Antihyperglycemic Algorithms for Type 2 Diabetes: Focus on Nonglycemic Outcomes

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Type 2 diabetes management continues to increase in complexity as more pharmacologic medication classes become available and high-quality clinical trials are completed. Because many antihyperglycemic agents could be appropriate for a given patient, expert treatment guidance is indispensable. Algorithms can help to guide clinicians toward initiating more evidence-based therapy and critically thinking about patient-centered factors that may influence their medication choices. High-quality cardiovascular, renal, and heart failure outcomes trials completed in the past several years have changed the paradigm of how we think about antihyperglycemic agents. Considerations for atherosclerotic cardiovascular disease, heart failure, and renal insufficiency now figure prominently in treatment algorithms for type 2 diabetes, and the results of recent outcomes trials have significantly transformed algorithmic guidelines published by diabetes, endocrinology, and cardiology associations.

The type 2 diabetes epidemic in the United States continues to burden patients, health care providers, health care systems, and society. Normalization of hyperglycemia, the hallmark abnormality of diabetes, is the focus of treatment to reduce microvascular disease morbidity and mortality but has a less prominent role in macrovascular disease prevention (1). Three large trials—ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (2), ACCORD (Action to Control Cardiovascular Risk in Diabetes) (3), and VADT (Veterans Affairs Diabetes Trial) (4)—explored improved glycemic control to reduce macrovascular disease outcomes in people with type 2 diabetes who also had or were at high risk for cardiovascular disease (CVD). All three trials, over a period of 3–7 years, reported no improvement in macrovascular outcomes with improved glycemia. In fact, the ACCORD trial (3) was prematurely stopped because of a 22% excess risk of mortality after 3.5 years.

However, well-established risk factors for CVD should be aggressively addressed. Obesity, hypertension, dyslipidemia, stroke, myocardial infarction (MI), heart failure (HF), and peripheral vascular disease are all more prevalent in people with type 2 diabetes than in those without diabetes and should be the focus of interventions to prevent or reduce CVD morbidity and mortality (5,6). Specifically, people with type 2 diabetes have a two- to fourfold higher risk of MI or stroke, and ∼65% of them will die of CVD (7). Historically, these CVD risks have been addressed separately, with a focus on glycemic control through lifestyle and antihyperglycemic pharmacologic therapy (8). Now, the results of cardiovascular outcomes trials (CVOTs) of several classes of antihyperglycemic agents are blurring the lines between micro- and macrovascular protection for people with type 2 diabetes.

Why Treatment Algorithms Are Needed for Type 2 Diabetes

The pharmacologic management of type 2 diabetes has become more complex over time. In 1995, there were limited options for oral treatment, including metformin and sulfonylureas, and clinicians used these agents before or in combination with insulin therapy. By 2000, α-glucosidase inhibitors (AGIs), thiazolidinediones (TZDs), and meglitinides had been added as oral options (9). There are now 12 classes of medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes.

With complexity often comes uncertainty, and algorithms for type 2 diabetes treatment have been developed (or recently updated) by multiple professional organizations,

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https://doi.org/10.2337/ds20-0067

in part, to help clinicians better understand the evidence-based placement of antihyperglycemic agents in the treatment hierarchy and implement strategies to help people with diabetes reach their recommended therapeutic goals. Expansion of the number of well-controlled trials of diabetes pharmacologic agents provided the evidence needed to support these algorithmic recommendations.

In this article, we briefly review the evidence for antihyperglycemic agents that have reported improved macrovascular outcomes and then concentrate on guidelines from national and international diabetes-relevant organizations that have been published in the past 2 years, as the diabetes treatment landscape has rapidly evolved. Well-designed algorithms start with a critical explanation of their grading and use of available scientific evidence. However, it should be kept in mind that algorithms should always be considered guidelines because they still must be individually tailored based on diverse patient-centered factors such as tolerability, contraindications, comorbidities, motivation, self-efficacy, and affordability cost (10).

Changes that have occurred over the past several years involving CVOTs conducted in populations with type 2 diabetes have reshaped how to pursue glycemic control. In response to concerns about the cardiovascular safety of rosiglitazone and muraglitazar, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted in 2008 to recommend completion of long-term cardiovascular safety trials or other "equivalent evidence" to ensure that there is no heightened CVD risk with new glucose-lowering medications (11,12). The primary aim of these trials was not to improve glycemic control, since the earlier ADVANCE, ACCORD, and VADT trials found no improvement in macrovascular outcomes with improved glycemia (2–4). Rather, the main aim of these newer trials was to compare exposure to the tested antihyperglycemic agents versus usual care to ensure the cardiovascular safety of the tested drugs. Since the FDA's 2008 guidance was published, a large number of CVOTs have been completed for agents in newer antihyperglycemic classes, including dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists. Benefits have been found with some agents and classes with regard to reduced risks for CVD, chronic kidney disease (CKD), and hospitalization for heart failure (HHF) with truly paradigm-shifting outcomes. Interestingly, the FDA released a new draft guidance document titled "Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control" on 9 March 2020 that does not expressly continue the requirement for dedicated CVOTs for diabetes medications (13). However, it does require a robust database of subjects exposed to the proposed drug for up to 2 years, including patients with CKD stage 3 or 4, CVD, and age ≥65 years (13).

Review of Key Evidence From CVOTs

Lifestyle intervention continues to be the cornerstone of treatment in all published algorithms for type 2 diabetes treatment. Such intervention may include dietary changes, increased physical activity, weight management strategies, diabetes self-management education, self-monitoring of blood glucose, and other strategies to improve glycemia. Aggressive management of CVD risk factors, including blood pressure and lipid control, antithrombotic therapy, and smoking cessation, is also emphasized in all national professional association algorithms.

Despite these strategies, it is understood that pharmacologic glycemic therapy is necessary in the majority of people with type 2 diabetes at or soon after diagnosis, and that leveraging the additional CVD and renal protection afforded by some antihyperglycemic agents may be advantageous. Currently, there is compelling evidence to support positive effects of the SGLT2 inhibitor and GLP-1 receptor agonist drug classes on cardiovascular, renal, and/or HF outcomes, and this evidence has been incorporated into the latest treatment algorithms.

Evidence From SGLT2 Inhibitor Trials

For SGLT2 inhibitors, the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial (14) with empagliflozin and the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program (15) with canagliflozin reported a significant reduction in three-point major adverse cardiovascular events (MACE), which included cardiovascular death, nonfatal MI, and nonfatal stroke in mostly secondary-prevention populations with type 2 diabetes (i.e., individuals with prior cardiovascular events). The DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial (16) with dapagliflozin reported similar outcomes in secondary-prevention patients with type 2 diabetes but no significant reduction in MACE for primary-prevention patients (i.e., those at risk for developing CVD). Renal composite outcomes and HHF were significantly reduced in primary- and secondary-prevention cohorts (14–16).

Two HF-specific trials of SGLT2 inhibitors in patients with HF with reduced ejection fraction—the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of

Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) (17) and the EMPEROR-REDUCED (Cardiovascular and Renal Outcomes With Empagliflozin in Heart Failure) (18) trials—reported significant reductions in HHF with dapagliflozin and empagliflozin, respectively. SGLT2 inhibitors also reduced the risk of a deleterious composite renal outcome, including increased serum creatinine, renal replacement therapy, and renal death in patients with type 2 diabetes and diagnosed renal insufficiency in the CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) (19) and DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) (20) trials.

Together, these trials have elevated the SGLT2 inhibitors (canagliflozin, empagliflozin, and dapagliflozin) as cardiorenal- and HHF-protective medications. People with type 2 diabetes and CVD in conjunction with renal insufficiency or HF, and those at high risk for these comorbidities, should be offered an SGLT2 inhibitors as part of their diabetes management regimen, irrespective of their level of glycemic control.

Evidence From GLP-1 Receptor Agonist Trials

GLP-1 receptor agonists have also been well studied in CVOTs. Longer-acting agents in this class (liraglutide, semaglutide, and dulaglutide) have reported positive results with regard to prevention of CVD events. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial (21), liraglutide significantly reduced three-point MACE, as did semaglutide in SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes) (22) and dulaglutide in the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial (23). Exenatide extended release (ER) dosed weekly in the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial (24) resulted in a reduction in three-point MACE that did not reach statistical significance ($P = 0.06$). The EXSCEL trial allowed SGLT2 inhibitors to be used as rescue therapy, which may have muted the cardioprotective effect. Two trials—ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) (25) and PIONEER-6 (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes) (26)—reported noninferiority of lixisenatide and oral semaglutide, respectively, compared with usual care. Lixisenatide is dosed daily, but pharmacokinetically does not last 24 hours, which may explain why it did not reduce cardiovascular events in patients with previous acute coronary syndrome, whereas the oral semaglutide study may have been underpowered and of a too-short duration to reveal positive cardiovascular outcomes. A dedicated CVOT is being conducted for oral semaglutide (27).

Overall, the preponderance of the evidence supports longer-acting GLP-1 receptor agonists for cardioprotection in people with type 2 diabetes and CVD. In addition, the REWIND trial (23) followed a large number of primary-prevention patients with type 2 diabetes (69% of those enrolled) who were at high risk of developing CVD. In contrast to CVOTs for the SGLT2 inhibitors, the REWIND trial found similar CVD benefits in its primary- and secondary-prevention cohorts. Thus, only the longer-acting GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide, and possibly exenatide ER) should be recommended to prevent cardiovascular events in patients with type 2 diabetes who have or are at high risk of developing CVD.

Evidence From DPP-4 Inhibitor Trials

All CVOTs of DPP-4 inhibitor agents were neutral in their primary outcomes for MACE, demonstrating safety but not superiority (28). This includes the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes) trial (29), which compared the DPP-4 inhibitor linagliptin to the sulfonylurea glimepiride.

There was a significant increase in HHF with saxagliptin in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus—Thrombolysis in Myocardial Infarction) trial (30) and a trend toward increasing HHF with alogliptin in the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial (31). Neither linagliptin in the CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) trial (32) nor sitagliptin in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial (33) reported an excess HHF risk.

Based on this evidence, use of saxagliptin or alogliptin is not recommended in patients with HF, and DPP-4 inhibitors overall are not recommended as first- or second-line therapies for people with type diabetes who have or are at risk for developing CVD.

Evidence From Pioglitazone Trials

Two cardiovascular safety trials of the TZD pioglitazone were conducted before or already underway when the FDA's 2008 guidance on CVOTs was issued. The PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial (34) involving patients with type 2 diabetes and

CVD found a nonsignificant reduction in its primary four-point MACE outcome (which added peripheral revascularization to the usual MACE components), but found a significant reduction in three-point MACE when peripheral revascularization was excluded. The IRIS (Insulin Resistance Intervention After Stroke) trial (35) in patients without diabetes who had previously had a stroke or transient ischemic attack found a decreased risk of subsequent stroke or MI; however, pioglitazone is not recommended as first- or second-line treatment for people with type 2 diabetes and CVD, likely because of the significant increases in weight and HHF noted in both of these trials (34,35).

Review of Current Type 2 Diabetes Treatment Guidelines

American Diabetes Association Guidelines

The treatment algorithm in the American Diabetes Association's (ADA's) *Standards of Medical Care in Diabetes—2021* (36) recommends metformin and lifestyle as initial treatment for type 2 diabetes, even when atherosclerotic cardiovascular disease (ASCVD), CKD, or heart failure with reduced ejection fraction (HFrEF) are present (Figure 1 and Table 1). Metformin has been on the market in the United States since 1995. It effectively lowers glucose, is safe if used as recommended, is inexpensive, and may reduce the risk of CVD and death versus sulfonylurea therapy (37). Also, the ADA guidelines note that most of the participants enrolled in CVOTs of antihyperglycemic medications were taking metformin at baseline.

The next step in the ADA algorithm depends on whether a patient has a diagnosis of ASCVD, CKD, or HFrEF or is at high risk (defined as >50% stenosis of coronary, carotid, and/or peripheral vessels or left ventricular hypertrophy). For patients with or at high risk for ASCVD, the ADA recommends the addition of an SGLT2 inhibitor or GLP-1 receptor agonist regardless of current A1C. In other words, even for people with type 2 diabetes and one or more of these comorbidities who attain their glycemic targets with metformin therapy, addition of a GLP-1 receptor agonist or SGLT2 inhibitor would still be warranted. If a patient is newly diagnosed with type 2 diabetes and has CVD, metformin and a GLP-1 receptor agonist or SGLT2 inhibitor can be started concurrently. The ADA favors the addition of a GLP-1 receptor agonist or SGLT2 inhibitor with proven, label-indicated CVD benefits in this population. If intolerance or a contraindication exists to agents in one of the classes, an agent from the other class may be considered.

The current ADA algorithm also includes a dedicated pathway for CKD and HF (Figure 1). If CKD with albuminuria or

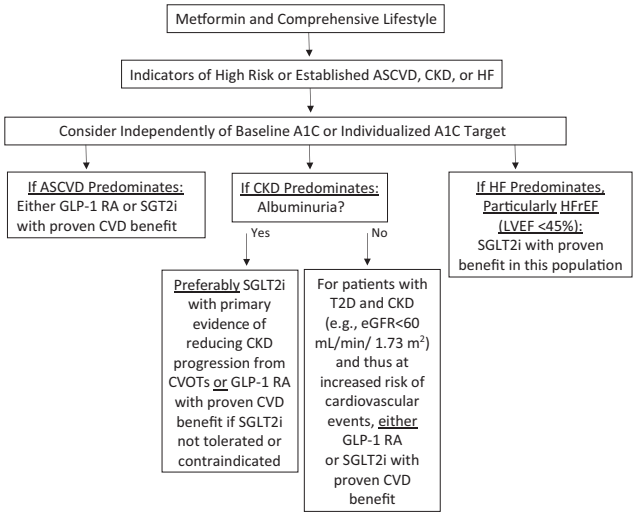

FIGURE 1 Abridged ADA pharmacologic treatment algorithm for type 2 diabetes (36). LVEF, left-ventricle ejection fraction; RA, receptor agonist; SGLT2i; SGLT2 inhibitor; T2D, type 2 diabetes.

HFrEF predominate, then an SGLT2 inhibitor with proven label-indicated benefit is preferred. If CKD without albuminuria is noted, the emphasis is placed on the CVD risk associated with CKD, and either an SGLT2 inhibitor or a GLP-1 receptor agonist may be used for cardioprotection. In other words, CKD algorithmically classifies patients with type 2 diabetes and CKD without albuminuria as being at high risk of CVD (38).

As previously mentioned, HFrEF outcome trials (17,18) with SGLT2 inhibitors have demonstrated that these agents decrease HHF, and renal outcomes trials of agents in this class (19,20) have shown reduced progression of CKD. Dapagliflozin is recognized for its HF and CKD outcomes data (17,20), canagliflozin for its renal data (19), and empagliflozin for its data on HF in people with type 2 diabetes (18).

In 2021, the American College of Cardiology (ACC) continued to endorse the ADA's Standards of Care section on cardiovascular disease and risk management, which included guidelines for the use of antihyperglycemic agents for CVD and HF (39). The European Association for the Study of Diabetes (EASD) copublished the ADA's type 2 diabetes treatment algorithm in 2018 and its update in 2019 (40,41). The continued endorsement of this approach from both the ACC and the EASD is implied.

American Association of Clinical Endocrinologists/ American College of Endocrinology Guidelines

Another widely followed algorithm in the United States was published by the American Association of Clinical

TABLE 1 Comparison of Recent Pharmacologic Therapy Algorithms for Glycemic Management in Type 2 Diabetes

Recommendation	ADA (36)	AACE/ACE (42)	ESC (43)	ACC/AHA (CVD Primary Prevention) (44)	ACC (CVD Secondary Prevention) (45)
Metformin as first-line therapy in patients with no CVD, CHF, or CKD	Yes	Yes	Yes	Yes	NA
Metformin as first-line therapy in patients with CVD, CHF, or CKD	Yes*	No	No	NA	No
Primary prevention: high-risk patients with multiple risk factors but without overt CVD, CKD, or HF	Metformin*	SGLT2 inhibitor or long-acting GLP-1 receptor agonist	SGLT2 inhibitor or GLP-1 receptor agonist if high risk of HF; GLP-1 receptor agonist if high risk of CVD	SGLT2 inhibitor or GLP-1 receptor agonist added to metformin if CVD risk factors and A1C ≥7%	SGLT2 inhibitor if high risk of CVD, CKD, or HF; GLP-1 receptor agonist if high risk of CVD
With comorbidities					
CVD	SGLT2 inhibitor or GLP-1 receptor agonist	SGLT2 inhibitor or long-acting GLP-1 receptor agonist	SGLT2 inhibitor or GLP-1 receptor agonist	NA	SGLT2 inhibitor or GLP-1 receptor agonist
HFrEF	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor	NA	SGLT2 inhibitor
CKD with albuminuria†	SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor‡ or GLP-1 receptor agonist‡	NA	SGLT2 inhibitor
CKD without albuminuria†	SGLT2 inhibitor or GLP-1 receptor agonist	SGLT2 inhibitor	SGLT2 inhibitor‡ or GLP-1 receptor agonist‡	NA	SGLT2 inhibitor

*Metformin is considered initial therapy, but additional and/or alternative agents may be considered in special circumstances, such as in individuals with established or increased risk of cardiovascular or renal complications. Addition is irrespective of A1C on metformin. †Only the ADA/EASD algorithm separates out CKD with or without albuminuria. The ACC algorithm states that, if eGFR is <30 mL/min/1.73 m^2, consider a GLP-1 receptor agonist. ‡SGLT2 inhibitors (empagliflozin, canagliflozin, or dapagliflozin) have class 1, level B, recommendation for CKD, whereas GLP-1 receptor agonists (liraglutide or semaglutide) have a class 2a, level B, recommendation. NA, not applicable.

Endocrinologists (AACE)/American College of Endocrinology (ACE) (Figure 2 and Table 1) (42). As a result of data from CVOTs, the ADA/EASD and AACE/ACE algorithms are quite similar in some, but not all, of their recommendations.

The order of medications in the AACE/ACE algorithm is hierarchical for recommended usage. Metformin is listed as first-line therapy if CVD, HF, and CKD are not present, but an SGLT2 inhibitor or long-acting GLP-1 receptor agonist is recommended as first-line therapy if these comorbidities are present. A long-acting GLP-1 receptor agonist is defined as an agent with effects lasting >24 hours. If metformin has already been prescribed, the same assessment for CVD, CKD, and HF should be carried out when considering combination therapy. As with the ADA algorithm, the recommended use of a GLP-1 receptor agonist or SGLT2 inhibitor is based on risk of comorbidities. Specifically, GLP-1 receptor agonist or SGLT2 inhibitor therapy should be used independent of glycemic control if a

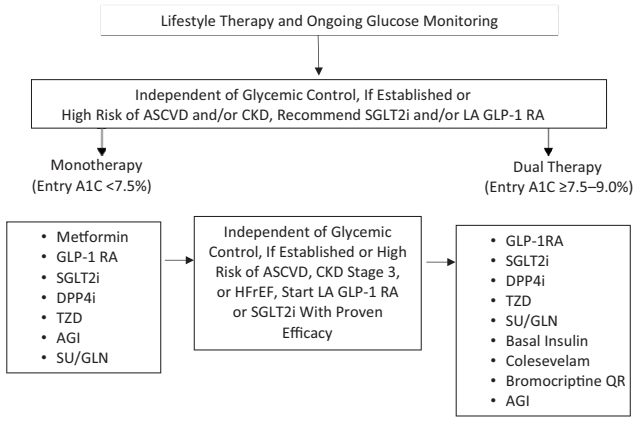

FIGURE 2 Abridged AACE/ACE comprehensive type 2 diabetes treatment algorithm (42). DPP4i, DPP-4 inhibitor; GLN, glinide (meglitinide); LA, long-acting; QR, quick release; RA, receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

patient is at high risk for or has established CVD, HFrEF, or CKD stage 3 or higher. Canagliflozin is recommended for CKD and dapagliflozin for HFrEF and, again, only GLP-1 receptor agonists with a duration of action >24 hours are recommended (40).

The AACE/ACE algorithm also includes all other current classes of type 2 diabetes medications for possible inclusion in combination therapy regimens. After metformin, GLP-1 receptor agonists, and SGLT2 inhibitors, the algorithm includes hierarchical use of DPP-4 inhibitors, TZDs, sulfonylureas, basal insulin, colesevelam, bromocriptine quick release, and AGIs.

Thus, although the ADA and AACE/ACE algorithms are similar with regard to patients with or at risk for comorbidities, first-line therapy in the AACE/ACE algorithm may be an SGLT2 inhibitor or a GLP-1 receptor agonist in certain patients, whereas metformin is always first-line therapy in the ADA algorithm. This difference emphasizes the refocus of the type 2 diabetes treatment from a glucocentric approach to one that recognizes the importance of selecting agents that not only provide some degree of glycemic control but also have a positive impact on risk of common and serious comorbidities.

European Society of Cardiology Guidelines

Several cardiology organizations have also released consensus guidelines to address evidence from CVOTs in type 2 diabetes (43–45). In 2019, the European Society of Cardiology (ESC), in collaboration with the EASD, published guidelines on diabetes, prediabetes, and CVD (43). This document offers comprehensive guidelines for CVD risk assessment, prevention, and treatment and includes a detailed review of CVOT data for each class of antihyperglycemic medication.

For both drug-naive or metformin-treated people with type 2 diabetes with or at very high or high risk of CVD, ESC recommends starting an SGLT2 inhibitor or a GLP-1 receptor agonist that is associated with reduction in cardiovascular events (Figure 3 and Table 1). The rationale for this stance is that generally equal numbers of patients in the intervention and usual care arms of the CVOTs were taking metformin; thus, metformin was unlikely to explain the reported benefits. The ESC defines very high risk as having type 2 diabetes and CVD or other target-organ damage or three or more major risk factors for CVD. High risk is defined as having a type 2 diabetes duration of ≥10 years without target-organ damage but with one or more additional risk factor for CVD. If A1C continues above goal, the algorithm adds metformin for drug-naive patients. If additional glycemic lowering is needed beyond what is provided by dual therapy, the addition of the other CVD protective class (i.e., adding a GLP-1 receptor agonist for those already taking an SGLT2 inhibitor or vice versa). People with type 2 diabetes and low or moderate risk for CVD may start metformin monotherapy. If additional glycemic lowering is needed in these patients, dual therapy with a GLP-1 receptor agonist or an SGLT2 inhibitor is not preferred over other choices.

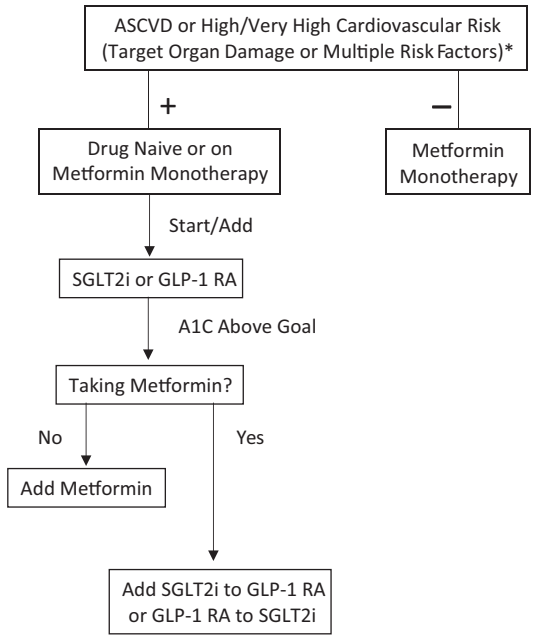

FIGURE 3 Abridged and modified ESC guidelines on type 2 diabetes, prediabetes, and CVD (43). *Very high risk is defined as having type 2 diabetes and CVD or other target-organ damage or three or more major risk factors for CVD. High risk is defined as having a type 2 diabetes duration of ≥10 years without target-organ damage but with one or more additional risk factor for CVD. RA, receptor agonist; SGLT2i, SGLT2 inhibitor.

The ESC guidelines identify the specific cardioprotective antihyperglycemic medications in each class, including the GLP-1 receptor agonists liraglutide, semaglutide, and dulaglutide and the SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin. These consensus guidelines were among the first to recommend an SGLT2 inhibitor or a GLP-1 receptor agonist as monotherapy before metformin in patients with type 2 diabetes who are at very high or high cardiovascular risk (43).

American College of Cardiology/American Heart Association Guidelines on Primary Prevention of CVD

In 2019, the ACC and the American Heart Association (AHA) published guidelines on the primary prevention of CVD; although not the main focus, algorithmic guidance for the treatment of type 2 diabetes in people without ASCVD was included (Figure 4*A* and Table 1) (44). The AHA and ACC recommend simultaneous lifestyle management, CVD

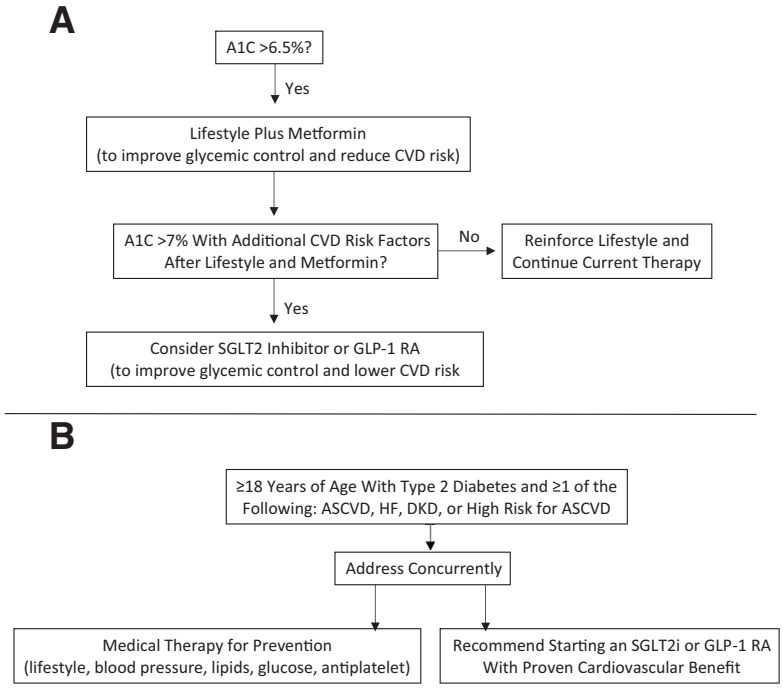

FIGURE 4 Abridged AHA/ACC guidelines for primary prevention (*A*) and ACC guidelines for secondary prevention (*B*) of CVD in type 2 diabetes (44,45).

risk factor management, and metformin therapy for people whose A1C is >6.5%. If A1C continues >7% despite these interventions and the patient has additional risk factors, the addition of an SGLT2 inhibitor or a GLP-1 receptor agonist should be considered to reduce both glycemia and CVD risk. These were some of the first guidelines to address the use of antihyperglycemic agents for the primary prevention of CVD.

ACC Guidelines for High Risk or Secondary Prevention of CVD in Type 2 Diabetes

In 2020, the ACC published an expert consensus decision pathway on CVD risk reduction in patients with type 2 diabetes, which was endorsed by the ADA and reviewed by representatives of numerous other professional organizations (45). The document concentrates almost exclusively on the use of SGLT2 inhibitors and GLP-1 receptor agonists for people with type 2 diabetes and high CVD risk. Algorithmically, patients with CVD, diabetic kidney disease (DKD) (reduced estimated glomerular filtration rate [eGFR] or albuminuria), or high risk for CVD (defined as end-organ damage such as left ventricular hypertrophy or retinopathy or multiple risk factors such as older age, hypertension, smoking, obesity, and dyslipidemia) should be started on an SGLT2 inhibitor or a GLP-1 receptor agonist offering proven CVD, DKD, or HF protection (Figure 4*B* and Table 1). For patients with CVD, a medication from either class may be recommended, whereas for those with HF or DKD, an SGLT2 inhibitor is recommended. If a patient's eGFR is <30 mL/min/1.73 m^2, then a GLP-1 receptor agonist is recommended instead.

Discussion

The presence of and high risk for CVD, CKD, and HF in patients with type 2 diabetes have clearly been identified in current treatment algorithms as cohesive reasons to consider intervention with specific antihyperglycemic agents. The evidence from outcomes trials that prompted the publication of these guidelines has also led to new label indications for SGLT2 inhibitors and GLP-1 receptor agonists for the treatment of these conditions in people with type 2 diabetes.

Of particular interest has been a shift in the recommended use of metformin, with most algorithms now recommending an SGLT2 inhibitor or a GLP-1 receptor agonist as first-line therapy for patients with type 2 diabetes who have or are at high risk for one or more of these comorbidities (Table 1). The ADA and AACE/ACE algorithms both recommend that a GLP-1 receptor agonist or an SGLT2 inhibitor be considered regardless of A1C for patients who have CVD, CKD, or HF, although the ADA algorithm recommends the addition of metformin before or concurrently with these agents (39,42). Early use of GLP-1 receptor agonists or SGLT2 inhibitors is reasonable based on the strength of the trial evidence regarding cardiovascular, renal, and HF outcomes. Metformin,

which has much less compelling evidence for CVD protection, can be used as a second- or third-line antihyperglycemic agent in high-risk patients.

Another point of interest is that most algorithms recommend consideration of combination therapy with an SGLT2 inhibitor and a GLP-1 receptor agonist in certain instances. The evidence that this combination affords additional CVD or CKD protection is not well established and is placed under the umbrella of additional glycemic control in the algorithms, usually as third-line therapy. It is possible that this combination could gain prominence if preliminary evidence continues to accrue. A post-hoc analysis of the EXSCEL trial explored the combination of exenatide ER and an SGLT2 inhibitor in 645 patients who were on both agents at some time during the trial. All-cause mortality (HR 0.41, 95% CI 0.17–0.95) and CVD death (HR 0.21, 95% CI 0.05–0.93) were both reduced versus exenatide ER therapy. In addition, the geometric mean eGFR difference over 1.5 years for the combination group versus exenatide ER was +2.38 mL/min/1.73 m^2 (95%CI 1.40–3.35, $P < 0.001$) (46). Combination therapy with agents in these two classes should be explored in a future well-conducted CVOT. The ESC algorithm (43) does recommend adding metformin after either an SGLT2 inhibitor or a GLP-1 receptor agonist and then, if triple therapy is warranted, adding a GLP-1 receptor agonist for those already taking an SGLT2 inhibitor or vice versa (Figure 3).

In summary, the use of longer-acting GLP-1 receptor agonists and SGLT2 inhibitors is increasing, in large part because of the strong body of positive data from trials assessing cardiovascular, renal, and HF outcomes. Treatment algorithms have appropriately changed to incorporate in these positive results. Although these algorithms play a valuable role by summarizing current evidence-based consensus opinion on the use of antihyperglycemic agents in clinical practice, the principles of patient-centered care must also be embraced in determining whether any given medication may be appropriate and beneficial for individual patients with type 2 diabetes.

DUALITY OF INTEREST

C.S.-H. is a speaker for Novo Nordisk. E.C. is a speaker for AstraZeneca. C.T. is a speaker for AstraZeneca, Novo Nordisk, and Xeris. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

C.S.-H. researched and wrote the manuscript and was involved in the discussion and manuscript revision. E.C. contributed to the discussion and reviewed/edited the manuscript. C.T. researched, contributed to the development of the figures, and edited the manuscript. C.S.-H. is the guarantor of this work and, as such, had full access to all of the data and takes responsibility for the integrity of the review.

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