (<30 for canagliflozin and ertugliflozin)

GLP-1 RAs

- Add GLP-1 RA with proven CVD benefit
  - **IF SGLT2** inhibitor **not tolerated** or **contraindicated**, or if **eGFR less than adequate**
  - **IN ADDITION** to SGLT2 inhibitor **if A1c above target**
- No significant effect on HF risk[11,12]
- Liraglutide, semaglutide, and dulaglutide reduce risk of MACE, particularly in patients with CVD[11,12]
- Reduce all-cause mortality[11,12]

OTHER AGENTS

- Consider **if A1c above target**
  - DPP-4 inhibitor (*not saxagliptin)* in the setting of HF (if not on GLP-1 RA)
  - Basal insulin
  - Sulfonylurea
- **AVOID** thiazolidinediones

ABBREVIATIONS

A1c, glycated hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; MACE, major adverse cardiovascular event; SGLT2, sodium-glucose co-transporter 2; T2D, type 2 diabetes

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CHAPTER 4

Overcoming Therapeutic Inertia: Practical Approaches

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INTRODUCTION

Therapeutic inertia is defined as the failure of health care professionals (HCPs) to initiate, intensify, or de-intensify therapy in a timely manner according to evidence-based clinical guidelines.[1] Clinical recommendations from the American Diabetes Association (ADA),[2] the European Association for the Study of Diabetes (EASD),[3] and the American Association of Clinical Endocrinologists (AACE)[4] suggest a glycated hemoglobin (HbA1c) of <7% for most adults with type 2 diabetes (T2D), with treatment re-evaluation every 3 to 6 months. Studies have shown that only about 50% of adults achieve the ADA-recommended HbA1c value of <7%.[5,6] Many adults with T2D do not receive timely treatment intensification in order to maintain glycemic goals.[7-10] This delay in treatment can result in long periods of hyperglycemia, increasing the risk of microvascular and macrovascular complications, decreasing patients' quality of life, and increasing health care costs.[11] The importance of early intensive glycemic control in T2D for reducing microvascular complications has been well established in large landmark trials.[12-14] The United Kingdom Prospective Diabetes Study 10-year post-trial follow-up demonstrated that early glycemic control provides a legacy effect with lasting reductions in microvascular complications and sustained cardiovascular (CV) benefits.[13,14] More recently, this has also been shown in a cohort study of almost 35,000 managed care patients with newly diagnosed T2D and at least 10 years of survival.[15] In this study, compared with HbA1c levels <6.5%, levels ≥6.5% in the first year after diagnosis were associated with increased microvascular and macrovascular events, and levels ≥7% were associated with increased mortality. The authors concluded that T2D control during the first year after diagnosis is strongly associated with future risk for diabetic complications and mortality.[15] Due to the progressive nature of T2D and β-cell function declining over time, most patients will eventually require multiple medications to maintain adequate glycemic control. To that effect, it has been shown in patients with T2D that the sodium-glucose co-transporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin, and empagliflozin can improve β-cell glucose sensitivity and function,[16-18] making these agents an attractive addition to the regimen.

In addition, SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to provide cardiorenal benefits, and thus, consideration of comorbid disease should be taken into account when selecting therapies to help patients meet glycemic goals. This is outlined in the 2020 ADA Standards of Medical Care in Diabetes, which recommend specific agents for people

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DISCLOSURES

Dr. Brunton has participated in advisory boards for Novo Nordisk, Abbott Diabetes, Bayer, Sanofi Aventis, and Xeris, and is a speaker for Novo Nordisk, Abbott Diabetes, Bayer, Lilly, and Xeris.

Dr. Miller is a speaker for Novo Nordisk, Abbott, Boehringer Ingelheim, AstraZeneca, and Eli Lilly.

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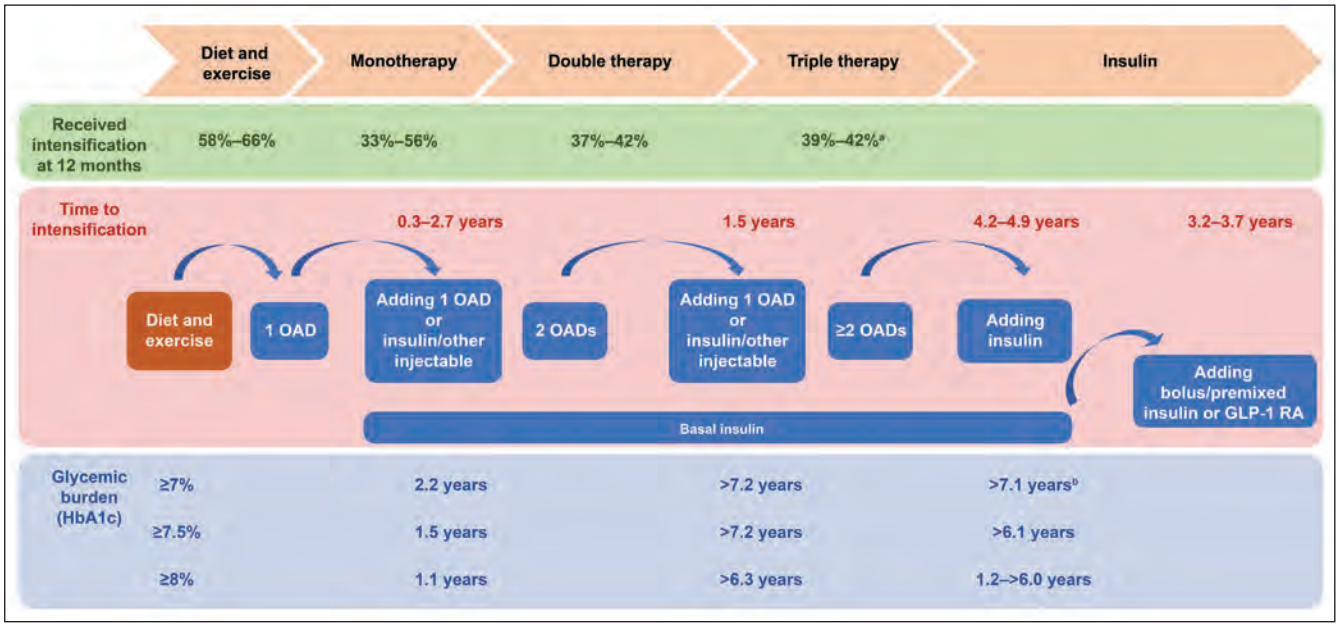
FIGURE 1 **Therapeutic inertia**[20]

Schematic of therapeutic inertia showing the proportion of patients above target receiving treatment intensification within 12 months (green); the median time to intensification from the time HbA1c is above the threshold (red); and the glycemic burden during a given period of time (blue).



Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; OAD, oral antidiabetes agent.

American Diabetes Association "Mata-Cases M, Franch-Nadal J, Gratacos M, Mauricio D. Therapeutic Inertia: Still a Long Way to Go That Cannot Be Postponed. *Diabetes Spectr*. 2020". Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

[a]Estimated in patients with two OADs and three OADs after 14 months.

[b]Estimated in patients with three OADs.

with indicators of high risk or established atherosclerotic cardiovascular disease (CVD), chronic kidney disease (CKD) or heart failure (HF).[2] These agents include SGLT2 inhibitors with evidence of reducing HF and/or CKD progression in CV outcomes trials (CVOTs), or a GLP-1 RA with proven CVD benefit if estimated glomerular filtration rate (eGFR) is less than adequate (eg, <30 mL/min/m^2).[2]

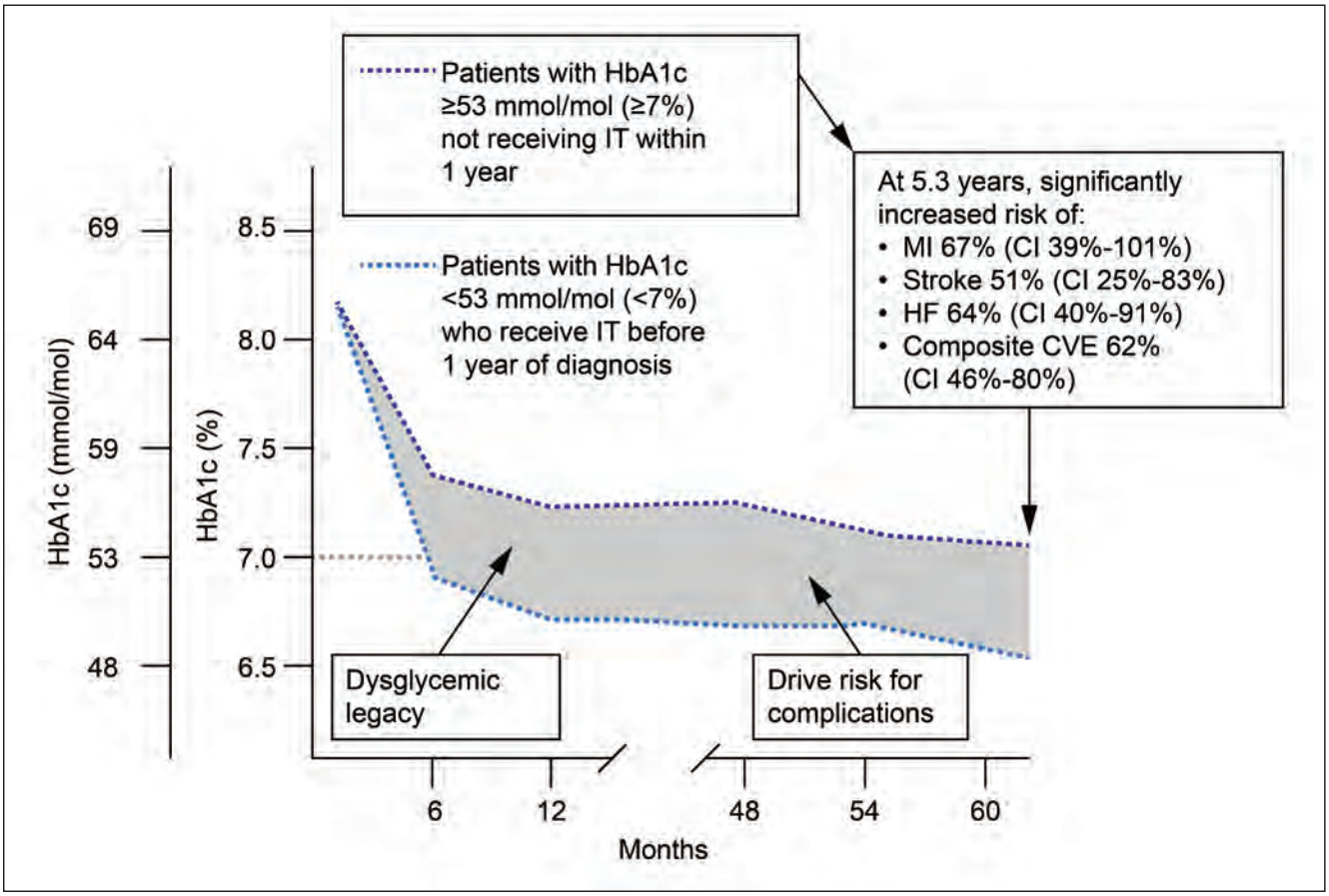
Because therapeutic inertia has such wide-reaching consequences, the ADA has recently launched a new initiative focused specifically on overcoming therapeutic inertia, which emphasizes that the issue is multifactorial involving a wide range of stakeholders, including patients, clinicians, health systems, payors, and the pharmaceutical industry.[19]

HOW WIDESPREAD IS THERAPEUTIC INERTIA?

Evaluating the prevalence of therapeutic inertia in patients with hyperglycemia is challenging, as measurement criteria are not standardized, making comparisons among studies difficult. Nevertheless, the authors of a systematic review of 53 studies concluded that therapeutic inertia is widespread and occurs at all stages of treatment. The median time to treatment intensification when HbA1c was above target was >1 year.[8] A medical database analysis of almost 21,000 US patients taking metformin showed that one-third of patients failed metformin therapy within 1 year; of those, 25% did not receive treatment intensification.[7] Of those who received treatment intensification, 34% received treatment intensification when their HbA1c was ≥9%, a level at which the addition of a single glucose-lowering agent is usually not effective. A real-world study of more than 80,000 UK participants with T2D revealed that for those with an HbA1c >7.5% it took almost 2 years to add one glucose-lowering agent, another 7 years to add a second drug, and 6 years to add a third.[10] Moreover, initiation of basal insulin is associated with a median wait time of almost 4 years.[9] If delays from all treatment steps are added up, patients could potentially spend up to 10 years with an HbA1c >7% and about 10 years with an HbA1c >8% from diagnosis until initiation of insulin[8,11,20] **(FIGURE 1)**. Therapeutic inertia extends beyond glycemia, with approximately 50% of patients with T2D not meeting their blood pressure or lipid goals,[21] and the percentage of patients achieving global vascular protection (ie, targets for HbA1c,

FIGURE 2 **Consequences of delayed treatment on CVD risk**[25]

The risk of CVD is shown for patients with HbA1c consistently ≥7% in the 2 years following diagnosis for whom treatment intensification is delayed by at least 1 year versus that of patients with HbA1c consistently <7% in the same period.



Abbreviations: CI, confidence interval; CVD, cardiovascular disease; CVE, cardiovascular event; HbA1c, glycated hemoglobin; HF, heart failure; IT, intensification of treatment; MI, myocardial infarction.

blood pressure, and low-density lipoprotein [LDL] cholesterol) is even lower at 23%.[21] One of the major complications of diabetes is diabetic nephropathy. Microalbuminuria is one of the earliest signs of diabetic nephropathy, and is associated with increased risk of end-stage renal disease, CVD, and all-cause mortality, yet many primary care HCPs do not regularly measure this parameter. A Dutch cohort study of more than 14,000 patients with T2D found that only 24% of patients received an albumin-creatinine ratio (ACR) measurement every year, and 21% of patients had never received such a measurement.[22]

WHAT ARE THE CONSEQUENCES OF THERAPEUTIC INERTIA?

Despite the evidence regarding good glycemic control preventing or delaying diabetes-related complications, many HCPs do not set and manage glycemic, blood pressure, and lipid goals appropriately.[23] These treatment delays may result in more rapid onset of diabetes-induced retinopathy, increased CV events (myocardial infarction [MI], HF, and stroke), and CKD.[11] A large retrospective cohort study of more than 105,000 patients with T2D showed that a 1-year delay in treatment intensification in those with an HbA1c ≥7.0% significantly increased the risk of MI, HF, stroke, and a composite of CV events **(FIGURE 2)**.[24,25] Furthermore, it has been estimated that inadequate glycemic control is responsible for >200,000 diabetes-related complications every year in North America alone, resulting in excess health care costs and mortality.[26]

TABLE 1 **Decoding the terminology**[1,33]

Compliance	• Oldest term, one-sided, implies no patient buy-in or input • "The extent to which the patient's behavior matches the prescriber's recommendations"
Adherence	• Now often replaces compliance and reflects that the treatment plan has been discussed between patient and provider, but the patient is not obliged to follow the plan • "The extent to which the patient's behavior matches agreed recommendations from the prescriber"
Concordance	• Takes the term adherence further to indicate that the treatment plan was not only discussed, but mutually agreed upon, giving appropriate weight to the patient's voice • The concept of concordance includes additional aspects such as effective communication, providing information to help the patient make an informed choice regarding treatment, and offering support to the patient during the entire course of treatment
Persistence	• Reflects the time period during which a patient is adherent

Who are the stakeholders?

Therapeutic inertia is a complex phenomenon influenced by many factors, which can be driven by multiple stakeholders, including HCPs, patients, and the health care system.

Health care professionals

Reasons for primary care HCPs not advancing care despite their patients not meeting defined targets in the management of chronic diseases, such as T2D, can include lack of awareness, time constraints, and limited resources. First, HCPs need to become aware of how they are contributing to therapeutic inertia. For example, HCPs may not refer their patients for diabetes education because they recognize that insurance coverage is suboptimal.[27] Moreover, many primary care HCPs may be unaware of actual patient barriers, assuming they know what prevents patients from adhering to their therapies.[27] While they may be aware that patients are concerned with high medication cost, they may be less aware that some patients worry more about disease complications.[28] HCPs can explain that older glucose-lowering medications available as low-cost generics may not protect against cardiac and renal complications, whereas newer glucose-lowering medications are expensive but offer other benefits.[2]

Guidelines for diabetes treatment, although meant to be useful for primary care HCPs, are constantly evolving and not always clear. For example, the 2018 ADA Standards of Medical Care in Diabetes recommended metformin as first-line therapy, but provided little guidance on the choice of second-line agents.[29] In the 2020 ADA Standards, the recommendations are more specific, outlining which agents to use for patients with atherosclerotic CVD, HF, or CKD.[2] To aid HCPs in managing the constantly growing list of glucose-lowering agents and the changes to insurance formularies, the ADA publishes an annual abridged version of the Standards of Medical Care in Diabetes for primary care HCPs.[30] In addition to ADA, AACE[31] and American Academy of Family Physicians (AAFP)[32] also emphasize early use of combination therapy. Additional barriers include a reluctance to advance medication intervention or begin insulin therapy, concerns about hypoglycemia, managing patients' comorbidities, and not prioritizing diabetes during the appointment.[30]

Patients

Medication adherence plays an important role in therapeutic inertia. *Adherence* is a term that now often replaces compliance and reflects that the treatment plan has been discussed between the patient and the HCP, but the patient is not obliged to follow the plan **(TABLE 1)**[33]; it is the term most commonly used in publications. The concept of *concordance* goes further to indicate that the treatment plan was not only discussed, but mutually agreed upon, giving appropriate weight to the patient's voice. Finally, *persistence* is a term that reflects how long a patient has been adherent.

Medication nonadherence is common with many chronic diseases. A meta-analysis of data from 376,000 patients using medications that prevent CVD (eg, antihypertensives, statins) showed that about 30% of patients who have had a prior MI and approximately 50% of patients who did not have an MI did not adhere to effective CV preventive treatment.[34] The consequences of CV medication nonadherence are dire, resulting in approximately 125,000 preventable deaths a year and as many as 40% of nursing home admissions in patients with T2D.[35]

Reasons for nonadherence to glucose-lowering agents cover a broad range of aspects, including denial of the disease, not realizing the consequences of poor glycemic control, concerns over managing a more complicated

TABLE 2 **Practice pearls for addressing therapeutic inertia**

Challenge	Strategies for therapeutic inertia-free practice
Maximizing limited office time	• Establish visits that prioritize diabetes care assessment • Follow ABC of diabetes at appointment (HbA1c, Blood pressure, Cholesterol) • Load or copy all diabetes technology or treatment aids at the visit • Telemedicine short interval follow up can assist in limited in-clinic time availability
HbA1c not at target	• Develop follow-up interval at the time of visit based on HbA1c target • Aim to change therapeutic intervention at every visit when target is not achieved
Patients need team assistance	• Establish an office-based protocol and inertia-busting strategy to facilitate diabetes-only appointments and follow up, medication adherence, and increased engagement • Outline tasks for office support staff, such as protocol for HbA1c target-based follow up, identification of persons with diabetes in the medical record, knowledge of office technology downloading protocol • Send electronic or staff-facilitated reminders • Refer all patients with T2D to DSMES • Leverage community resources • Consider virtual coaching • Care coordination outside your practice

Abbreviations: DSMES, Diabetes Self-Management Education and Support Services; HbA1c, glycated hemoglobin; T2D, type 2 diabetes.

regimen, and lack of support.[36,37] A retrospective cohort study of almost 200,000 patients with diabetes and comorbidities showed that patients were taking more than 6 different medication classes, including glucose-lowering and lipid-lowering agents, antihypertensives, and antidepressants/anti-anxiety drugs.[38] Moreover, older adults may be prescribed as many as 20 different medications to take each day,[39] making adherence and persistence difficult. In the United States, approximately 1 in 5 new prescriptions are never filled, and among those filled, about 50% are taken incorrectly with regard to timing, dosage, frequency, or duration.[40] A retrospective cohort analysis of more than 60,000 patients with T2D showed that medication persistence is strongly influenced by medication class,[23] with metformin demonstrating the longest persistence of approximately 3 years, followed by sulfonylureas (~2 years) and dipeptidyl peptidase-4 (DPP-4) inhibitors (1.7 years).[23] Another retrospective, observational cohort study in more than 40,000 patients with T2D from the MarketScan claims databases compared medication persistence in those receiving SGLT2 inhibitors or sulfonylureas.[41] Compared with those receiving a sulfonylurea, a significantly greater percentage of patients receiving an SGLT2 inhibitor were adherent (61.4% vs 53.9%, respectively), and persistent (76.1% vs 68.9%, respectively).[41] These findings should be taken into account when choosing a treatment for patients with T2D.

The most frequent concerns patients have include complications from their disease, and adverse effects of medications such as hypoglycemia and weight gain.[10] Concerns specific to insulin use include the perception of insulin initiation (treatment escalation) as a "failure," an increase in the complexity of the treatment regimen (titration and injection), being averse to injections, and the perception that insulin requires refrigeration.[9]

Health care system

Factors that can contribute to therapeutic inertia in the health care system include the lack of individualized clinical guidelines, suboptimal communication between physicians and staff, and lack of a patient support system. Additionally, lengthy and complicated processes of dealing with health insurance companies, proving medical necessity and potential appeals, lack of alignment between pharma-sponsored copay systems and Medicare, and changing formularies are all issues that take a great deal of time and energy for primary care HCPs.[36]

APPROACHES TO OVERCOMING THERAPEUTIC INERTIA IN PRIMARY CARE PRACTICES

The diabetes-focused appointment

The first step in creating a therapeutic inertia-free practice is creating awareness that the treatment of patients with T2D is not advanced in a timely manner (**TABLE 2**). It is important to establish appointments that prioritize diabetes management over other issues. These diabetes-

focused appointments should be scheduled based on ADA recommendations: every 6 months if the patient's HbA1c is ≤7% on 2 occasions, every 2 to 3 months if the HbA1c is >7% but ≤9%, and every 1 to 2 months if the HbA1c is >9%, until the HbA1c target has been achieved.[42] The following items should be covered: ABCs (HbA1c, blood pressure, cholesterol); a review of medications with a focus on adherence, administration, and side effects; and whether patients experience barriers with obtaining or taking their medications.

Primary care HCPs should also review adherence to dietary and lifestyle suggestions, and share helpful information during the diabetes-focused appointment. Patients with T2D can be encouraged to eat the majority of their daily calories before 3PM.[43] They also should aim for a diet that includes 5 servings of fruits and vegetables daily and is high in lean proteins, healthy fats, and non-processed carbohydrates (ie, intact food). HCPs and patients can work together to set specific, attainable, and measureable goals to achieve in the next month, such as adding 1 serving of vegetables a day, increasing daily activity by 15 minutes per day, or incorporating 2 days a week of strength training with stretch bands or hand weights. In addition, the office staff can facilitate referral to medical nutrition therapy as well as Diabetes Self-Management Education and Support Services (DSMES).[44] The Centers for Disease Control and Prevention provides a toolkit to assist with coverage of these services (https://www.cdc.gov/diabetes/dsmes-toolkit/reimbursement/benefit-policies.html).

To assess patients' glycemic status, data from self-monitoring blood glucose (SMBG) meters or continuous glucose monitoring (CGM) devices need to be downloaded and logbooks/data reviewed with the patient. Real-time (RT) CGM measures glucose levels continuously and provides feedback via alarms/alerts, whereas intermittently scanned CGM takes values continuously but displays data only when scanned with a smart phone app or reader.[45] When used properly, RT-CGM and intermittently scanned CGM are useful tools to lower HbA1c or reduce hypoglycemia episodes in adults with T2D who are not meeting glycemic targets.[45] The use of CGM brings the patient's glucose levels out of the past and into the present, and enables consideration of future outcomes. Specifically, CGM data can be used to determine a patient's Time in Range (TIR) – the time that blood glucose is between 70 and 180 mg/dL.[46] Recent data suggest that improvement in TIR is associated with fewer diabetes complications; thus CGM adds useful information to help prevent poor outcomes, and also helps to validate HbA1c findings.[46]

Discussions of lifestyle and medication adherence and ways to improve them should be followed by any adjustment of therapy based on the overall picture (HbA1c, SMBG logs, TIR). Finally, an action plan should be established and the next appointment scheduled.

Engaging the team

In order to create an inertia-free environment, primary care HCPs must take an integrated approach involving the whole team; this includes the front desk, medical assistants, physician assistants, nurse practitioners, certified diabetes educators (CDEs), registered dietitians, and pharmacists, and others as appropriate. Everybody in the office needs to be aware of inertia-busting steps and promote those methods with the patient. Although an inertia-free environment starts in the primary care practice, it can be supported and extended outside the office. As noted earlier, to aid patients in reaching their goals, all patients should be referred to DSMES. Those using CGM devices require instruction on how to calibrate their device and how to understand readings that are discordant from their symptoms.[45] Remote monitoring of CGM devices and other virtual resources may be appropriate.

Additionally, help with care coordination and reimbursement support can make a big difference in patient success. To that effect a number of community resources are available, including patient advocates, community health workers, churches, as well as various websites (211.org, auntbertha.com) and virtual coaching services (Livongo, Onduo, PackHealth), which can address treatment barriers by enabling data-driven, individualized support from anywhere.[47] Virtual coaching connects patients with someone to keep them on track with their health goals, talk to them via the app, and keep them accountable without requiring patients to travel. For HCPs, the ADA has a new initiative to help physicians, nurse practitioners, physician assistants, pharmacists, dietitians, and diabetes educators with tools to overcome therapeutic inertia (https://professional.diabetes.org/meeting/other/overcoming-therapeutic-inertia).

Finally, assistance with reimbursement support can also help a patient obtain prescribed medications. HCPs and office staff can facilitate the prior authorization process. If a specific branded medication is considered necessary, include documentation that guided the decision process in the patient's chart, such as the duration of disease, current standards of care recommendations, prior treatments used without success, comorbid conditions and related secondary benefits such as CV or kidney protection.[48] This way, the information is in the electronic

medical record should it be required. To help with costs, consider utilizing manufacturer coupons for patients with commercial insurance. Medicare patients may be eligible for pharmaceutical-sponsored patient payment assistance; these forms are often easy to complete. Finally, HCPs may be able to offer medication samples during specific times of the year to help their Medicare patients once they hit the "donut hole."

Educating and engaging the patient

Primary care HCPs should act as a coach for their patients, not like a referee. The goal is to empower patients, and to teach them critical thinking so they can begin to make their own decisions about their diabetes care. It is important to remind patients regularly of the chronic nature of T2D, and that the progressive failure of beta cells may require medication changes/adjustments in the future. Educate patients on microvascular and macrovascular diabetes-related comorbidities, such as retinopathy, MI, HF, stroke, and CKD. Let them know how effective disease management using medications with secondary indications (eg, GLP-1 RAs and SGLT2 inhibitors) can lessen these risks. Use the teach-back method to check for understanding. Ask how they feel about adding medications to their current regimen, and manage patient expectations—there is no quick fix for T2D, and some medications may need to be taken for a lifetime. It is important to keep your patients motivated and to comment on their positive achievements. The goal is always to stay ahead of their disease, not fall behind.

Research has shown that primary care HCPs often only have a modest understanding of their patients' beliefs, such as preferences for getting involved in their health care, need for information, perceptions of health condition, beliefs about treatment effectiveness, level of health literacy, and mental status.[49] One example is the significant disconnect between what patients believe and what clinicians think patients believe regarding their concerns about weight gain, hypoglycemia, and pain from injections or finger sticks.[50] It is therefore best not to assume anything, and instead pose the right questions to the patient. This is especially important when it comes to medication adherence. In view of the fact that 50% of patients do not take their medications regularly, and in order to gauge patient adherence to treatment, it is vital for primary care HCPs to ask the right questions. Rather than asking, "Are you taking your medication regularly?," which only allows for a yes or no answer, it may be better to use questions like: "How often do you forget to take your medication?" or "Many of my patients with diabetes tend to forget to take their medication occasionally, do you experience the same?" or "I know that when *I* need to take medication it's very hard for me to remember every dose. How many pills do you think you've missed this week?" This allows the patient to be honest, which in turn allows the HCP to ask why doses were missed and develop a strategy with the patient.

CONCLUSIONS

Therapeutic inertia in primary care is a common occurrence and prevents patients with T2D from reaching their glycemic goals, increasing their risk of diabetes-related morbidity and mortality. Primary care HCPs can play a critical role in overcoming therapeutic inertia by making appropriate changes in their practice setting, scheduling diabetes-specific appointments, changing therapeutic interventions whenever HbA1c goals are not met, and enlisting the support from other health care HCPs and virtual and community resources. ●

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Therapeutic Inertia

How to Create a Proactive Primary Care Practice

What is therapeutic inertia?

Failure of health care professionals to **initiate, intensify, or de-intensify** therapy in a **timely** manner according to evidence-based clinical guidelines[1]

Prevalence of therapeutic inertia

Only **23%** of adults with diabetes achieve **all 3 goals**[2]

HbA1c	Blood pressure	Cholesterol
<7%	<130/80 mm Hg	<100 mg/dL

Potential consequences of therapeutic inertia in diabetes[3,4]

MICROVASCULAR COMPLICATIONS

Nephropathy · Neuropathy · Retinopathy

MACROVASCULAR COMPLICATIONS

Myocardial infarction · Heart failure · Stroke

DECREASED QUALITY OF LIFE

INCREASED HEALTH CARE COSTS[5]

Factors contributing to therapeutic inertia

PATIENTS

- Denial of disease
- Too many medicines
- Adverse effects
- Lack of education about diabetes
- Poor engagement

HEALTH CARE PROFESSIONALS

- Lack of awareness
- Make assumptions about their patients
- Perception of patient inability to access treatment

HEALTH CARE SYSTEM

- Lack of alignment among health systems and payor guidelines and standard of care guidelines
- Patient support systems fragmented and not utilized

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Building an inertia-free practice

Engage the team to identify and overcome inertia in your practice setting

- Front desk
- Medical assistants
- Advanced practice providers (physician assistants and nurse practitioners)
- Certified Diabetes Educators and registered dietitians
- Pharmacists

Utilize "inertia-busting" steps

- Remind patients that this is a **diabetes-focused appointment** and that other issues should be discussed separately
- Send **reminders** to bring a list of medications and any technology from glucose meters/logs
- Schedule **follow-up appointment** based on current HbA1c target before patient leaves
- **Commit to changing** therapy at every visit when improvement in HbA1c is not achieved

Schedule a diabetes-focused appointment[6]

Follow-up appointment time interval

- Every 6 months if HbA1c is ≤7% on 2 occasions
- Every 2-3 months if HbA1c is ≤9% and not at target
- Every 1-2 months if HbA1c >9%, until first HbA1c target is reached

Consider point-of-care HbA1c

Download diabetes management technology

Review medication adherence and potential adverse effects

Conclude with an action plan and schedule the next appointment

Engage and educate the patient

- Act as a coach for your patients, not like a referee
- Keep your patients motivated, comment on their positive achievements
- Be aware of, and honest about, the barriers you place on your own practice
- Often there is a significant disconnect between what patients believe and what clinicians think patients believe
- Educate patients on the progressive nature of the disease
- Don't assume anything, ask the right questions, allow the patient to be honest

Notes

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