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2 Clarke Drive, Suite 100
Cranbury, NJ 08512 • (609) 716-7777

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Managing Type 2 Diabetes and the Role of Sodium-Glucose Cotransporter 2 Inhibitors

Impact of Type 2 Diabetes

DIABETES IS A CHRONIC, progressive disease. It is characterized by elevated blood glucose levels resulting from defects in the body related to insulin secretion, insulin action, or both.¹⁻³ According to the 2020 CDC National Diabetes Statistics Report, an estimated 34.2 million Americans (about 1 in 10) have diabetes; type 2 diabetes (T2D) accounts for 90% to 95% of cases.^{4,5} Further, an additional 88 million American adults (1 in 3) have prediabetes, increasing their risk for T2D.⁶

T2D most often develops in people aged over 45 years, but children, teens, and young adults are also developing the disease in increasing numbers.^{4,5} Patients with diabetes often present with and are at a higher risk for comorbidities such as atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and renal disease.^{3,7-9} The results of a systematic review of global clinical records from a 10-year period showed that approximately one-third of patients with T2D had cardiovascular disease (CVD) as a comorbidity.¹⁰ Further, approximately two-thirds of deaths in people with diabetes are due to CVD, including ischemic heart disease, other forms of heart disease, principally congestive HF, and stroke.¹¹

Additionally, the presence of HF is an independent risk factor for developing diabetes.⁹ About 12% of patients with T2D have established HF, and approximately 3.3% of patients with T2D develop HF each year.⁹ Further, the presence and severity of chronic kidney disease (CKD) highlights individuals with a heightened risk for adverse health outcomes, such as HF.^{12,13} The CDC estimates that approximately 1 in 3 Americans with diabetes may have CKD, with diabetes further accounting for 38% of reported causes of end-stage kidney disease in the United States.¹⁴ Further, in patients with diabetes, the presence of albuminuria is an independent risk factor for mortality.¹⁵

It is essential that health care providers identify predictors of excess mortality in patients with T2D to optimally target risk-reduction strategies. Patients with T2D would benefit from more aggressive preventive programs to prevent CVD. Programs that set stringent standards are more likely to reduce the incidence of cardiovascular morbidity and mortality.⁹

Treatment Goals and Guidelines

Treatment goals for T2D center on maintaining a patient's quality of life by preventing or delaying associated complications and comorbidities. Treatment goals focus around glycemic control and CVD risk factor management. The American Diabetes Association (ADA) recommends regular patient follow-up and, importantly, a patient-centered approach to optimize treatment outcomes.^{16,17}

Lifestyle modifications, including losing weight, increasing physical activity, and adopting a healthy diet, remain first-line strategies for the management of T2D.^{16,18} However, most patients with T2D are unable to control hyperglycemia with diet and exercise and require pharmacotherapy. Generally, monotherapy with an oral hypoglycemic agent is initiated; however, owing to the progressive nature of the disease, most patients will eventually require combination therapy and ultimately injectable treatments as monotherapy or part of polytherapy.^{19,20} The ADA states that early combination therapy can be considered in some

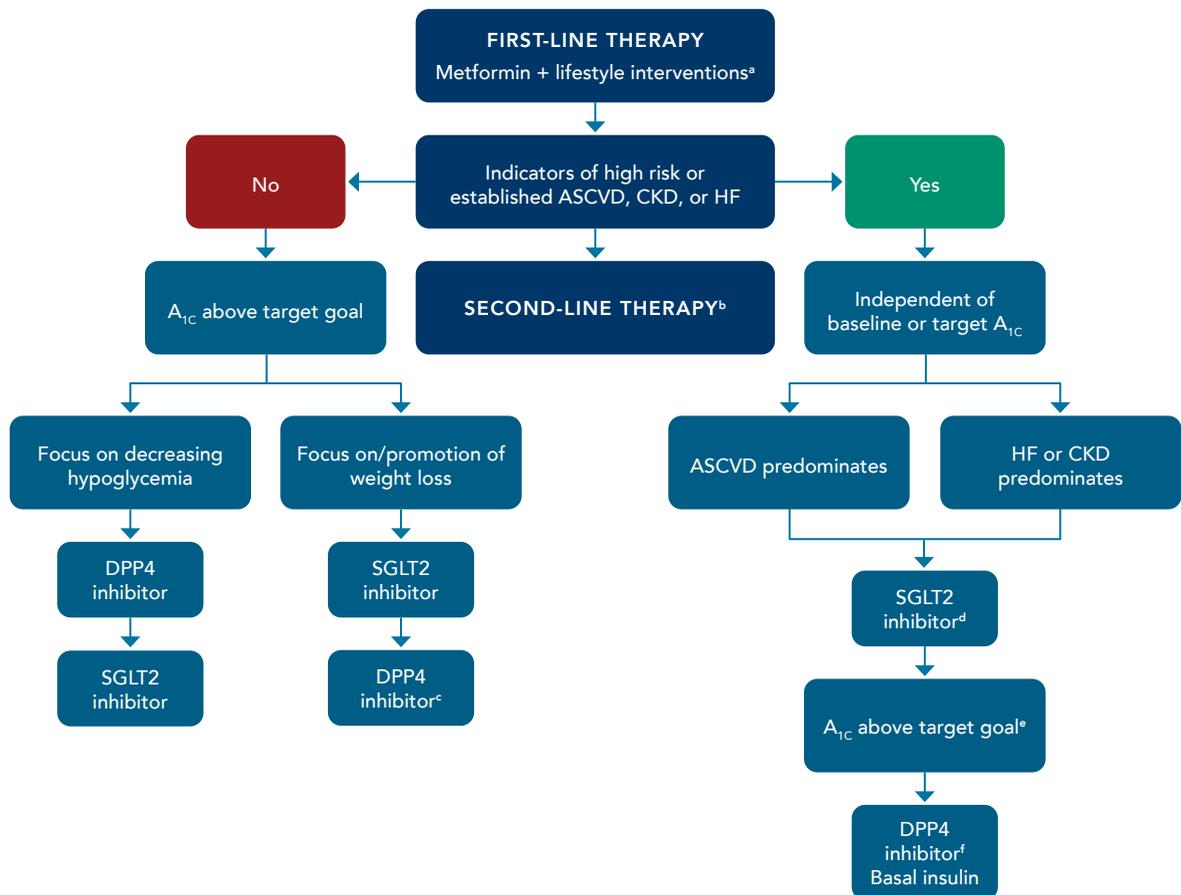
patients at treatment initiation to extend the time to treatment failure.²⁰ Pharmacologic therapy should take a stepwise approach, taking into account individual patient characteristics and the presence of comorbid diseases and complications.²⁰

Prior consensus statements by the ADA and the European Association for the Study of Diabetes focus on efficacy in reducing hyperglycemia, with treatment tolerability and safety being primary factors in glucose-lowering medication selection.^{16,21} However, an update to treatment recommendations was added to the latest 2020 consensus report. This update is due to new evidence regarding the

benefit of specific medications to reduce mortality, HF, and progression of renal disease in the setting of established CVD in patients with T2D.^{16,20}

The ADA has adopted these updates in their 2020 recommendations, *Standards of Medical Care: 9. Pharmacologic Approaches to Glycemic Treatment–2020* and *10. Cardiovascular Disease and Risk Management–2020*.^{17,20} The current ADA T2D treatment guidelines are based on indicators of high risk or established ASCVD, CKD, and HF, with glycated hemoglobin (A_{1C}) target levels also considered (**Figure**).²⁰ The ADA has suggested a treatment cascade, initiating with monotherapy treatment (such as

FIGURE. ADA Recommendations for SGLT2 Inhibitor and DPP4 Inhibitor Use if Metformin Alone Has Failed²⁰



A_{1C} , glycated hemoglobin; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4, dipeptidyl peptidase-4; HF, heart failure; SGLT2, sodium-glucose cotransporter 2. Adapted from American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes–2020. *Diabetes Care*. 2020;43(suppl 1):S98-S110. doi:10.2337/dc20-S009

^aPrescribed whenever these become new clinical considerations, regardless of background glucose-lowering medication.

^bAdditional second-line therapies include glucagon-like peptide 1 receptor agonists, thiazolidinediones, and sulfonylureases. For patients without established ASCVD and no indicators of high ASCVD risk, HF, or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Rather, drug choice is based on avoidance of adverse effects, particularly hypoglycemia and weight gain; cost; and patient preferences.

^cDPP4 inhibitor based on weight neutrality.

^dSGLT2 inhibitor with proven CVD benefit.

^eIf further intensification is needed or patient cannot handle SGLT2 inhibitor, additional agents should be chosen for CV safety.

^fNot saxagliptin in conditions of HF.

metformin) and progressing through dual or triple therapy options depending on patient characteristics and preferences (Figure).²⁰

T2D Available Drug Treatment Options Per Updated ADA Guidelines

Metformin

The ADA states that metformin is the preferred initial pharmacologic agent for the treatment of T2D and should be started at the time T2D is diagnosed unless there are contraindications.²⁰ However, as stated previously, T2D is a progressive disease and often requires additional therapy with combinations of drugs that have complementary mechanisms of action.²² As such, many patients will require dual combination therapy to achieve their target A_{1C} level.²⁰ Current recommendations are to use a stepwise addition of medications to metformin to maintain A_{1C} at target levels (Figure).²⁰

DPP4

Dipeptidyl peptidase-4 (DPP4) inhibitors are oral diabetic agents that are placed as an add-on second-line therapy after metformin failure as insulinotropic agents that have no intrinsic hypoglycemia risk.^{18,23} There are currently four DPP4 inhibitors available in the United States that have been approved by the FDA (**Table 1**).²⁴⁻⁴⁰

All four DPP4 inhibitors appear to have similar efficacy in terms of glucose-lowering ability.⁴⁰ A notable favorable characteristic of DPP4 inhibitors is their efficacy and safety profile in patients with impaired renal function.²³ Further, in phase 3 clinical trials, DPP4 inhibitors have shown good safety and tolerability profiles. The most frequent adverse events (AEs) observed were nasopharyngitis and skin lesions, although 2 studies showed an increased rate of hospitalization due to HF.^{23,29,41,42} As CVD outcomes and safety are a concern for the T2D patient population, mortality and morbidity associated with therapy options should be considered when making treatment selections.

Several CVD outcomes trials have been completed, comparing DPP4 inhibitors with placebo against the

backdrop of standard diabetes care, and the DPP4 inhibitors have been shown to have a neutral effect on CVD outcomes.^{40,41,43,44} Meta-analyses, however, suggest a possible increased risk of acute HF or hospitalized HF with certain DPP4 inhibitors versus placebo; more research is required to explore these observations.^{45,46} As DPP4 inhibitors come with the possible heightened risk of negative CVD effects, they are suggested as second-line therapy as an add-on to metformin in patients with T2D who need to control hypoglycemia but have no preexisting CVD.^{20,23,45}

In assessing the cardiovascular safety profiles of antidiabetic drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitor therapies have emerged with robust evidence for reducing the risk of adverse CVD outcomes in people with T2D who have either established CVD or are at risk of developing CVD and HF.⁸ Additional benefits have also been seen in those at risk of renal decline and progression to CKD.⁸

SGLT2 Inhibitors

SGLT2 inhibitors are a fast-growing class of diabetes drugs given their convenient oral route of administration, strong A_{1C} efficacy data, observed reductions in body weight, and antihypertensive effects. Importantly, these drugs show similar efficacy from early through late stages of diabetes.⁴⁷ The FDA has approved four SGLT2 inhibitor-based therapies for use in T2D patients, as they have been shown to convey CVD protective effects and delay the progression of CKD;⁴⁸⁻⁵⁰ clinical trial data are summarized in **Table 2**.⁴⁸⁻⁵⁷ The primary outcomes for all available studies were a combination of composite end points of CVD death, myocardial infarction (MI) or ischemic stroke, and HF or hospitalization due to HF.^{18,48-50} A reduction in risk of HF, MI, and stroke are the most common CVD benefits noted in SGLT2 inhibitor clinical studies (Table 2).⁴⁸⁻⁵⁷ The most common AEs noted in most trials were an increased risk of genital infections in the SGLT2 inhibitor population compared with placebo, although the CANVAS trial also noted a higher incidence of amputations.⁴⁸⁻⁵⁰

TABLE 1. Currently Available DPP4 Inhibitor Monotherapies and Fixed-Dose Combination Therapies Containing DPP4 Inhibitors for Use in the Treatment of Type 2 Diabetes²⁴⁻⁴⁰

SGLT2 inhibitor	SGLT2 inhibitor + metformin	DPP4 inhibitor	DPP4 inhibitor + metformin	DPP4 inhibitor + SGLT2 inhibitor
Canagliflozin	Canagliflozin + metformin	Linagliptin	Linagliptin + metformin	
Dapagliflozin	Dapagliflozin + metformin	Saxagliptin	Saxagliptin + metformin	Dapagliflozin + saxagliptin
Empagliflozin	Empagliflozin + metformin	Sitagliptin	Sitagliptin + metformin	Empagliflozin + linagliptin
Ertugliflozin	Ertugliflozin + metformin			Ertugliflozin + sitagliptin

DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.

TABLE 2. SGLT2 Inhibitor Clinical Trials in Type 2 Diabetes Treatment⁴⁸⁻⁵⁷

Drug; clinical trial	Population studied: T2D + additional comorbid condition(s):	N	Mean age (y)	Dosing and schedule	Primary outcomes	Adverse events	Conclusions
Canagliflozin; CANVAS/ CANVAS-R	Aged ≥30 years with symptomatic ASCVD or aged ≥50 years with ≥2 of the following: Diabetes for ≥10 years, smoking, SBP >140 mm Hg, on antihypertensives, micro-/macroalbuminuria, HDL-C <38.7 mg/dL, eGFR >30 mL per minute per 1.73 m ²	10,142	63	CANVAS: canagliflozin 100 or 300 mg CANVAS-R: initial dose of canagliflozin 100 mg daily, optional increase to 300 mg daily starting at week 13	Composite death from CVD causes, nonfatal MI, or stroke	Genital infections Extracellular volume depletion Diuresis Lower extremity amputations	Rate of the primary outcome was lower with canagliflozin than with placebo (26.9 vs 31.5 participants, respectively, per 1000 patient-years) Possible benefit with respect to the progression of albuminuria (HR, 0.73; 95% CI, 0.67-0.79) 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes (HR, 0.60; 95% CI, 0.47-0.77)
Canagliflozin; DECLARE-TIMI 58	Established ASCVD or at risk for ASCVD	17,160	64	Canagliflozin 10 mg once daily	MACE, composite of CV death, or hospitalization for HF	Fournier's gangrene Diabetic ketoacidosis Genital infections	No decrease in rate of MACE (8.8% dapagliflozin vs 9.4% placebo; HR, 0.93; 95% CI, 0.84-1.03; P=.17) Lower rate of CVD death or hospitalization for HF (4.9% vs 5.8%, respectively; HR, 0.83; 95% CI, 0.73-0.95; P=.005) Lower rate of hospitalization for HF (HR, 0.73; 95% CI, 0.61-0.88; P=.005)
Empagliflozin; EMPA-REG	Established CVD, eGFR 30 mL per minute per 1.73 m ² of body surface area	7020	63	Empagliflozin 10 mg or 25 mg once daily	Composite death from CV causes, nonfatal MI, or stroke	Genital infections Urosepsis	Death from CVD causes (3.7% empagliflozin vs 5.9% placebo; 38% relative risk reduction) Hospitalization for HF (2.7% and 4.1%, respectively; 35% relative risk reduction) Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction)
Empagliflozin + linagliptin	Aged ≥18 years with BMI ≤45 kg/m ² and A _{1c} >53 to ≤91 mmol/mol Stable metformin treatment and on diet and exercise plan	674	56	FDC: Empagliflozin 25 mg/ linagliptin 5 mg Empagliflozin 10 mg/ linagliptin 5 mg SA: Empagliflozin 25 mg Empagliflozin 10 mg Linagliptin 5 mg once daily	Change from baseline A _{1c} at week 24	Urinary tract infections Genital infections	Adjusted mean A _{1c} changes from baseline: Empagliflozin 25 mg/ linagliptin 5 mg, 1.19% Empagliflozin 10 mg/ linagliptin 5 mg, -1.08% Empagliflozin 25 mg, -0.62% Empagliflozin 10 mg -0.66% Linagliptin 5 mg, -0.70% (P<.001 for all comparisons)

(Continued)

TABLE 2. (Continued) SGLT2 Inhibitor Clinical Trials in Type 2 Diabetes Treatment⁴⁸⁻⁵⁷

Drug; clinical trial	Population studied: T2D + additional comorbid condition(s):	N	Mean age (y)	Dosing and schedule	Primary outcomes	Adverse events	Conclusions
Ertugliflozin + sitagliptin; Phase 3 VERTIS FACTORIAL	≥18 years of age A _{1c} ≥7.5% to ≤11.0% Stable metformin monotherapy	1232	55	5 treatment groups: SA: Ertugliflozin 5 mg Ertugliflozin 15 mg Sitagliptin 100 mg FDC: Ertugliflozin 5 mg/ sitagliptin 100 mg Ertugliflozin 15 mg/ sitagliptin 100 mg Once daily	Change from A _{1c} at week 26	Genital mycotic infections Urinary tract infections	Significant reductions in A _{1c} for both FDC compared with SA (<i>P</i> < .001 for all comparisons)
Ertugliflozin + metformin + sitagliptin; VERTIS SITA	≥8 weeks treatment of metformin (≥1500 mg/d) and sitagliptin (100 mg/d) A _{1c} 7.0% to 10.5% (53-91 mmol/mol)	462	59	Ertugliflozin 5 mg or Ertugliflozin 15 mg Once daily	Change from A _{1c} at week 26	Genital mycotic infections Nasopharyngitis Urinary tract infections	A _{1c} mean changes -0.7% (-7.5 mmol/mol) and -0.8% (-8.3 mmol/mol) for ertugliflozin 5 and 15 mg, (both <i>P</i> < .001) compared with placebo
Ertugliflozin + metformin	Aged 18 to 70 years A _{1c} 7.0 to 11.0% Stable metformin treatment	328	54	Ertugliflozin 1, 5, 10 or 25 mg Sitagliptin 100 mg (positive control) Once daily, morning	A _{1c} change from baseline to week 12	Upper respiratory infection Diarrhea Urinary tract infections	Mean A _{1c} significantly decreased for all ertugliflozin treatment groups (<i>P</i> ≤ .002)
Saxagliptin + dapagliflozin	Aged ≥18 years A _{1c} ≥8.0% to ≤12.0% Stable metformin treatment	534	54	FDC: Saxagliptin 5 mg, dapagliflozin 10 mg plus metformin Saxagliptin 5 mg, placebo plus metformin Dapagliflozin 10 mg, placebo plus metformin	Adjusted mean change from baseline A _{1c} at week 24	Urinary tract infections Genital infections	Adjusted mean A _{1c} baseline change: Saxagliptin+dapagliflozin+metformin: 1.5% Saxagliptin+metformin: -0.9% (<i>P</i> < .0001) Dapagliflozin+metformin: 1.2% (<i>P</i> < .02, compared with Saxagliptin+dapagliflozin +metformin)
Ertugliflozin; VERTIS-CV	Aged ≥40 years A _{1c} 7.0% to 10.5% Established ASCVD of the coronary, cerebral, and/or peripheral arterial systems	8238	64	Ertugliflozin 5 mg or 15 mg Once daily	CV death, nonfatal MI, or stroke	Urinary tract infection and genital mycotic infection Acute kidney injury Diabetic ketoacidosis	Primary outcome, CV death, nonfatal MI, or stroke for ertugliflozin vs placebo <i>P</i> < .001 for noninferiority: CV death: 1.8% ertugliflozin vs 1.9% (<i>P</i> = 0.39) Nonfatal MI: 1.7% ertugliflozin vs 1.6% (<i>P</i> = 0.66) Stroke: 0.8% ertugliflozin vs 0.8% (<i>P</i> = 0.99) HF hospitalization: 2.5% ertugliflozin vs 3.6% (<i>P</i> = 0.006)

A_{1c}, glycated hemoglobin; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; SA, single agent; SBP, systolic blood pressure; T2D, type 2 diabetes; UA, unstable angina.

Fixed-Dose Treatment Combinations

Although the above treatment options present favorable rationales for the use of each agent, there are current data to support initial combination therapy to more rapidly attain glycemic goals.^{58,59} Clinical trials have demonstrated that this approach is superior to sequential addition of medications, in terms of extending time to primary and secondary failure and decreasing risk of associated complications.^{60,61}

DPP4 inhibitors and metformin-based fixed-dose combinations are accessible and may safely be used in T2D patients to reach treatment goals (Table 2).^{23,48-57} Fixed-dose combinations of DPP4 and SGLT2 inhibitors can also be used (as dual therapy when metformin is contraindicated or not tolerated, or as triple therapy with metformin) to achieve treatment goals in patients with T2D (Table 2).^{23,48-57} DPP4 and SGLT2 inhibitor combinations have complementary actions that have resulted in additive reductions of glycemic and blood pressure parameters.^{23,52} Findings of recent clinical trials of triple-therapy combinations with DPP4 and SGLT2 inhibitors have demonstrated significant clinical benefit over the use of each individual component when utilized on a background of metformin (Table 2).⁴⁸⁻⁵⁷ A phase 3, randomized, double-blind, parallel-group study by Defronzo et al, examining different treatment combinations of empagliflozin and linagliptin as compared with each ingredient individually, noted more significant reductions in A_{1c} levels from baseline for those patients receiving the combination treatments ($P < .001$ for all comparisons) (Table 2).⁴⁸⁻⁵⁷ Further, SGLT2 inhibitors and metformin-based combinations have demonstrated reductions in glycemia, blood pressure, body weight, and albuminuria in people with diabetes.^{48,53-55,62} A study by Pratley et al demonstrated that in T2D patients with inadequate glycemic control with metformin, co-administration of ertugliflozin (5 or 15 mg) with sitagliptin (100 mg) provided significantly greater improvements in measures of glycemic control compared with addition of either agent alone ($P < .001$ for all comparisons).⁵³ Notably, in a phase 3 randomized double-blind, active controlled, parallel group study, patients on a fixed dose treatment of saxagliptin + dapagliflozin + metformin experienced a lower rate of AE compared with those patients on treatments of either saxagliptin or dapagliflozin alone.⁵⁶

While these results illustrate that a fixed-dose combination treatment can help attain T2D treatment goals, the choice of treatment should be tailored to each individual and their T2D prognosis and comorbidities. For those patients with T2D and no elevated CV risk DPP4 inhibitors, such as sitagliptin, are a safe and effective treatment option and can lead to similar treatment outcomes. A randomized, double-blind, placebo- and active-controlled, parallel group, double-dummy, dose-ranging study by Amin et al demonstrated that a lower dose combination

of ertugliflozin (5 mg) plus metformin lead to similar A_{1c} reductions when compared with a higher dose of sitagliptin (100 mg) alone.⁵⁵ Ultimately the choice of treatment regimen should be made through an open dialogue taking into consideration patient treatment goals, T2D comorbidities, and patient lifestyle and preferences.

Summary

Despite more than 200 years of research on lifestyle management of diabetes and more than 50 years of comparative-effectiveness research in diabetes, innumerable unanswered questions regarding the management of T2D remain.¹⁶ T2D treatment guidelines have evolved to adapt to the larger picture of disease, but T2D still carries a significant burden of illness and unmet need. T2D treatment is further complicated by patient comorbidities and their associated risk factors. Optimizing treatment pathways can help alleviate the burden of disease and reach treatment goals for this patient population.

SGLT2 inhibitors, a new option recommended by the ADA 2020 guidelines either as single agents or in fixed-dose combinations with other treatments, offer patients the option to take advantage of benefits beyond stabilization of A_{1c} levels. SGLT2 inhibitors have shown favorable CVD effects, including a reduction in the risk of hospitalization for HF, predominantly in patients with T2D and established CVD^{48,49,51}; they have also been shown to delay the progression of kidney disease.⁵¹ ♦

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