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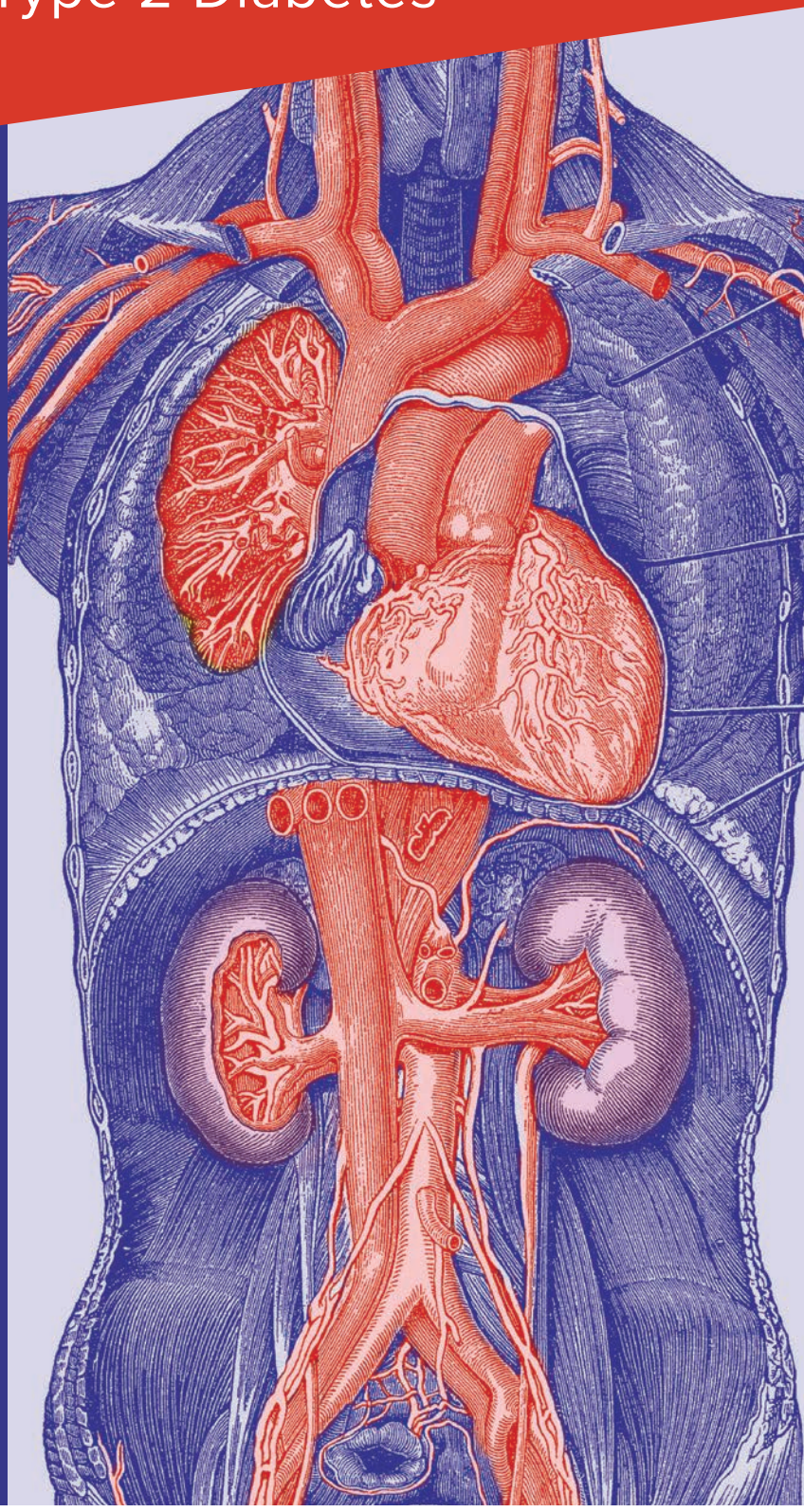
Person-Centered, Outcomes-Driven Treatment:

A New Paradigm for Type 2 Diabetes in Primary Care



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Credit: Mehau Kulyk/Science Source;
Description: Torso blood vessels. Historical artwork of a human torso that has been dissected to show major blood vessels (arteries and veins, both red).

Person-Centered, Outcomes-Driven Treatment:

A New Paradigm for Type 2 Diabetes in Primary Care

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ABSTRACT | Primary care providers are well-positioned to help patients with type 2 diabetes achieve glycemic control while reducing their risks of serious complications such as atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease. Recent outcomes trials of glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors have revealed that these agents offer cardiorenal benefits beyond their glucose-lowering effects. The American Diabetes Association and the European Association for the Study of Diabetes now recommend a person-centered approach to type 2 diabetes treatment through which a patient's multimorbidities, preferences, characteristics, and barriers are considered alongside A1C in individualizing the diabetes management plan. Here, we review the evidence supporting this guidance and describe how to implement the new holistic approach. Research has demonstrated the potential for offering a continuum of benefit from primary through tertiary prevention of microvascular and macrovascular disease while also achieving glycemic targets. The new outcomes-based guidelines provide a roadmap for integrating this newfound knowledge into clinical practice.

Type 2 diabetes affects approximately 90% of the estimated 463 million people diagnosed with diabetes worldwide (1). In the United States, about 12% of the population has diabetes, about one-fourth of whom are undiagnosed (2), and the direct and indirect costs of diabetes were estimated to be $327 billion in 2017 (3). People living with diabetes are at higher risk of long-term complications, with increased morbidity and premature mortality (4). Nearly one-third of people with type 2 diabetes have atherosclerotic cardiovascular disease (ASCVD), encompassing myocardial infarction (MI), unstable angina, stroke, and peripheral arterial disease. Diabetes also conveys increased risks of several microvascular complications such as eye, nerve, and foot conditions and is one of the most common causes of chronic kidney disease (CKD) (5), which affects 20–40% of people with diabetes, often leading to end-stage renal disease (ESRD) (6–10). A comprehensive and multifactorial treatment approach that starts at diagnosis and widens to address a continuum of risk over the course of a patient's lifetime is essential to mitigate the excess morbidity and mortality associated with diabetes. Primary care providers (PCPs) are uniquely positioned to offer people with type 2 diabetes a continuum of care that matches the continuum of risk from primary through tertiary prevention of microvascular and macrovascular complications.

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The latest American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus guidelines on hyperglycemia management and the ADA's *Standards of Medical Care in Diabetes—2020*, which incorporate the ADA/EASD guidelines, recommend an approach that represents a paradigm shift in the management of type 2 diabetes (11–15). The most dramatic difference between these guidelines and their earlier iterations is that the traditional "glucocentric" strategy, emphasizing A1C-lowering as the primary consideration in therapy selection, has given way to a more expansive approach that seeks to tailor the pharmacotherapeutic regimen to the specific needs of each patient.

Although these guidelines describe the new approach as "patient-centered," some have advocated a transition to "person-centered" (16,17), which we will use here to emphasize the holistic nature of the new paradigm. The person-centered approach allows and encourages clinicians—especially PCPs who treat the vast majority of people with type 2 diabetes—to take issues other than A1C into account in a shared decision-making process with their patients. Presence or high risk for ASCVD, CKD, and heart failure (HF), as well as patients' needs, preferences, sociodemographic characteristics, access limitations, and financial barriers, all now take a place alongside A1C as key considerations in designing the most appropriate diabetes management plan for each patient.

This substantial change in approach resulted, in large part, from an explosion in available antidiabetic medications during the past decade. The ever-expanding therapeutic armamentarium, which now includes multiple agents in 12 different drug classes (11,12), has the potential to overwhelm clinicians and has likely contributed to therapeutic inertia and therapeutic nihilism (18–20). However, recent cardiovascular outcomes trials (CVOTs), particularly those conducted with glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, have helped to refocus diabetes clinical practice in new and exciting ways. The dramatic results of these trials have provided evidence not only of the cardiovascular safety of these agents, but also of their potentially life- and organ-saving benefits (21,22). Although metformin continues to be the preferred initial glucose-lowering pharmacotherapy in type 2 diabetes, ADA and EASD now recommend a GLP-1 receptor agonist, an SGLT2 inhibitor, or both as add-on therapies in patients with or at high risk for ASCVD, CKD, or HF.

The key CVOTs that have informed these recommendations and their clinical implications are reviewed in this monograph. This timely publication also provides an opportunity for PCPs to better understand the new holistic approach to managing type 2 diabetes. We focus on how the latest ADA/EASD consensus guidelines and ADA *Standards of Care* set out a strategy that is both relevant and uniquely suited to primary care. We include a detailed description of this new strategy and its rationale and summarize the key evidence supporting it. Although type 2 diabetes management is moving away from the strictly glucocentric stepwise algorithm of the past, early glucose control remains important, and we explain where and how attaining individualized A1C targets fits into this more expansive approach.

An Approach Made for Primary Care

KEY POINTS

- **PCPs may experience difficulty in staying abreast of rapid advancements in knowledge of and treatments for type 2 diabetes, which could contribute to therapeutic inertia.**
- **Clinical trials of new medications, once focused on the surrogate endpoint of A1C, now yield a wealth of data on actual clinical events associated with diabetes complications.**
- **Type 2 diabetes management has evolved from a glucocentric to a more holistic, person-centered approach.**

With more than 1.5 million cases diagnosed annually (2) and a myriad of available medications and treatment strategies, type 2 diabetes is both the most common and the most complicated chronic disease encountered daily in primary care. Numerous factors contribute to high rates of diabetes, including a high prevalence of obesity, predispositions based on genetics and race/ethnicity, and social determinants of health. For example, the prevalence of diabetes is 60% higher among non-Hispanic blacks and people of Hispanic ethnicity than among non-Hispanic whites, and 12.6% of U.S. adults with less than a high school education have diagnosed diabetes compared to 7.2% of those with a higher education level (2).

The consequences of these inequities are serious, because the consequences of having diabetes are

serious. Diabetes was the seventh leading cause of death in 2017, contributes to mortality from four of the six other most common causes of death, more than doubles a person's cardiovascular risks, and contributes to increased risks of cancer and dementia (23–27).

A dramatic increase in the prevalence of diabetes in the past 40 years has resulted in diabetes truly being a "primary care disease." Diagnosed diabetes in the United States increased from about 2.5% of the population in 1980, to nearly 4.5% in 2000, to its current rate of >10% (Figure 1) (28). There simply are not enough diabetes specialists to provide care for the vast majority of these patients; thus, PCPs have become, and will continue to be, the clinicians who provide most of the care for patients with type 2 diabetes in the United States.

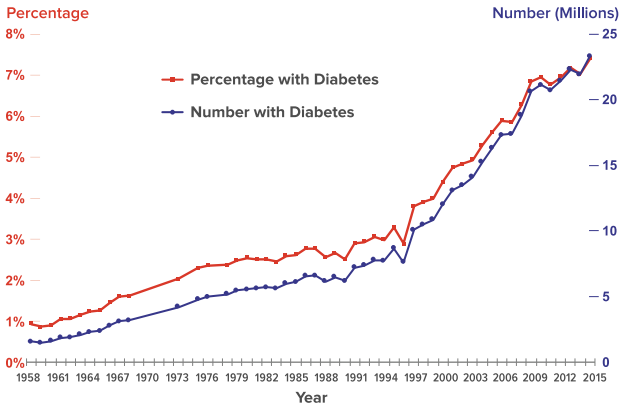

FIGURE 1 Number and percentage of U.S. population with diagnosed diabetes, 1958–2015 (28).

THE DIABETES KNOWLEDGE EXPLOSION AND ITS RELEVANCE FOR PRIMARY CARE

Few areas of medicine have changed as much in the past 20 years as the field of diabetes. Most clinicians practicing today were taught that type 2 diabetes was the direct result of reduced insulin secretory capacity of the pancreas in combination with increasing peripheral insulin resistance. In 2009, the term "ominous octet" was used to describe the eight different organ systems—brain, intestine, adipose tissue, kidney, muscle, liver, and pancreatic α- and β-cells—that contribute to diabetes and are therefore therapeutic targets for its treatment (29). Most of these aspects of diabetes pathophysiology were unknown when the majority of today's clinicians attended medical school.

Until the mid-1990s, only two drug classes were available in the United States for the treatment of type 2 diabetes: insulin and sulfonylureas. Since then, 10 new classes of medications have come to market, accounting for more than 20 new medications and numerous products combining drugs from different classes (Figure 2) (30). More than 560 additional diabetes-related medications are in development (31). It is no wonder that PCPs have found it extremely challenging to stay current with the rapid advancement in pharmacologic therapy for type 2 diabetes (18).

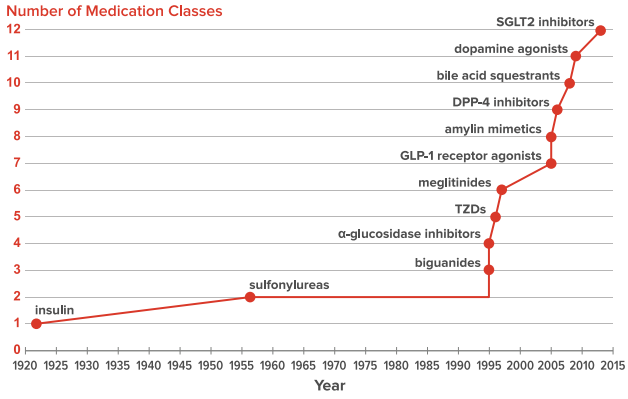

FIGURE 2 Introduction of type 2 diabetes medications in the United States. Adapted from ref. 30.

The Danger of Therapeutic Inertia

The sheer number of available medications can lead to uncertainty about which ones to choose for any given patient, which in turn can result in therapeutic inertia (32). "Therapeutic inertia" refers to the lack of timely adjustment to the treatment regimen when a patient's therapeutic goals are not met (19). This concept is important because about half of patients with diabetes do not meet a general A1C target of <7% (a proportion that has remained constant for more than a decade despite numerous therapeutic advances [33]), and failure to attain a target A1C increases the likelihood of developing complications (34). Therapeutic inertia occurs throughout the course of diabetes management, from initiation of the first antihyperglycemic agent to intensification of insulin to deintensification of the treatment regimen when called for, leaving many patients with poor glycemic control or at undue risk for long periods (19,35,36).

Many factors contribute to therapeutic inertia at the patient, provider, and health system levels (19). One major issue for PCPs is the challenge of staying up to date with the burgeoning number of diabetes medications. The social sciences literature suggests that having many choices can lead to "decision paralysis" (37); for clinicians, it can lead to either doing nothing or simply prescribing the medications they are most used to rather than the best medications for a given patient.

Examinations of prescribing patterns have yielded findings that reflect therapeutic inertia. For example, a recent exploration of real-world prescribing patterns for >1 million people with diabetes (38) showed that 77% of patients were initially started on metformin. During a mean follow-up of 3.4 years after starting metformin, 48% of these patients began taking a second antidiabetic medication, at a mean A1C of 8.4%. The most commonly prescribed second agent was a sulfonylurea, accounting for 46% of second-line agents.

Sulfonylureas have a clear place in the treatment of type 2 diabetes as effective low-cost agents; however, their drawbacks, specifically their association with weight gain and increased hypoglycemia, make them a suboptimal choice for many patients compared to agents in newer drug classes. Many nonsulfonylurea medications have a lower incidence of hypoglycemia and are either weight neutral or promote weight loss. Also, as previously mentioned, newer GLP-1 receptor agonists and SGLT2 inhibitors offer substantial benefits with regard to cardiovascular and renal outcomes, making them important options for the sizeable proportion of people with diabetes who also have cardiovascular disease (CVD), CKD, or both.

SURROGATE ENDPOINTS VERSUS CLINICAL EVENTS

Another important development in the past two decades has been the recognition of the difference between surrogate endpoints and real clinical events (39). A surrogate endpoint is a measurable effect used in clinical trials to represent the true clinical benefit of a medication. Although a surrogate endpoint is not an actual clinical event of interest, it serves as an alternative, or surrogate, meant to represent the event of interest.

The prime example in diabetes is the traditional use of A1C as a surrogate endpoint in the assessment of the effectiveness of diabetes drugs, with the assumption that sufficiently lowering A1C would lead to reductions in the development of long-term complications. Thus, the focus was on a drug's efficacy in lowering A1C—not on whether it actually reduced the number of clinical events related to diabetes complications. What clinicians and people with diabetes really care about, however, is decreasing the likelihood of developing complications over time (i.e., primary prevention). The landmark Diabetes Control and Complications Trial in patients with type 1 diabetes (40), published in 1993, was the first study to demonstrate the link between glycemic control and microvascular disease. In 1998, the U.K. Prospective Diabetes Study (UKPDS) (41) confirmed that intensive glucose-lowering also reduced microvascular complications in type 2 diabetes. A decade later, 10-year follow-up data from the UKPDS showed that intensive therapy to reduce hyperglycemia also reduced macrovascular complications (42), and a macrovascular benefit was also found after 17 years in the DCCT's type 1 diabetes observational follow-up cohort (43).

Recognizing the difference between surrogate and clinical endpoints, research trials of new diabetes medications began to be designed to measure actual clinical outcomes, including cardiovascular events and CKD progression. Consistent with and furthering this focus, the U.S. Food and Drug Administration (FDA) in 2008 issued a seminal statement of guidance to the pharmaceutical industry that would change the course of diabetes pharmacotherapeutic research and development (44). The FDA called for industry to conduct long-term CVOTs to establish the cardiovascular safety of new diabetes drugs. Whereas previous drug trials had aimed to demonstrate efficacy in lowering the surrogate endpoint of A1C, from 2008 on, new medications would need to be proven as safe as placebo with regard to actual cardiovascular events to earn FDA approval.

NEWER DIABETES MEDICATIONS REDUCE CLINICAL EVENTS

As will be discussed in greater detail elsewhere in this monograph (p. 12 and p. 16), recent CVOTs have provided important new evidence that improved outcomes—specifically the prevention or delay of cardiovascular and renal disease—may be determined not only by the degree of A1C reduction achieved, but also by the choice of agents used to achieve that reduction.

Agents from three new drug classes—dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists—have come to market since the FDA issued its guidance, all having been evaluated in rigorous CVOTs. Trials of the DPP-4 inhibitors all demonstrated cardiovascular safety compared to placebo, but none demonstrated superiority over placebo (i.e., cardiovascular benefit) (45–48). However, trials of several SGLT2 inhibitors and GLP-1 receptor agonists have not only proven their cardiovascular safety, but also demonstrated the beneficial effects of reducing major adverse cardiovascular events (MACE), hospitalization for HF (HHF), and/or progression of CKD. Meta-analyses of these trials (21,22,49) suggest that agents from both classes

reduce the risk of MACE by 11–12% in patients with type 2 diabetes and established ASCVD. SGLT2 inhibitors also reduce the risk of HHF by 31%, whereas GLP-1 receptor agonists have no significant effect on HHF. Agents from both classes reduce the risk of progression of CKD, including macroalbuminuria, but only SGLT2 inhibitors have demonstrated a reduction in the risk of a renal composite including worsening estimated glomerular filtration rate (eGFR), ESRD, and renal death (hazard ratio [HR] 0.55, P <0.001) (21,49). Whereas the glucose-lowering effects of SGLT2 inhibitors are blunted at an eGFR <45 mL/min/1.73 m^2, the renal and cardiovascular benefits have been seen down to an eGFR of 30 mL/min/1.73 m^2 (50). It is unclear whether using agents from both drug classes in combination would provide an additive cardiovascular benefit, although the use of such combinations has been studied (51,52).

EVOLUTION OF CLINICAL PRACTICE RECOMMENDATIONS

The recent significant expansion of the evidence base for the treatment of type 2 diabetes has led in turn to frequent updates to guidelines for managing hyperglycemia. Recent clinical practice guidelines have moved from the glucocentric model to a more person-centered approach that matches the individualized needs of patients and their existing comorbidities to the characteristics and benefits afforded by specific medications (11–15).

In 2009, ADA and EASD published their first consensus report on the medical management of hyperglycemia in type 2 diabetes (53). The evidence has changed so rapidly in recent years that it is hard to believe it has only been a decade since these guidelines stated:

> *Except for their differential effects on glycemia, there are insufficient data at this time to support a recommendation of one class of glucose-lowering agents, or one combination of medications, over others with regard to effects on complications. . . . In other words, the salutary effects of therapy on long-term complications appear to be predicated predominantly on the level of glycemic control achieved rather than on any other specific attributes of the intervention used to achieve glycemic goals.*

In 2012, and again in 2015, joint ADA/EASD position statements were published calling for a person-centered approach (54,55). These guidelines delineated five medication characteristics—efficacy, hypoglycemia risk, effect on weight, side effects, and cost—that clinicians should take into consideration when deciding which medication to use after initial treatment with metformin for a given patient.

The latest ADA/EASD consensus report, simultaneously published in the United States and Europe in 2018 (11,12) and updated at the end of 2019 (13,14), has further refined the personalized approach to diabetes management. By integrating the latest evidence from CVOTs, the consensus committee clarified and expanded on factors clinicians should consider in seeking to match medication choices to patients' specific needs. ADA, in turn, incorporated these recommendations into its 2020 *Standards of Care* (15).

This person-centered approach can guide clinicians in selecting wisely from available medications. It should also help to reduce therapeutic inertia secondary to clinical uncertainty regarding the wealth of options to help patients optimize their glycemic control. Based on the collective evidence on actual clinical events from CVOTs, the latest guidelines provide a roadmap for selecting the right medication at the right time for each patient.

A New Approach for a New Era: The Case for Person-Centered Care

KEY POINTS

- **A person-centered approach that addresses patients' multimorbidities, needs, preferences, and barriers and includes diabetes education and lifestyle interventions as well as pharmacologic treatment is essential to effective diabetes management.**
- **Selection of add-on therapy after metformin should be based not only on a patient's A1C, but also on the presence of comorbidities such as ASCVD, HF, and CKD, as well as the patient's clinical characteristics, risks for side effects, and socioeconomic factors.**

Management of type 2 diabetes has become increasingly complex. As previously noted, numerous new drug classes have entered the market. Furthermore, the disease not only affects people from many cultures and diverse backgrounds, but now increasingly affects younger as well as older people (56). It is also

associated with multimorbidity (57). Thus, individuals with diabetes face diverse life challenges, requiring clinicians to adopt a personalized approach when delivering care. Additionally, the focus of care has expanded far beyond glucose-lowering alone and now includes the need to manage comorbid conditions such as obesity, ASCVD, and CKD (58), while also addressing mental health and the adverse psychological consequences of living with this chronic disease (59).

The most recent guidance from ADA and EASD recognizes the increasing challenges facing PCPs trying to navigate these complexities in today's rapidly evolving climate (11–15). These guidelines offer a more holistic approach to meeting the diverse needs of individuals with diabetes, informed by the latest evidence on both pharmacological and nonpharmacological interventions. The recommendations most relevant to primary care are discussed below.

UNDERLYING PRINCIPLES OF PERSON-CENTERED DIABETES CARE

Diabetes Management Decision Cycle

Central to the ADA/EASD consensus guidelines is the decision cycle for person-centered management (Figure 3). This model shifts from the traditional management goal of achieving glycemic control to the broader goals of preventing complications and optimizing quality of life. Its aim is to put people with type 2 diabetes at the center of their own care by promoting holistic assessment and shared decision-making between clinicians and patients to arrive at mutually agreed upon management plans. A person-centered approach that acknowledges the competing demands of multimorbidity and is respectful of and responsive to individuals' preferences and barriers, including limited access to and prohibitive costs of therapies, is essential to effective diabetes management. This model is intended to build management around individual patients, taking into consideration their personal preferences, clinical characteristics, and comorbidities, and to consider the benefits and risks of glucose-lowering medications in this context. Shared decision-making that presents the risks and benefits of alternative treatment options is a useful strategy to arrive at the best treatment course for each person (13,14).

Overall, the ethos of care moves away from an emphasis on general treatment targets to one on individual goals based on the whole person. Central to this process is the need for clinicians to be culturally sensitive and to consider factors such as patients' health beliefs, possible literacy deficits and cognitive impairments, and fears or concerns when considering treatment choices, given the impact of such factors on treatment efficacy (13,14).

Diabetes Self-Management Education and Support

The latest guidelines specifically identify diabetes self-management education and support (DSMES) as a key intervention to enable individuals to make informed decisions and empower them to assume responsibility for the day-to-day management of their condition. The ADA/EASD consensus committee's evidence review highlighted DSMES as a cost-effective intervention with a robust evidence base demonstrating improvement in patient knowledge and clinical and psychological outcomes, as well as positive impacts on medication adherence, glycemic control, and all-cause mortality (60,61). Recommended core components of DSMES have been described in detail elsewhere (62,63).

Renewed Focus on Lifestyle Interventions

Importantly, the ADA/EASD consensus recommendations remind clinicians that lifestyle interventions, particularly those focusing on weight loss, obesity management, and physical activity, remain pivotal to type 2 diabetes management (13,14). The consensus committee placed lifestyle interventions, including consideration of diet quality, energy restriction, and physical activity, alongside glucose-lowering drugs as potential components of the diabetes management plan. Although no specific diet is preferred, dietary approaches including the Mediterranean, DASH (Dietary Approaches to Stop Hypertension), low-carbohydrate, and vegetarian eating patterns are highlighted. The guidance advocates increasing physical activity through various strategies, including common activities such as swimming and walking and less frequently practiced options such as yoga and tai chi. The aim should be to support lifestyle changes that are feasible and sustainable and to develop a regimen tailored to the patient's preferences. All overweight and obese people with diabetes should be advised of the health benefits of weight loss and encouraged to engage in programs of intensive lifestyle management and, in particular, energy restriction, including meal replacement programs.

NEW CONSIDERATIONS FOR PHARMACOLOGICAL GLUCOSE-LOWERING THERAPY

The latest ADA/EASD consensus guidelines and ADA *Standards of Care* still recommend metformin as first-line therapy for most people with type 2 diabetes (11–15). This guidance largely relates to historical data from the UKPDS, although there is continued discussion regarding the possible cardiovascular benefit of metformin (64). At present, metformin has a well understood safety profile and a low risk of hypoglycemia and is an inexpensive option that is accessible worldwide (64).

Deciding What Comes After Metformin

The latest treatment guidelines provide an algorithm for intensifying pharmacological therapy beyond metformin that represents a true paradigm shift from earlier recommendations. Now, rather than selecting drugs mostly on the basis of their glucose-lowering efficacy, the new guiding principle is that drugs should be selected based on the presence of comorbidities,

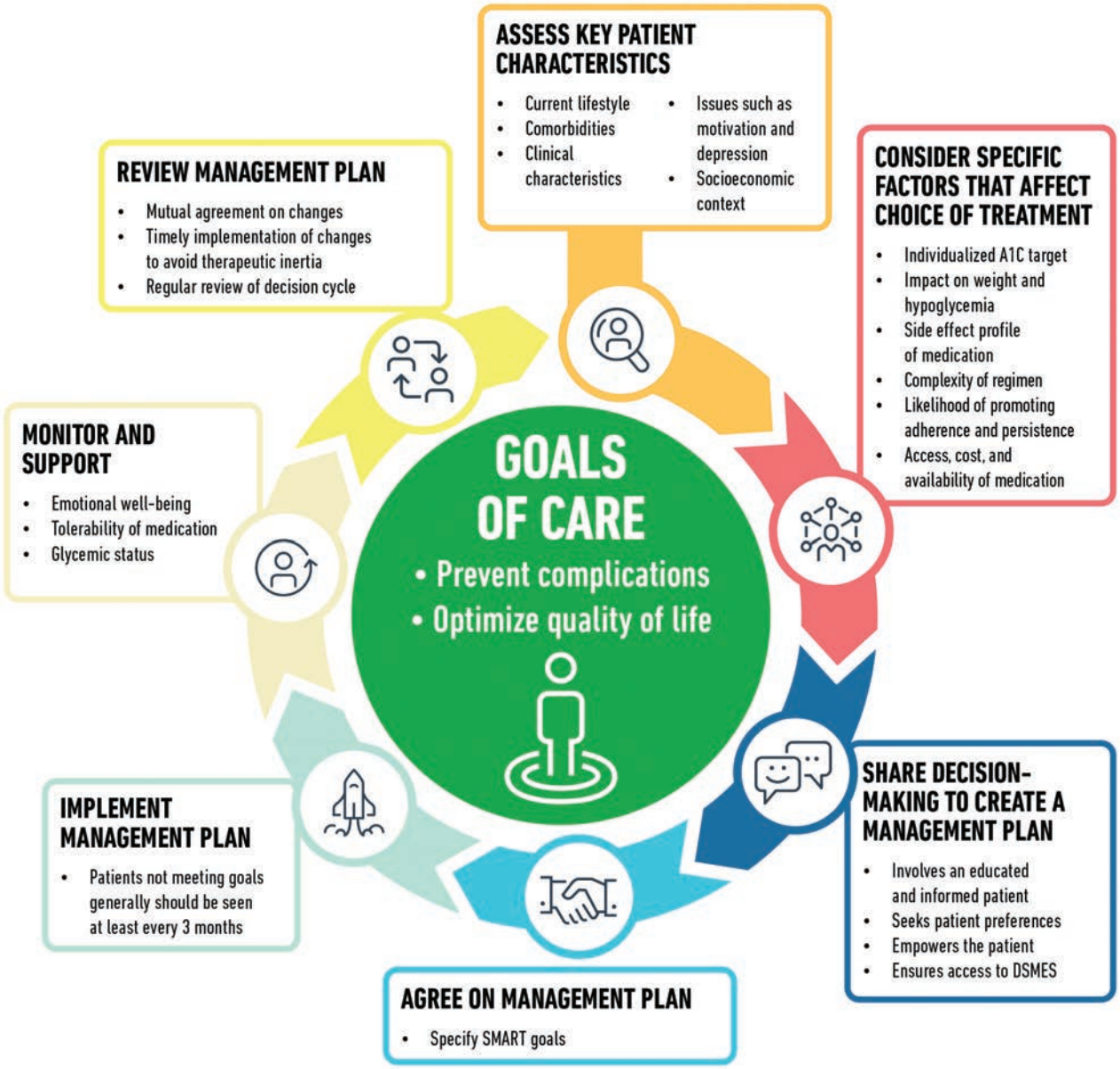

FIGURE 3 Decision cycle for person-centered glycemic management in type 2 diabetes. SMART, specific, measurable, achievable, realistic, time limited. Adapted from refs. 11 and 12.

particularly ASCVD, HF, or CKD, while also taking into account patients' clinical characteristics, risks for side effects, and socioeconomic factors.

When considering the next step after metformin, clinicians should ask the key questions listed in Table 1. The answers will help them navigate through a series of algorithms included in the ADA/EASD consensus guidelines to aid management decisions (11–14). Figures 4 and 5 summarize the decision-making process for intensifying from monotherapy to triple combination therapy in patients with ASCVD, HF, or CKD. The classes of noninsulin glucose-lowering therapies that are available globally and considered after metformin are sulfonylureas, thiazolidinediones (TZDs), GLP-1 receptor agonists, SGLT2 inhibitors, and DPP-4 inhibitors. To aid clinicians in the decision-making process and inform their discussions with patients, Figure 6 provides a succinct overview of the relative attributes of each of these drug classes. Insulin should be considered as part of any combination regimen when hyperglycemia is severe or to maintain glycemic control once progression of the disease overcomes the effects of other agents. The addition of basal insulin, either human NPH or one of the long-acting insulin analogs, to oral agent regimens is a well-established approach that is effective for many patients (15).

TABLE 1 Comorbidity Considerations for Intensifying Type 2 Diabetes Therapy After Metformin

When selecting the next step in type 2 diabetes management after metformin for a given patient, clinicians should consider the following questions:

• Does the individual have preexisting ASCVD or indicators of high risk for ASCVD?
  • Established ASCVD includes a previous MI, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization of the coronary, carotid, or peripheral arteries.
  • Indicators of high risk for ASCVD include ≥55 years of age with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy.

• Does the individual have HF (particularly HFrEF) or CKD (eGFR of 30–60 mL/min/1.73 m^2) or a UACR >30 mg/g Cr?
• Is there a compelling need to avoid weight gain or promote weight loss in this individual?
• Is there a compelling reason to avoid hypoglycemia in this individual?
• Is medication cost the major issue for this individual?

ECG, electrocardiogram.

When ASCVD Predominates

- **Who?** Patients with preexisting ASCVD or indicators of high risk for ASCVD (≥55 years of age with left ventricular hypertrophy or coronary, carotid, or lower-extremity artery stenosis >50%).
- **Which drug class?** A GLP-1 receptor agonist with proven cardiovascular benefit (i.e., an approved indication for reducing cardiovascular events) is the preferred choice after metformin.
- **Additional information.** A GLP-1 receptor agonist should be added for these patients *independent* of their baseline A1C or individualized A1C target. If further intensification is required or for patients who are unable to tolerate a GLP-1 receptor agonist, there are other options. An SGLT2 inhibitor with proven cardiovascular benefit can be added if a patient's eGFR is in line with the specific agent's prescribing information. A DPP-4 inhibitor can be added for patients not taking a GLP-1 receptor agonist, or basal insulin, a TZD, or a sulfonylurea can be considered.

When HF or CKD Predominates

- **Who?** Patients with HF—particularly HF with reduced ejection fraction (HFrEF; left ventricular ejection fraction <45%)—or CKD (particularly with an eGFR of 30–60 mL/min/1.73 m^2 or a urine albumin-to-creatinine ratio [UACR] >30 mg/g creatinine [Cr], particularly UACR >300 mg/g Cr).
- **Which drug class?** An SGLT2 inhibitor with evidence of reducing HF and/or CKD progression is preferred after metformin.
- **Additional information.** Ensure that patients' eGFR is in line with the specific agent's prescribing information. An SGLT2 inhibitor should be added for these patients *independent* of their baseline A1C or individualized A1C target. If an SGLT2 inhibitor is not tolerated or contraindicated or if a patient's eGFR is not adequate for SGLT2 inhibitor use, add a GLP-1 receptor agonist with proven cardiovascular benefit. If further intensification is required, a DPP-4 inhibitor (but not saxagliptin in the setting of HF) can be added for patients not taking a GLP-1 receptor agonist, or basal insulin or a sulfonylurea can be considered.

When There Is a Compelling Need to Minimize Hypoglycemia

- **Who?** Patients who do not have established or high risk of ASCVD, HF, or CKD in whom avoiding hypoglycemia was identified during the decision cycle process as a priority (e.g., for those at high risk of hypoglycemia

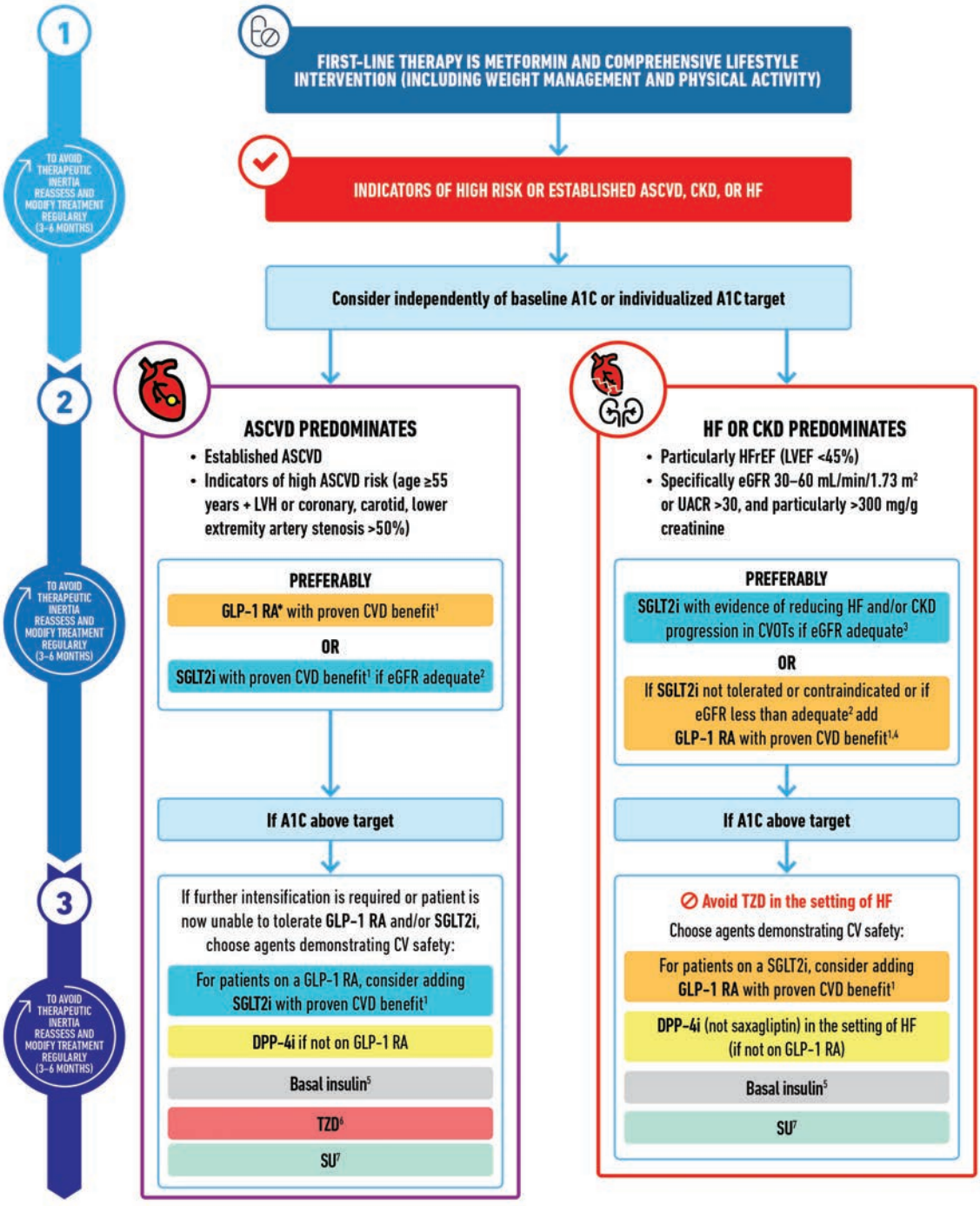

FIGURE 4 Choosing glucose-lowering medication for patients with indicators of high risk or established ASCVD, CKD, or HF. [1]Proven CVD benefit means having an indication for reduction of CVD events. [2]SGLT2 inhibitor labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. [3]Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and in CKD progression. Canagliflozin has shown reduction in a composite primary renal outcome. Dapagliflozin has shown reduction in HF. [4]Use caution with GLP-1 receptor agonists in ESRD. [5]Degludec and U-100 glargine insulins have demonstrated CVD safety. [6]Low dose may be better tolerated though less well studied for CVD effects. [7]Choose later-generation sulfonylurea to lower risk of hypoglycemia. Glimepiride has shown similar cardiovascular safety to DPP-4 inhibitors. *Recommendations regarding GLP-1 receptor agonist use when ASCVD predominates, discussed in more detail on p. 8, are based on recent evidence and expert opinion; therefore, they differ slightly in emphasis from corresponding recommendations in the 2020 ADA *Standards of Care*. CV, cardiovascular; DPP-4i, DPP-4 inhibitor; GLP-1RA, GLP-1 receptor agonist; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea. Adapted from refs. 13 and 14.

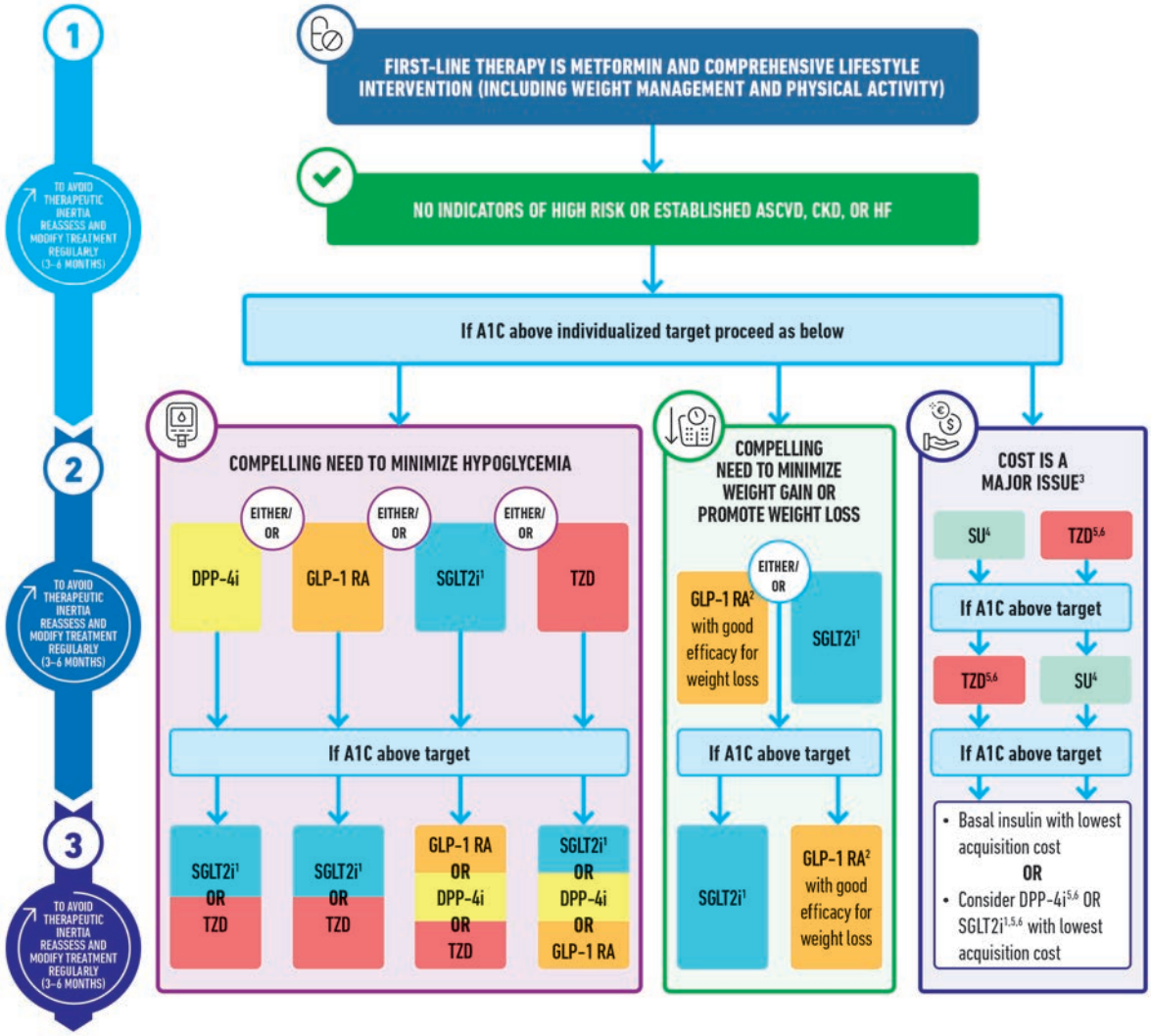

FIGURE 5 Choosing glucose-lowering medication if there is a compelling need to minimize hypoglycemia, there is a compelling need to minimize weight gain or promote weight loss, or cost is a major issue. Beyond these steps, many patients with type 2 diabetes will eventually require and benefit from further intensification to insulin therapy. [1]SGLT2 inhibitor labeling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. [2]Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide. [3]If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities). [4]Choose later-generation sulfonylurea to lower risk of hypoglycemia. Glimepiride has shown similar cardiovascular safety to DPP-4 inhibitors. [5]Consider region-specific costs of drugs. In some countries, TZDs are relatively more expensive and DPP-4 inhibitors are relatively less expensive. [6]See figure 6. The cost of these drugs is relatively similar in the United States. DPP-4i, DPP-4 inhibitor; GLP-1RA, GLP-1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea. Adapted from refs. 13 and 14.

who have had previous problematic hypoglycemic events, who are elderly with comorbidities and living alone, or who have occupational concerns).

- **Which drug class?** Preferred options include DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and TZDs. In these patients, sulfonylureas and insulin should be avoided.
- **Additional information.** When added to metformin, agents from all of these classes have an equally low risk of hypoglycemia; therefore, the choice may be further informed by individual preferences (e.g., for injectable or oral agents) and cost.

When There Are Compelling Weight-Related Concerns

- **Who?** Patients who do not have established or high risk of ASCVD, HF, or CKD in whom minimizing weight gain or promoting weight loss is a priority.
- **Which drug class?** Two classes of glucose-lowering drugs are preferred in this scenario: GLP-1 receptor agonists and SGLT2 inhibitors.

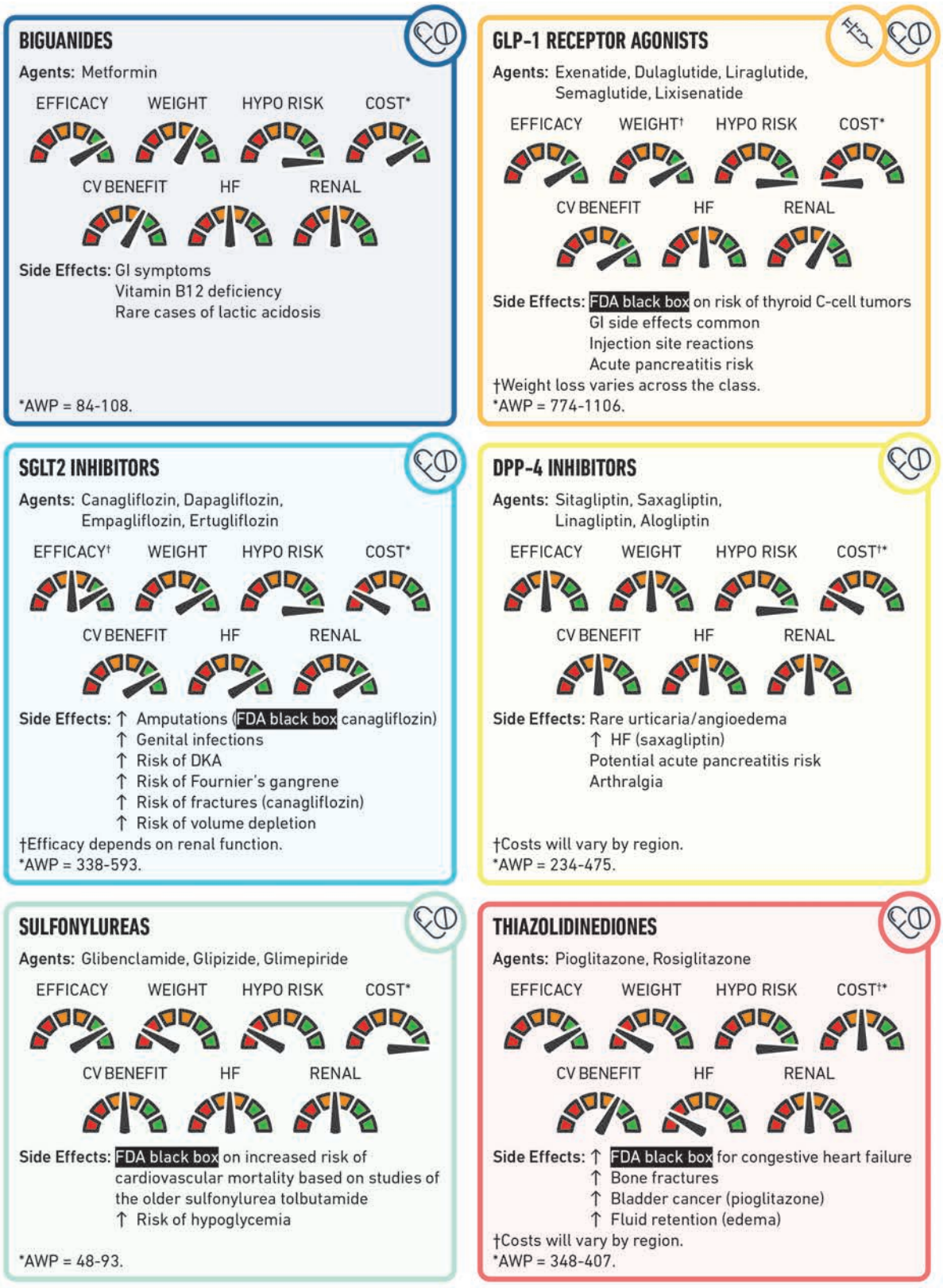

FIGURE 6 Relative attributes of the main glucose-lowering drug classes (excluding insulin). Cost information is from ref. 15., but consider region-specific costs of drugs, which can vary widely. In some countries, TZDs are relatively more expensive and DPP-4 inhibitors are relatively less expensive. AWP, average wholesale price in USD. CV, cardiovascular; DKA, diabetic ketoacidosis; GI, gastrointestinal; HYPO, hypoglycemia.

- **Additional information.** A GLP-1 receptor agonist with good efficacy for weight loss should be selected. There is significant heterogeneity among the agents in this class with regard to weight effects, with semaglutide having the strongest data for weight loss and lixisenatide the weakest. Robust and consistent weight loss is seen across all SGLT2 inhibitors. If triple therapy is required, the combination of an SGLT2 inhibitor with a GLP-1 receptor agonist could be used, although this could be an expensive option (51,52). Another option for patients not taking a GLP-1 receptor agonist would be one of the DPP-4 inhibitors, which are weight neutral.

When Cost Is an Issue

- **Who?** Any patient for whom cost is an important consideration. Many patients around the world struggle with medication costs. The ADA/EASD consensus committee acknowledged the importance of financial considerations within treatment algorithms, and such considerations are also a major focus of ADA's 2020 *Standards of Care* (15).
- **Which drug class?** Sulfonylureas and TZDs are the least expensive noninsulin therapies.
- **Additional information.** The recent CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes) trial (65) compared the sulfonylurea glimepiride to the DPP-4 inhibitor linagliptin and found no between-group differences in the primary MACE endpoint or in A1C achieved. The DPP-4 inhibitor demonstrated a modest weight loss benefit of 1.5 kg compared to glimepiride and had a significantly lower rate of hypoglycemia, although severe hypoglycemia was relatively uncommon in the trial. These findings provide reassurance regarding the use of glimepiride, which is both inexpensive and effective. Patient education and low or variable dosing of a later-generation sulfonylurea may be strategies to mitigate the risk of hypoglycemia.

Further Guidance

Imparting effective and empathetic lifestyle advice remains a crucial component of shared decision-making with patients. Additionally, clinicians and patients should reach agreement on a management plan that seeks to avoid therapeutic inertia by ensuring the timely intensification of therapy if treatment targets are not met and the timely deintensification of treatment, if necessary, to avoid putting patients at undo risk of harm. All of these goals can be achieved by adhering to the underlying principles of the consensus guidelines described above and periodically repeating the decision cycle shown in Figure 3 to assess and adjust the therapeutic regimen to meet patients' changing needs and circumstances.

The evidence on which the current guidelines were based is summarized in detail in the next two sections, followed by a discussion of the continued importance of glycemic control, as assessed by A1C, within the new, outcomes-driven approach.

Preventing Cardiovascular Events Across the Continuum of Risk

KEY POINTS

- Traditional cardioprotective strategies include smoking cessation, blood pressure and LDL cholesterol lowering, use of renin-angiotensin-aldosterone system (RAAS) blockers, and—among people at high risk—low-dose aspirin therapy.
- New glucose-lowering medications with proven cardioprotective benefits should also be included for patients with type 2 diabetes who have or are at risk for ASCVD. These drugs include the GLP-1 receptor agonists albiglutide, dulaglutide, liraglutide, and semaglutide and the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin.
- Expeditious use of appropriate cardioprotective strategies and therapies in primary care could dramatically reduce the burden of ASCVD in people with type 2 diabetes.

Cardiovascular events account for a large portion of the health burden of diabetes, and their cost has been estimated to be $37.3 billion annually in the United States alone (3). This burden was demonstrated in a large epidemiologic analysis of 34,198 people with type 2 diabetes and 1,921,260 people without diabetes who were followed within a linked British database (66). As shown in Figure 7, during a median of 5.5 years, people with diabetes were 1.5–2 times more likely than those without diabetes to experience 10 of the 12 types of serious cardiovascular events included.

This higher risk and its associated morbidity, mortality, and costs highlight the importance of testing whether therapeutic strategies can reduce

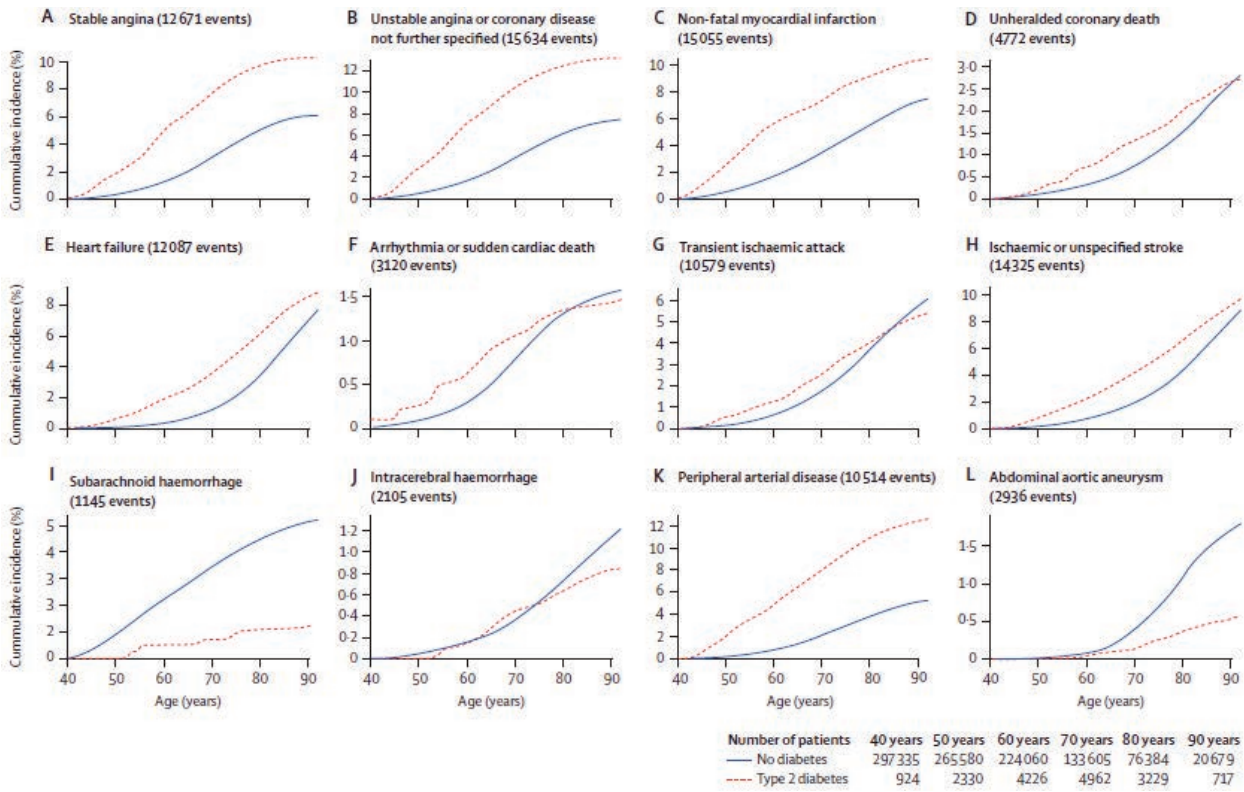

FIGURE 7 Event curves illustrating the cumulative incidence of various cardiovascular events during a median follow-up of 5.5 years in a large British population-based cohort study. People with diabetes (red dotted lines) were 1.5–2 times more likely than those without diabetes (blue solid lines) to suffer all types of cardiovascular events with the exceptions of subarachnoid hemorrhage and aortic aneurysms. Reprinted with permission from Shah AD, et al. Lancet Diabetes Endocrinol 2015;3:105–113 (ref. 66).

cardiovascular events in people with diabetes. Fortunately, a growing number of such strategies have been proven effective in large, well-conducted, international, randomized controlled trials (RCTs). These approaches can be broadly divided into those that are not prescribed for glucose lowering and those that are. Both categories, and their supporting evidence, are reviewed below.

CARDIOPROTECTIVE THERAPIES THAT ARE NOT PRESCRIBED FOR GLUCOSE LOWERING

Many large RCTs have shown that cardioprotective therapies that are effective in people without diabetes are also effective in people with diabetes. These include smoking cessation; blood pressure lowering to <130/80 mmHg (67); lowering of LDL cholesterol with statins, ezetimibe, and PCSK9 inhibitors (68,69); and use of RAAS blockers such as ACE inhibitors or angiotensin II receptor blockers (ARBs) (70). This category also includes low-dose aspirin (100 mg/day), albeit with one important caveat.

As documented in a recent long-term trial conducted in a primary prevention population of people with diabetes and no previous cardiovascular event (71), those assigned to aspirin were 12% less likely to experience a cardiovascular event but 29% more like to experience a major bleed. This translated into 1.1% fewer cardiovascular events and 0.9% more serious bleeds during a mean follow-up of 7.4 years. Thus, in this relatively low-risk population in which the incidence of a vascular event in untreated people was ~1.3% per year, the cardiovascular benefits and harms of aspirin were similar. This example highlights two important principles related to the use of a drug for preventing cardiovascular events in people at high versus low cardiovascular risk. These are discussed below.

Harms and Benefits in Primary and Secondary Prevention Populations: A Tutorial

It is axiomatic that a therapy should only be prescribed to prevent MACE when the benefit clearly outweighs the harm. Benefits are typically presented as either relative risks or HRs, which reflect the proportional reduction in the incidence of the event in someone receiving the therapy compared to someone not receiving the therapy.

Thus, if an untreated person's 10-year incidence of MACE is 30%, the use of a therapy that reduces it to 24% (i.e., an absolute risk difference of 6%) would be consistent with a relative risk of 0.8, or a relative risk reduction of 0.2, or 20%. Similarly, if a person's 10-year incidence was 3%, the same therapy would reduce it by the same 20%, which in this case would reflect an incidence of 2.4% (i.e., an absolute risk reduction of 0.6%). Thus, relative risk differences (i.e., 20% in both scenarios) are independent of the absolute incidence of the event, whereas absolute risk differences vary with the incidence of the event (i.e., 6 vs. 0.6%).

Increases in the incidence of harms (e.g., serious bleeds) caused by a therapy (e.g., aspirin) tend to occur for reasons unrelated to the incidence of events (e.g., cardiovascular events) or the reduction of that incidence resulting from use of the therapy. Thus, a drug that may cause net harm in people at low risk of a cardiovascular event may provide a net benefit in people at higher risk.

These issues are particularly relevant to understanding and interpreting the evidence from recent CVOTs with regard to primary versus secondary prevention. The incidence of MACE in a particular population also directly affects the ability of a clinical trial to demonstrate that a therapy is effective. First, the number of people who need to be enrolled in a clinical trial is inversely related to the expected incidence of MACE in untreated people in the control group (Figure 8, Panel A). Because people who have had a previous event such as an MI (i.e., a secondary prevention population) are more likely to have an event than those who have never had an event (i.e., a primary prevention population), fewer such people would need to be in a trial to show that a drug is effective for secondary prevention than for primary prevention, even if it works equally well in both groups. Second, for a trial with a fixed number of participants, the higher the incidence of the event within the control group, the higher the probability (i.e., power) will be that the trial will detect a beneficial effect of the drug (if it is indeed effective). Thus, if a 5-year trial involving 10,000 people randomly assigns 5,000 people to a drug that reduces cardiovascular events by 20% and 5,000 people to a placebo, that trial will have a 90% chance of detecting the cardiovascular benefit if the overall incidence of the event in the control group is 2.5% per year, but only a 55% chance if the control group incidence is 1% per year (Figure 8, Panel B). Therefore,

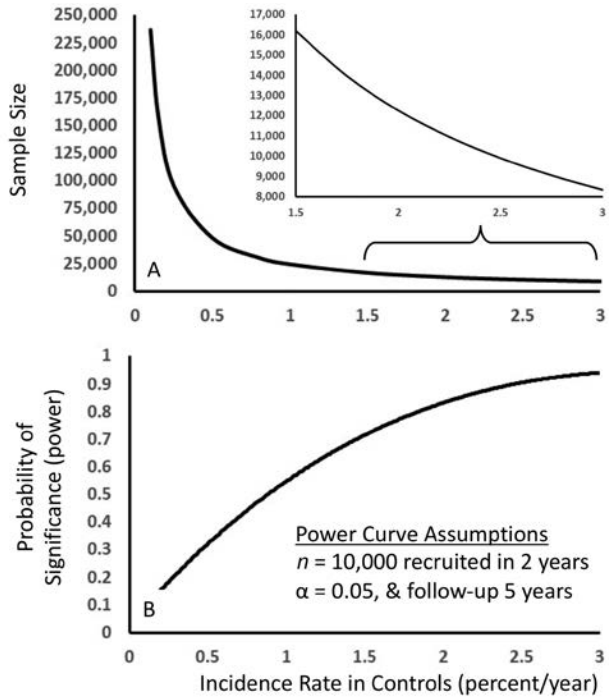

FIGURE 8 Panel A shows the relationship between the annual incidence rate of an event in the control group and the required sample size for a 5-year clinical trial that has a 90% probability or power to detect a 20% reduction of the event rate in the treatment group. Panel B shows the probability of detecting this same 20% difference (i.e., the power) for different incidence rates in the control group if the trial's sample size is fixed at 10,000.

if that 10,000-person trial of a truly cardioprotective drug is conducted in a low-risk population and does not demonstrate reduced cardiovascular events, it is because of the low probability of detecting the effect in those people and not because the drug is ineffective.

CARDIOPROTECTIVE THERAPIES THAT ARE ALSO PRESCRIBED FOR GLUCOSE LOWERING

The 12 different drug classes used for glucose-lowering in people with diabetes include sulfonylureas, biguanides (mainly metformin), meglitinides, insulin, TZDs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, α-glucosidase inhibitors, an amylin agonist (pramlintide), a bromocriptine formulation, and colesavalam (11,12). Many of the specific drugs within these classes have been included in large, international CVOTs that were designed to specifically assess the effect of the drug on serious cardiovascular events. To date, these trials have shown that eight drugs grouped within three of these classes significantly reduce MACE, usually a composite that includes the

first occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular causes. These eight include four different GLP-1 receptor agonists (albiglutide, dulaglutide, liraglutide, and semaglutide), three SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin), and one TZD (pioglitazone) (72).

Not all of the drugs in these classes have been found to significantly reduce MACE (e.g., among the GLP-1 receptor agonists, lixisenatide, exenatide, and oral semaglutide did not show such a benefit [73–75]). Moreover, each drug is unique, and each trial had several characteristics that differentiated it from the others. Indeed, the most prudent conclusions regarding a specific drug's cardiovascular effects come from the trial that tested that specific drug and not from one that tested other drugs within the same class. Nevertheless, consistent effects on clinical outcomes noted in drugs from the same class underlie meta-analyses of effects within a particular class and clinical practice guidelines regarding various drug classes. The cardiovascular effects of these drugs and their noncardiovascular harms are summarized below.

GLP-1 Receptor Agonists

Drugs in this class lower glucose levels by acting on the GLP-1 receptor. They also modestly reduce appetite, weight, and systolic blood pressure and increase heart rate. Common side effects, including nausea, diarrhea, and abdominal discomfort, are short-term and usually abate within the first 1–2 months of therapy.

CVOTs have tested the cardiovascular effects of seven of these drugs in people with *1*) recent acute coronary syndrome (lixisenatide [73]), *2*) a history of stable CVD (albiglutide [76]), and *3*) ambulatory people with either a history of CVD or multiple cardiovascular risk factors (dulaglutide [77], liraglutide [78], and parenteral and oral semaglutide [75,79]). A carefully conducted meta-analysis of these trials estimated that, overall, these drugs reduce MACE by 12% with little significant heterogeneity across trials (21). This meta-analysis also showed that GLP-1 receptor agonists significantly reduce MI, stroke, death from cardiovascular causes, and all-cause mortality as individual outcomes (Table 2). Additionally, it supported the hypothesis that the effect on stroke may be greater than the effect on MI. Most importantly, no serious adverse events were identified.

Primary Versus Secondary Prevention with GLP-1 Receptor Agonists

The first few positive CVOTs conducted subgroup analyses to determine whether the tested drug reduced cardiovascular events in subgroups of participants who did and did not have preexisting CVD (i.e., those who were at high versus low risk of having a cardiovascular event during the trial). Because very few low-risk people without a prior cardiovascular event were included in these early trials, the cardiovascular effects of GLP-1 receptor agonists in a primary prevention population were uncertain. With the recent completion of a trial reporting reduced cardiovascular events in a mainly primary prevention population (77), there were sufficient numbers to robustly assess the efficacy of this class of drugs for both primary and secondary prevention. The absence of any difference in effect across these two subgroups both in the trial (interaction *P* for difference in effect = 0.97) (77) and in two meta-analyses of data from all of the trials (interaction *P* = 0.22) (21,80) provides reassuring evidence of benefit for *both* primary and secondary prevention of

TABLE 2 Meta-Analyzed Effect of GLP-1 Receptor Agonists on Cardiovascular Outcomes from Seven Trials with an Overall Median Follow-up of 3.2 Years

Cardiovascular Event	GLP-1 Receptor Agonist (*n* = 27,977)	Placebo (*n* = 28,027)	HR (95% CI)	Number Needed to Treat (95% CI)	*P*
MI, stroke, cardiovascular death	2,948	3,304	0.88 (082–0.94)	75 (50–151)	<0.0001
Cardiovascular death	1,277	1,471	0.88 (0.81–0.96)	163 (103–489)	0.003
Fatal or nonfatal MI	1,540	1,662	0.91 (0.84–100)	193 (109–NA)	0.043
Fatal or nonfatal stroke	721	852	0.84 (0.76–0.93)	209 (139–477)	<0.0001
All-cause death	1,916	2,246	0.88 (0.83–0.95)	108 (77–260)	0.001

Adapted from ref. 21. NA, not applicable.

cardiovascular events. Hence, PCPs should consider these potential benefits across the continuum of prevention for their patients with diabetes. These findings are reflected in the 2019 update to the ADA/EASD consensus report and the 2020 ADA *Standards of Care* (13–15).

SGLT2 Inhibitors

SGLT2 inhibitors lower glucose levels by promoting glycosuria (81). They also reduce weight and systolic blood pressure. Common side effects of these drugs are an increased urine volume and increased risk of urogenital yeast infections, particularly in women.

CVOTs of three drugs in this class have now been completed in people with *1*) type 2 diabetes and stable CVD (empagliflozin [82]), *2*) type 2 diabetes and either previous CVD or multiple cardiovascular risk factors (canagliflozin and dapagliflozin [83,84]), *3*) type 2 diabetes and renal insufficiency (canagliflozin [85]), and *4*) HFrEF, both with and without type 2 diabetes (dapagliflozin [86]). Systematic reviews of these trials have estimated that drugs in this class reduce MACE by a modest 7% overall (primary and secondary prevention) (87). More importantly, however, they estimate that these drugs also reduce the composite outcome of cardiovascular death and HHF by >23% with no difference in those with or without prior CVD (22). Thus, SGLT2 inhibitors, like GLP-1 receptor agonists, can be used appropriately for *both* primary and secondary prevention of cardiovascular events.

TZDs

TZDs lower glucose levels by increasing the biologic effect of insulin. They confer additional benefits in lowering blood pressure and reducing visceral fat, but also have adverse effects, including weight gain, fluid retention, edema, and increased risk of fractures (88). However, they also reduce the incidence of diabetes (89,90). One well conducted CVOT of pioglitazone, the only routinely prescribed TZD, recruited people at high risk for diabetes with previous ischemic stroke or transient ischemic attack (91). In this trial, pioglitazone reduced the composite outcome of fatal or nonfatal MI or stroke by 24%, while increasing the risk of fractures, weight gain, and edema. Thus, although pioglitazone offers both diabetes prevention and cardiovascular benefits, its use must be weighed against its potential to cause harm in individual patients.

To recap, large, well-conducted, RCTs have successfully identified a formulary of drug therapies that clinicians can use to reduce cardiovascular events in people with type 2 diabetes. Some of these therapies (GLP-1 receptor agonists, SGLT2 inhibitors, and TZDs) concomitantly lower glucose levels. Whether the glucose-lowering effect contributes to their cardiovascular effect remains the subject of debate (92,93). Importantly, these therapies were tested on a background of cardioprotective therapies that do not lower glucose levels. Although the cardiovascular effects of combining the three cardioprotective glucose-lowering therapies are unknown, there is no contraindication to using them together.

The broad array of evidence-based cardioprotective therapies now available has the potential to dramatically reduce cardiovascular events in people with type 2 diabetes. Their expeditious use in primary care practice, either alone or in combination with other current or future therapies, will clearly reduce and could one day eliminate the twofold higher risk of cardiovascular events in people with diabetes.

Renal Protection Across the Continuum of Risk

KEY POINTS

- **SGLT2 inhibitors and GLP-1 receptor agonists are important for both the prevention and treatment of CKD in type 2 diabetes. SGLT2 inhibitors are especially preferred for patients with type 2 diabetes and CKD, but if their use is not possible, a GLP-1 receptor agonist with cardiovascular benefit may be used.**
- **Early use of these beneficial agents in high-risk patients with diabetes should reduce progression of renal and cardiovascular complications.**
- **PCPs play a crucial role in implementing the new guidelines for managing patients with type 2 diabetes and CKD.**

CKD is a common comorbidity in patients with type 2 diabetes. Patients with both conditions are at risk for both progressive kidney dysfunction and serious cardiovascular complications. Although CKD is likely not entirely preventable, recent trials have shown that preferential use of agents in the SGLT2 inhibitor and GLP-1 receptor agonist classes can help to reduce the risk of important cardiorenal complications. The latest

guidelines from ADA and EASD (11–15) were revised in light of this recent evidence. Specifically, these guidelines now call for the preferential use of these beneficial agents for patients with any manifestation of CKD, even if they are already meeting their glycemic targets. PCPs are exceptionally well-positioned to incorporate these medications early in the course of type 2 diabetes and in turn improve important health outcomes for their patients with type 2 diabetes.

CKD PREVALENCE AND DEFINITION

CKD affects an estimated 37 million people in the United States and accounts for >$100 billion in annual Medicare costs alone (94). The criteria for CKD include any of the following if persistent for >3 months (95):

- eGFR <60 mL/min/1.73 m^2
- UACR ≥30 mg/g Cr
- Any other marker of kidney damage such as nephrotic or nephritic syndrome, urinalysis or radiologic abnormality, or hypertension caused by kidney disease

CKD RISK FACTORS AND RISKS

Numerous risk factors contribute to the development of CKD, only some of which are modifiable (Table 3). In the United States, diabetes and hypertension are the main causes of CKD and are responsible for ~75% of kidney failure cases (94). CKD not only increases the risk of progression to ESRD requiring dialysis or kidney transplantation, but is also associated with an increased risk of cardiovascular complications and death. In fact, people with CKD are at greater risk for premature death than for progression to ESRD (94). This is particularly true for patients with macroalbuminuria (UACR >300 mg/g Cr) (96). The National Kidney Foundation and other groups have proposed a risk classification of CKD by GFR (for clinical purposes generally calculated and referred to as eGFR) and albuminuria categories (Figure 9) (97,98). Referral to a nephrologist is recommended as indicated in Figure 9 and is also reasonable if the etiology of a patient's kidney disease is not clear.

TABLE 3 CKD Risk Factors

Modifiable risk factors:

- Diabetes
- Hypertension
- Acute kidney injury
- Frequent use of nonsteroidal antiinflammatory medications
- Autoimmune disease
- Kidney stones/obstruction
- Other lifestyle factors

Nonmodifiable risk factors:

- Family history of CKD, diabetes, or hypertension
- Age ≥60 years (eGFR declines normally with age)
- Race/ethnicity (African Americans, Hispanics, Asians, Pacific Islanders, and Native Americans are disproportionately affected)
- Sex (more common in women than in men)
- Genetic factors

DIABETIC KIDNEY DISEASE

Diabetic kidney disease, or diabetic nephropathy, is generally characterized by persistent albuminuria, hypertension, progressive decline in eGFR, and a significantly increased risk of cardiovascular morbidity and mortality. Patients with diabetes and a reduced eGFR have a sixfold increase in mortality rate compared to those without kidney disease, and the mortality rate is increased more than tenfold in patients with both reduced eGFR and albuminuria (99). CKD may already be present at the time of diagnosis of type 2 diabetes because hyperglycemia often is present for many years before diabetes is detected, and many patients with diabetes also have concomitant hypertension or other CKD risk factors (97). Therefore, patients with type 2 diabetes should be screened for evidence of CKD (eGFR and UACR) starting at the time of diabetes diagnosis.

Guidelines for the management of patients with both CKD and diabetes now include interventions designed to reduce the risk of progressive renal dysfunction, address such patients' heightened cardiovascular risk, and enhance the safety of their glucose-lowering medication regimen. Because these measures apply even to patients with very early manifestations of CKD, PCPs play a key role in implementing the guidelines, thereby preserving the health of many patients with both diabetes and kidney dysfunction.

CKD SCREENING AND MONITORING

ADA recommends that urinary albumin (spot UACR) and eGFR be assessed at least annually in all patients with type 2 diabetes. Those with moderately reduced eGFR or severely increased albuminuria should be reassessed more frequently, at least twice per year (97). Patients found to have an eGFR <60 mL/min/1.73 m^2

CKD is classified based on:
- Cause
- GFR (G)
- Albuminuria (A)

GFR Categories (mL/min/1.73 m²), description and range				Albuminuria Categories, description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60–89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15–29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

FIGURE 9 Risk of CKD progression, frequency of visits, and referral to nephrology according to GFR and albuminuria. The GFR and albuminuria grid depicts the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, dark red). The numbers in the boxes are a guide to the frequency of visits (number of times per year). Green can reflect CKD with normal GFR and UACR only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements three times per year; and dark red requires measurements four times per year. These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient, must be taken into account. "Refer" indicates that nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. Reprinted with permission from Vassalotti JA et al. Am J Med 2016;129:153–162.e7 (ref. 98).

should have their medication doses reviewed and adjusted as appropriate for their stage of CKD and should be counseled to avoid nephrotoxic agents. As kidney function declines, patients should also be monitored for worsening hypertension, signs and symptoms of volume overload, anemia, and electrolyte abnormalities.

MANAGING CKD IN TYPE 2 DIABETES

A multifactorial approach to the management of patients with type 2 diabetes and CKD is recommended (97). Well-established approaches to nutrition modification, blood pressure management, and glycemic targets are of demonstrated benefit and remain the cornerstones of care for these patients. Although many of the general principles for the care of patients with diabetes also apply to those with CKD, their care should be further modified to reduce the risk of progressive kidney dysfunction and cardiovascular complications.

Dietary Management

Restriction of daily dietary protein intake to ~0.8 g/kg body weight is recommended to slow eGFR decline in patients with CKD who do not require dialysis. Dietary sodium restriction to <2,300 mg/day may be helpful for blood pressure management and avoidance of volume overload. Patients with more advanced CKD may also require potassium restriction to avoid hyperkalemia, particularly in the setting of ACE inhibitor ARB use.

Blood Pressure Management

ADA recommends a general blood pressure target of <140/90 mmHg for all patients with diabetes to reduce

cardiovascular and CKD risk. A lower target (e.g., <130/80 mmHg) may be appropriate for some patients, including those with CKD, who are at increased risk for cardiovascular complications and progression of kidney disease. The lower target should be considered especially in those with ≥300 mg/day albuminuria. An ACE inhibitor or ARB is recommended as first-line therapy for patients with type 2 diabetes and hypertension with or without elevated UACR, and especially for those with an eGFR <60 mL/min/1.73 m^2 or macroalbuminuria. Combined use of an ACE inhibitor and an ARB, which increases the risk of impaired kidney function and hyperkalemia, should be avoided. Other guidance on blood pressure management is summarized in the ADA *Standards of Care* (100) and reviewed in detail in a 2017 ADA position statement on the topic (101).

Glycemic Targets

More intensive glycemic control is effective in reducing the risk of microvascular complications, including diabetic nephropathy, in patients with type 2 diabetes. In the UKPDS, the intensive control group achieved a mean A1C of 7.0% compared to 7.9% in the conventional group (41). Intensive control significantly reduced the risk of any diabetes-related endpoint, primarily attributable to a 25% reduction in the risk of microvascular complications. A subsequent meta-analysis (102), which included data from the UKPDS and other trials assessing intensity of glycemic control in patients with more complicated type 2 diabetes of longer duration, found that intensive glycemic control reduced by 20% the risk of a composite primary kidney endpoint that included development of macroalbuminuria, ESRD, and renal death.

These findings support a general A1C target of <7% in adults with type 2 diabetes to minimize the risks of complications, including new or worsening diabetic nephropathy (103). However, progressive CKD may limit the types of glucose-lowering medications that can be used safely. In particular, the risk of hypoglycemia will be higher in patients with a reduced eGFR who are using sulfonylureas or insulin for glycemic control. Individualization of the pharmacologic regimen is important in patients with established significant comorbidities such as advanced CKD. In such patients, less stringent A1C goals (e.g., <8%) may be more appropriate (103). In very advanced CKD, A1C values may be less reliable, and use of other assessments such as fingerstick blood glucose values, continuous glucose monitoring data, or fructosamine measurements may be helpful in guiding the adjustment of glucose-lowering medications (103).

GLUCOSE-LOWERING MEDICATIONS TO REDUCE CARDIORENAL RISK

As discussed earlier, guidelines for the management of patients with type 2 diabetes and ASCVD, HF, or CKD have changed dramatically in recent years. Although glycemic control remains a cornerstone of diabetes management, CVOTs of newer glucose-lowering medications have shown that agents in the GLP-1 receptor agonist and SGLT2 inhibitor classes convey particular benefits important to both the prevention and treatment of CKD in patients with type 2 diabetes.

Meta-analyses of trials enrolling patients with type 2 diabetes and either established ASCVD or multiple risk factors for MACE have demonstrated evidence of renal protection with the use of these newer agents (49). Specifically:

- Both GLP-1 receptor agonists (HR 0.82, 95% CI 0.75–0.89, P <0.001) and SGLT2 inhibitors (HR 0.62, 95% CI 0.58–0.67, P <0.001) reduced progression of CKD, including macroalbuminuria.
- SGLT2 inhibitors, but not GLP-1 receptor agonists, also reduced the risk of worsening eGFR, ESRD, or renal death (HR 0.55, 95% CI 0.48–0.64, P <0.001).

Additional analyses of data from the CVOTs of SGLT2 inhibitors suggest that reductions in risks of MACE and HF seen with SGLT2 inhibition were similar in patients with an eGFR higher or lower than 60 mL/min/1.73 m^2 at baseline, whereas agents in this drug class reduced the risk of stroke only in patients with reduced kidney function (104).

The more recent CREDENCE (Canagliflozin and Renal End points in Diabetes with Established Nephropathy Clinical Evaluation) trial (85) specifically enrolled patients with type 2 diabetes and CKD (mean UACR >900 mg/g Cr and mean eGFR 56 mL/min/1.73 m^2) who were randomized to either the SGLT2 inhibitor canagliflozin or placebo to determine the effect of therapy on a composite outcome of ESRD, doubling of serum Cr, or renal or cardiovascular death. It is important to note that the CREDENCE trial was halted early for efficacy in reducing the risk of that outcome; in addition, a 32% reduction in the risk of progression to ESRD was seen with canagliflozin therapy. The precise mechanisms through which SGLT2 inhibition conveys these benefits are not clear but appear to be independent of glucose

lowering. Importantly, although the glucose-lowering effects of SGLT2 inhibitors are blunted at lower eGFRs, the cardiovascular benefits are seen in patients with an eGFR as low as 30 mL/min/1.73 m^2. Although all of the SGLT2 inhibitors have a threshold eGFR below which their use is not indicated, the benefits of this drug class in patients with CKD have become increasingly clear. In particular, as a result of the CREDENCE trial, canagliflozin is now indicated for use in patients with CKD and eGFR as low as 30 mL/min/1.73 m^2.

To recap, SGLT2 inhibitor therapy should be considered to reduce the risks of CKD progression and cardiovascular complications in patients with type 2 diabetes and CKD if eGFR is adequate. The evidence for benefit is particularly strong in patients with macroalbuminuria. If SGLT2 inhibitor therapy is contraindicated or not tolerated in such a patient, a GLP-1 receptor agonist with proven cardiovascular benefit may be considered to reduce the risk of cardiovascular events and progression of albuminuria (15,97). Although metformin remains the recommended first-line therapy for type 2 diabetes, in patients with CKD, the addition of an SGLT2 inhibitor or a GLP-1 receptor agonist should be considered irrespective of the need for additional glucose lowering (Figure 4).

OTHER MEDICATION SAFETY ISSUES

Most patients with type 2 diabetes will eventually require multiple glucose-lowering medications to achieve and maintain adequate glycemic control. Medication choices may become complex in patients with a reduced eGFR because many glucose-lowering agents require dose adjustment, have a heightened risk for adverse side effects, or are simply contraindicated in advanced CKD. Key principles pertaining to the safe and effective use of commonly prescribed glucose-lowering medications in patients with type 2 diabetes and CKD are summarized in Table 4 (15,105).

TABLE 4 Safety and Effectiveness Considerations for Commonly Prescribed Glucose-Lowering Medications in Patients with Type 2 Diabetes and CKD (15,105)

Drug Class	Hypoglycemia Risk?	Impact on CKD	Effect on MACE	Effect on HF	Use and Dosing Considerations
Biguanides (metformin)	No	Neutral	Possible long-term benefit	Neutral	Contraindicated if eGFR <30 mL/min/1.73 m^2
SGLT2 inhibitors	No	Beneficial	Beneficial (dapagliflozin neutral)	Beneficial (ertugliflozin effect to be determined)	Renal dose adjustment required (canagliflozin indicated for use to eGFR ≥30 mL/min/1.73 m^2)
GLP-1 receptor agonists	No	Beneficial (primarily reduced progression of albuminuria)	Beneficial (lixisenatide, exenatide neutral; oral semaglutide effect to be determined)	Neutral	Use with caution when initiating or up-titrating dose in patients with reduced eGFR; renal dose adjustment required for lixisenatide and exenatide
DPP-4 inhibitors	No	Neutral	Neutral	Neutral (exception: increased risk with saxagliptin)	May be used in all stages of CKD; all agents except linagliptin require renal dose adjustment
TZDs	No	Neutral	Neutral	Increased risk	No dose adjustment required; generally not recommended in renal impairment due to potential for fluid retention
Sulfonylureas	Yes	Neutral	Neutral	Neutral	Dose cautiously if used to reduce risk hypoglycemia; avoid use of glyburide
Insulin	Yes	Neutral	Neutral	Neutral	Dose cautiously; lower doses needed with reduced eGFR

Keeping an Eye on Glycemic Control

KEY POINTS

- Therapies that improve cardiovascular and renal outcomes (i.e., GLP-1 receptor agonists, SGLT2 inhibitors, statins, ACE inhibitors or ARBs, and aspirin) should be initiated in appropriate patients with type 2 diabetes to reduce complications irrespective of patients' glucose, lipid, and blood pressure levels.
- Such therapies should be implemented in tandem with, not instead of, efforts to achieve glucose, blood pressure, and lipid targets.
- Achieving early and sustained glycemic control reduces short- and long-term complications, and PCPs are best positioned to implement glycemic control measures from to time of diabetes diagnosis.

As has been emphasized throughout this publication, ADA and EASD now recommend that patients with type 2 diabetes who also have or are at high risk for ASCVD, HF, or CKD receive appropriate therapies to reduce adverse outcomes irrespective of their A1C (11–15). Some may interpret this change to mean that glycemic control is not as important a goal to achieve as it used to be, but that interpretation would be incorrect. The diagnosis of diabetes remains dependent on glucose levels, and hyperglycemia continues to be the main cause of or a major contributor to many of its complications.

The ultimate purpose of managing diabetes is to improve patients' quality and quantity of life by reducing the burden of adverse outcomes while minimizing the burden of treatment. To achieve this end, a multifactorial, multidisciplinary approach is necessary, as evidenced in the landmark STENO-2 (Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria) study (106). Such an approach includes the use of beneficial therapies such as statins, RAAS blockers, aspirin, GLP-1 receptor agonists, and SGLT2 inhibitors where appropriate, but also the achievement of glucose (A1C), blood pressure, and cholesterol targets, smoking cessation, and the adoption of healthy lifestyle behaviors (15).

BENEFITS OF ACHIEVING GLYCEMIC TARGETS

The benefits of glycemic control in reducing adverse outcomes have been demonstrated in trials in both type 1 and type 2 diabetes. These prospective RCTs compared the effects of lower and higher glycemic targets on both microvascular and macrovascular complications of diabetes.

Microvascular Complications

In type 1 diabetes, the DCCT and its observational follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study proved conclusively that achieving an A1C of ~7% (compared to 9%) resulted in significantly fewer microvascular complications in both the short and long term (40,107). In type 2 diabetes, several studies have examined the effects of glycemic control across a spectrum of patients. The UKPDS included patients who had newly diagnosed diabetes and found that lower A1C reduced microvascular complications in the short term and that these benefits persisted during long-term follow-up, even after between-group differences in glycemic control dissipated (a phenomenon called a "legacy effect") (41,42). Three other landmark trials, ACCORD (Action to Control Cardiovascular Risk in Diabetes) (108), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (109), and the VADT (Veterans Affairs Diabetes Trial) (110), each included patients with type 2 diabetes who had longer durations of diabetes at baseline, many of whom also had established CVD at baseline. Some, but not all, microvascular complications were reduced in the groups with lower A1C targets (111). The benefits seen in the short term mostly persisted in long-term follow-up studies (112–114). Thus, a strong body of evidence confirms that achieving lower glycemic targets reduces microvascular complications in both type 1 and type 2 diabetes.

Macrovascular Complications

The evidence regarding whether improving glycemic control reduces macrovascular complications is not as conclusive. In type 1 diabetes, the DCCT did not demonstrate macrovascular benefit in the short term, likely because of the young age of its participants (mean age 27 years) and the trial's relatively short duration (9 years) (40). However, the EDIC observational follow-up study of the DCCT cohort did

demonstrate long-term macrovascular benefits of early glycemic control, with a reduction in cardiovascular events apparent at 17 years and persisting to 30 years of follow-up (43,115). Thus, in type 1 diabetes, it is now widely accepted that achievement of lower glycemic targets reduces macrovascular complications.

In type 2 diabetes, data regarding such an association have been inconsistent. In the UKPDS, which had participants who were newly diagnosed with diabetes, the interventional trial did not demonstrate macrovascular benefit in the overall population, but subsequent observational follow-up did show a reduction in macrovascular outcomes after 10 years (42). In studies that evaluated patients at high CVD risk with longer durations of diabetes and more baseline comorbidities (ACCORD, ADVANCE, and the VADT), glucose-lowering strategies that achieved lower glycemic targets did not reduce macrovascular outcomes in the short term (108–110). In fact, there was an unexpected increase in mortality with lower targets in the ACCORD trial that remains unexplained but has not been replicated in the other studies (108). After 10 years of follow-up, however, a reduction in macrovascular events was demonstrated in the VADT (116) but not in the ACCORD (117) or ADVANCE (112) trials.

In light of the available evidence, it is accepted that improved glycemic control reduces macrovascular complications in type 1 diabetes in the long term; however, in type 2 diabetes, the benefits are derived when glycemic control is achieved early in the disease, and such a strategy should be implemented more cautiously in individuals with long diabetes durations and multiple comorbidities. This understanding has resulted in changes to clinical practice guidelines to emphasize the importance of individualizing glycemic targets (118).

ACHIEVING GLYCEMIC TARGETS EARLY AND SAFELY

The trials summarized above consistently demonstrated that glycemic control is most effective when achieved early and then sustained. The legacy effect found in both the DCCT and the UKPDS follow-up cohorts means that individuals who achieve glycemic control earlier will continue to have reduced risks for complications that persist for decades compared to those who implement tighter glycemic control later in the course of the disease. These benefits of early glycemic remain apparent even when compared to groups who started later but achieved a similar degree of glycemic control.

PCPs are thus best positioned to reduce adverse outcomes by helping patients achieve and sustain glycemic control from the time of diagnosis. ADA recommends glycemic targets of A1C <7%, preprandial plasma glucose of 80–130 mg/dL, and postprandial plasma glucose <180 mg/dL for many non-pregnant adults with diabetes (103). However, glycemic control should be achieved safely while minimizing hypoglycemia. Thus, these targets should be individualized balancing the benefits, which may take a long time to manifest, with the risks, which may be acute. Factors that should be taken into account when individualizing glycemic targets include a patient's risk of hypoglycemia or other adverse outcomes, disease duration, life expectancy, comorbidities, ASCVD status, preferences, and available resources and support (103). Many of these considerations are especially important with regard to older adults with diabetes. The ADA *Standards of Care* provides a framework for selecting reasonable glycemic goals for these patients (118).

WHERE DOES GLYCEMIC CONTROL FIT IN THE NEW TREATMENT PARADIGM?

With all the well-deserved excitement generated by recent cardiovascular and renal outcomes trials and the corresponding changes in international guidelines, there is a risk of losing sight of the ongoing importance of glycemic control in diabetes management. Conversely, a narrow focus on the need to achieve and maintain glycemic control has prevented some patients from receiving beneficial therapies because they have already achieved their A1C target. Neither of these circumstances is appropriate.

Again, the ultimate goal of managing diabetes is to improve quality and quantity of life by reducing complications while minimizing treatment burden. Doing so requires a multifactorial approach to achieving metabolic targets while also implementing beneficial therapies in appropriate patients. These therapies improve outcomes independent of their primary indications (e.g., glucose, cholesterol, or blood pressure lowering); thus, they should be added for appropriate patients irrespective of their lipid profile, blood pressure, or A1C. However, all of the recent outcomes trials were conducted with an expectation that investigators were still implementing guidelines-based multifactorial care. Indeed, the implementation of therapies proven

to improve outcomes will only enhance patients' ability to achieve these multifactorial targets. In addition, not all patient-important adverse outcomes were reduced in the CVOTs; for example, the tested therapies did not reduce retinopathy or neuropathy. Therefore, clinicians must continue working to reduce patients' risks of such outcomes, which can be accomplished through the achievement of adequate glycemic control.

It is time to implement a multifactorial approach that includes both the use of therapies to reduce adverse outcomes in appropriate patients *and* the achievement of glycemic targets. These concepts are complementary, not competitive.

Conclusion

In their most recent guidelines on type 2 diabetes treatment, ADA and EASD unveiled a holistic, person-centered approach that represents a paradigm shift in the pharmacologic management of hyperglycemia. Numerous glucose-lowering therapies have come to market in the past two decades, offering new opportunities to treat type 2 diabetes more safely and effectively. However, this explosion in therapeutic options has been overwhelming to many clinicians. Earlier guidelines set out a primarily glucocentric approach to achieving specific A1C targets through progressively complex algorithms involving the stepwise addition of oral agents and injectable medications over time. These recommendations generally offered little direction regarding which agents should be used preferentially in different patients and at different stages of disease progression, often leaving clinicians more confused. The resulting clinical uncertainty regarding the plethora of treatments and how best to use them in turn has no doubt contributed to therapeutic inertia (19,34,35).

Fortunately, recent CVOTs have yielded a wealth of evidence demonstrating the safety and efficacy of newer glucose-lowering medications. More importantly, they have also identified opportunities presented by several of these drugs—particularly those in the GLP-1 receptor agonist and SGLT2 inhibitor classes—to protect against or treat the serious and common diabetes comorbidities of ASCVD, HF, and CKD. The retooled ADA/EASD guidelines, based on the accumulated evidence from these CVOTs, now offer a clear roadmap for selecting glucose-lowering medications while taking into account each patient's comorbidity status, as well as other clinically relevant issues such as weight and hypoglycemia concerns, potential access or cost limitations, and personal preferences. The latest guidelines can help clinicians select the most appropriate medications at the most appropriate times for each patient, with the ultimate goal of optimizing patients' health and quality of life.

This new, person-centered approach is especially relevant to PCPs, who are best positioned to help patients achieve early and sustained glycemic control while also reducing their risks of developing or worsening complications. PCPs have always focused on disease prevention. The recent outcomes trials have revealed the potential for offering a continuum of benefit from primary through secondary and tertiary prevention of microvascular and macrovascular disease, while still striving to achieve glycemic targets. Thus, it is incumbent on PCPs to become familiar with these new guidelines and to adopt them in daily clinical practice.

There has never been a better opportunity to improve our patients' lives. With outcomes-based guidelines now in hand, we have both the ability and the responsibility to integrate this wealth of newfound knowledge into our everyday clinical practice.

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Author Contributions

Lead author S.B.H. reviewed all content and wrote the introduction and conclusion sections. A.Y.Y.C. wrote the section titled "Keeping an Eye on Glycemic Control." M.J.D. wrote the section titled "A New Approach for a New Era: The Case for Person-Centered Care." H.C.G. wrote the section titled "Preventing Cardiovascular Events Across the Continuum of Risk." J.B.G. wrote the section titled "Renal Protection Across the Continuum of Risk." N.S. wrote the section titled "An Approach Made for Primary Care." All authors reviewed and edited the manuscript and approved the final version for publication. S.B.H. is the guarantor of this work.

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