Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the prior position statements, published in 2012 and 2015, on the management of type 2 diabetes in adults. A systematic evaluation of the literature since 2014 informed new recommendations. These include additional focus on lifestyle management and diabetes self-management education and support. For those with obesity, efforts targeting weight loss, including lifestyle, medication, and surgical interventions, are recommended. With regards to medication management, for patients with clinical cardiovascular disease, a sodium–glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide 1 (GLP-1) receptor agonist with proven cardiovascular benefit is recommended. For patients with chronic kidney disease or clinical heart failure and atherosclerotic cardiovascular disease, an SGLT2 inhibitor with proven benefit is recommended. GLP-1 receptor agonists are generally recommended as the first injectable medication.

The goals of treatment for type 2 diabetes are to prevent or delay complications and maintain quality of life (Fig. 1). This requires control of glycemia and cardiovascular risk factor management, regular follow-up, and, importantly, a patient-centered approach to enhance patient engagement in self-care activities (1). Careful consideration of patient factors and preferences must inform the process of individualizing treatment goals and strategies (2,3).

This consensus report addresses the approaches to management of glycemia in adults with type 2 diabetes, with the goal of reducing complications and maintaining quality of life in the context of comprehensive cardiovascular risk management and patient-centered care. The principles of how this can be achieved are summarized in Fig. 1 and underpin the approach to management and care. These recommendations are not generally applicable to patients with monogenic diabetes, secondary diabetes, or type 1 diabetes, or to children.

Data Sources, Searches, and Study Selection

The writing group accepted the 2012 (4) and 2015 (5) editions of this position statement as a starting point. To identify newer evidence, a search was conducted on PubMed for randomized clinical trials (RCTs), systematic reviews, and meta-analyses

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M.J.D. and J.B.B. were co-chairs for the Consensus Statement Writing Group. D.A.D'A., J.F., W.N.K., and D.J.W. were the writing group members for the American Diabetes Association. C.M., G.M., P.R., and A.T. were writing group members for the European Association for the Study of Diabetes.

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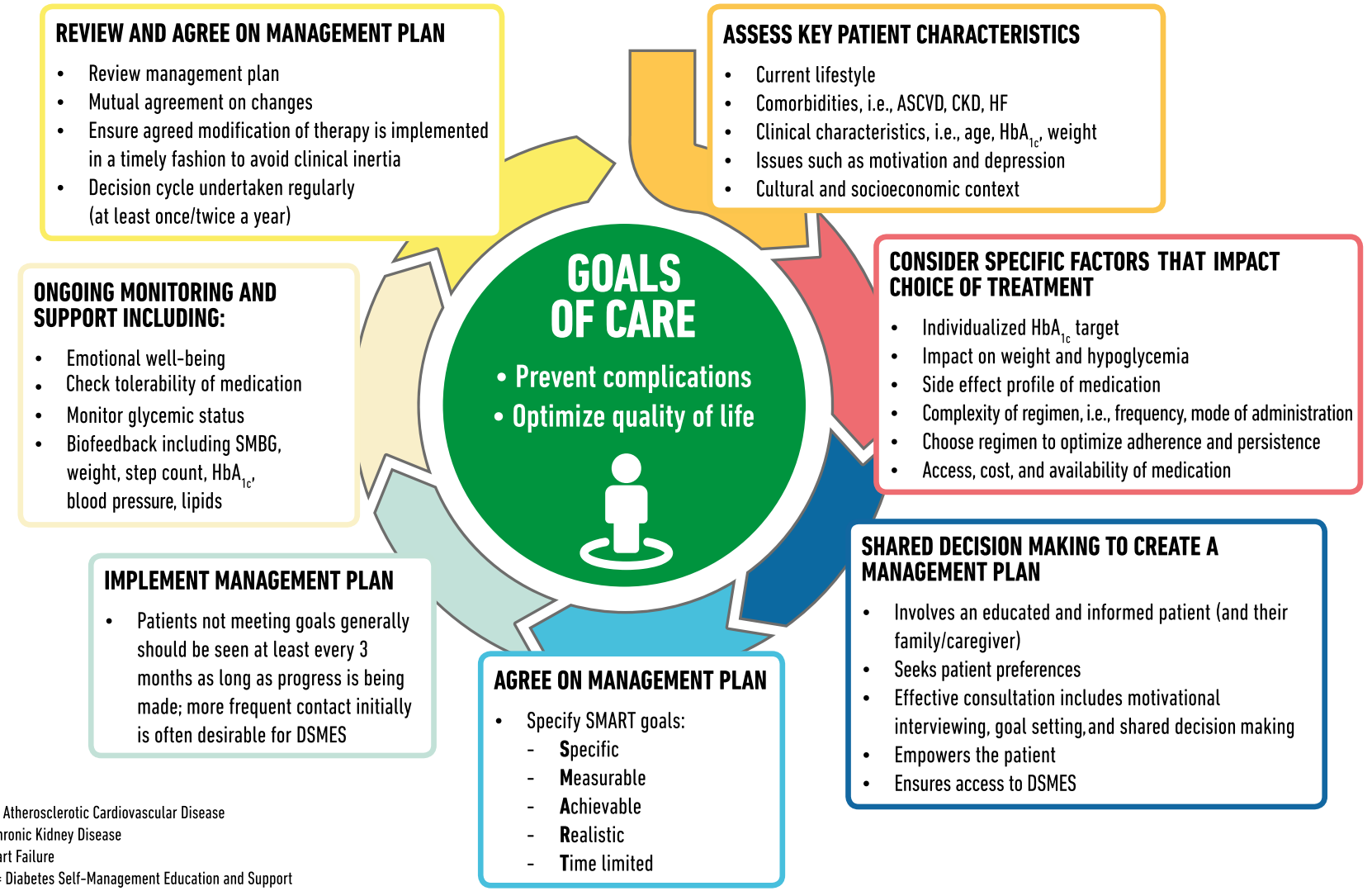
DECISION CYCLE FOR PATIENT-CENTERED GLYCEMIC MANAGEMENT IN TYPE 2 DIABETES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Figure 1—Decision cycle for patient-centered glycemic management in type 2 diabetes.

published in English between 1 January 2014 and 28 February 2018; eligible publications examined the effectiveness or safety of pharmacological or nonpharmacological interventions in adults with type 2 diabetes mellitus. Reference lists were scanned in eligible reports to identify additional articles relevant to the subject. Details on the keywords and the search strategy are available at https://doi.org/10.17632/h5rcnxpk8w.1. Papers were grouped according to subject, and the authors reviewed this new evidence to inform the consensus recommendations. The draft consensus recommendations were peer reviewed (see "Acknowledgments"), and suggestions incorporated as deemed appropriate by the authors. Nevertheless, though evidence-based, the recommendations presented herein are the opinions of the authors.

The Rationale, Importance, and Context of Glucose-Lowering Treatment

Lifestyle management, including medical nutrition therapy (MNT), physical activity, weight loss, counseling for smoking cessation, and psychological support, often delivered in the context of diabetes self-management education and support (DSMES), are fundamental aspects of diabetes care. The expanding number of glucose-lowering treatments—from behavioral interventions to medications and surgery—and growing information about their benefits and risks provides more options for people with diabetes and providers, but can complicate decision making. In this consensus statement, we attempt to provide an approach that summarizes a large body of recent evidence for practitioners in the U.S. and Europe.

Marked hyperglycemia is associated with symptoms including frequent urination, thirst, blurred vision, fatigue, and recurring infections. Beyond alleviating symptoms, the aim of blood glucose lowering (hereafter, referred to as glycemic management) is to reduce long-term complications of diabetes. Good glycemic management yields substantial and enduring reductions in onset and progression of microvascular complications. This benefit has been demonstrated most clearly early in the natural history of the disease in studies using metformin, sulfonylureas, and insulin but is supported by more recent studies with other medication classes. The greatest absolute risk reduction (ARR) comes from improving poor glycemic control, and a more modest reduction results from near normalization of glycemia (6). The impact of glucose control on macrovascular complications is less certain. Because the benefits of intensive glucose control emerge slowly, while the harms can be immediate, people with longer life expectancy have more to gain from intensive glucose control. A reasonable HbA_{1c} target for most nonpregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) is around 53 mmol/mol (7%) or less (6). Glycemic treatment targets should be individualized based on patient preferences and goals, risk of adverse effects of therapy (e.g., hypoglycemia and weight gain), and patient characteristics, including frailty and comorbid conditions (2).

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in people with type 2 diabetes (7). Diabetes confers substantial independent ASCVD risk, and most people with type 2 diabetes have additional risk factors such as hypertension, dyslipidemia, obesity, physical inactivity, chronic kidney disease (CKD), and smoking. Numerous studies have demonstrated the benefits of controlling modifiable ASCVD risk factors in people with diabetes. Substantial reductions in ASCVD events and death are seen when multiple ASCVD risk factors are addressed simultaneously, with long-standing benefits (8,9). Comprehensive implementation of evidence-based interventions has likely contributed to the significant reductions in ASCVD events and mortality seen in people with diabetes in recent decades (10). ASCVD risk management in its many forms is an essential part of diabetes management that is beyond the scope of this statement, but physicians should be aware of the importance of multifactorial treatment in type 2 diabetes (7).

Glucose Management: Monitoring

Glycemic management is primarily assessed with the HbA_{1c} test, which was the measure studied in trials demonstrating the benefits of glucose lowering (2). The performance of the test is generally excellent for NGSP-certified assays and laboratories (www.ngsp.org) (11). As with any laboratory test, HbA_{1c} has limitations (2). Because there is variability in the measurement of HbA_{1c}, clinicians should exercise judgment, particularly when the result is close to the threshold that might prompt a change in therapy. HbA_{1c} results may be discrepant from the patient's true mean glycemia in certain racial and ethnic groups, and in conditions that alter red blood cell turnover, such as anemia, end-stage renal disease (ESRD) (especially with erythropoietin therapy), and pregnancy, or if an HbA_{1c} assay sensitive to hemoglobin variants is used in someone with sickle cell trait or other hemoglobinopathy. Discrepancies between measured HbA_{1c} and measured or reported glucose levels should prompt consideration that one of these may not be reliable (12).

Regular self-monitoring of blood glucose (SMBG) may help with self-management and medication adjustment, particularly in individuals taking insulin. SMBG plans should be individualized. People with diabetes and the health care team should use the data in an effective and timely manner. In people with type 2 diabetes not using insulin, routine glucose monitoring is of limited additional clinical benefit while adding burden and cost (13,14). However, for some individuals, glucose monitoring can provide insight into the impact of lifestyle and medication management on blood glucose and symptoms, particularly when combined with education and support. Novel technologies, such as continuous or flash glucose monitoring, provide more information. However, in type 2 diabetes, they have been associated with only modest benefits (15).

Principles of Care

Consensus recommendation

- Providers and health care systems should prioritize the delivery of patient-centered care.

Providing patient-centered care that acknowledges multimorbidity, and is respectful of and responsive to individual patient preferences and barriers, including the differential costs of therapies, is essential to effective diabetes management (16). Shared decision making, facilitated by decision aids that show the absolute benefit and risk of alternative treatment options, is a useful

strategy to arrive at the best treatment course for an individual (17–20). Providers should evaluate the impact of any suggested intervention, including self-care regimens, in the context of cognitive impairment, limited literacy, distinct cultural beliefs, and individual fears or health concerns given their impact on treatment efficacy.

DSMES

Consensus recommendation

- All people with type 2 diabetes should be offered access to ongoing DSMES programs.

DSMES is a key intervention to enable people with diabetes to make informed decisions and to assume responsibility for day-to-day diabetes management. DSMES is central to establishing and implementing the principles of care (Fig. 1). DSMES programs usually involve face-to-face contact in group or individual sessions with trained educators, and key components are shown in Table 1 (21–25). While DSMES should be available on an ongoing basis, critical junctures when DSMES should occur include at diagnosis, annually, when complications arise, and during transitions in life and care (22).

DSMES programs delivered from diagnosis can promote medication adherence, healthy eating, and physical activity, and increase self-efficacy. In type 2 diabetes, high-quality evidence has consistently shown that DSMES is a cost-effective intervention in the health care systems studied. DSMES significantly improves clinical and psychological outcomes, improves glycemic control, reduces hospital admissions, improves patient knowledge, and reduces the risk of all-cause mortality (22,26–31). The best outcomes are achieved in those programs with a theory-based and structured curriculum and with contact time of over 10 h. While online programs may reinforce learning, there is little evidence they are effective when used alone (27).

Consensus recommendation

- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medications.

Suboptimal adherence, including poor persistence, to therapy affects almost half of people with diabetes, leading to suboptimal glycemic and cardiovascular disease (CVD) risk factor control as well as increased risk of diabetes complications, mortality, hospital admissions, and health care costs (32–36). Though this consensus recommendation focuses on medication adherence (including persistence), the principles are pertinent to all aspects of diabetes care. Multiple factors contribute to inconsistent medication use and treatment discontinuation, including patient-perceived lack of medication efficacy, fear of hypoglycemia, lack of access to medication, and adverse effects of medication (37). Medication adherence (including persistence) varies across medication classes and careful consideration of these differences may help improve outcomes (38). Ultimately, patient preference is a major factor driving the choice of medication. Even in cases where clinical characteristics suggest the use of a particular medication based on the available evidence from clinical trials, patient preferences regarding route of administration, injection devices, side effects, or cost may prevent their use by some individuals (39).

Therapeutic inertia, sometimes referred to as clinical inertia, refers to failure to intensify therapy when treatment targets are not met. The causes of therapeutic inertia are multifactorial, occurring at the level of the practitioner, patient, and/or health care system (40). Interventions targeting therapeutic inertia have facilitated improved glycemic control and timely insulin intensification (41,42). For example, multidisciplinary teams that include nurse practitioners or pharmacists may help reduce therapeutic inertia (43,44). A fragmented health care system may contribute to therapeutic inertia and impair delivery of patient-centered care. A coordinated chronic care model, including self-management support, decision support, delivery system design, clinical information systems, and community resources and policies, promotes interaction between more empowered patients and better prepared and proactive health care teams (45).

Table 1—Key components of DSMES (21,23–25)

• Evidence-based
• Individualized to the needs of the person, including language and culture
• Has a structured theory-driven written curriculum with supporting materials
• Delivered by trained and competent individuals (educators) who are quality assured
• Delivered in group or individual settings
• Aligns with the local population needs
• Supports the person and their family in developing attitudes, beliefs, knowledge, and skills to self-manage diabetes
• Includes core content; i.e., diabetes pathophysiology and treatment options; medication usage; monitoring, preventing, detecting, and treating acute and chronic complications; healthy coping with psychological issues and concerns; problem solving and dealing with special situations (i.e., travel, fasting)
• Available to patients at critical times (i.e., at diagnosis, annually, when complications arise, and when transitions in care occur)
• Includes monitoring of patient progress, including health status, quality of life
• Quality audited regularly

DSMES is a critical element of care for all people with diabetes and is the ongoing process of facilitating the knowledge, skills, and ability necessary for diabetes self-care as well as activities that assist a person implementing and sustaining behaviors needed to manage their diabetes on an ongoing basis. National organizations in the U.S. and Europe have published standards to underpin DSMES. In the U.S., these are defined as DSMES "services," whereas in Europe they are often referred to as "programs." Nevertheless, the broad components are similar.

RECOMMENDED PROCESS FOR GLUCOSE-LOWERING MEDICATION SELECTION: WHERE DOES NEW EVIDENCE FROM CARDIOVASCULAR OUTCOMES TRIALS FIT IN?

In prior consensus statements, efficacy in reducing hyperglycemia, along with tolerability and safety were primary factors in glucose-lowering medication selection. Patient preferences, glycemic targets, comorbidities, polypharmacy, side effects, and cost were additional

important considerations. For every individual, the choice of glucose-lowering medication should be underpinned by lifestyle management, DSMES, and the patient-centered care principles outlined in Fig. 1.

Figure 2 describes our new consensus approach to glucose lowering with medications in type 2 diabetes. Because of the new evidence for the benefit of specific medications to reduce mortality, heart failure (HF), and progression of renal disease *in the setting of established CVD*, their use was considered compelling in this patient group. Thus, we recommend that providers consider a history of CVD very early in the process of treatment selection. Other factors affect the choice of glucose-lowering medications, particularly in the setting of patient-centered care. In addition to CVD, we recommend early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence treatment selection (Figs. 2–6).

Implications of New Evidence From Cardiovascular Outcomes Trials

The major change from prior consensus reports is based on new evidence that specific sodium–glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists improve cardiovascular outcomes, as well as secondary outcomes such as HF and progression of renal disease, in patients with established CVD or CKD. Therefore, an important early step in this new approach (Fig. 3) is to consider the presence or absence of ASCVD, HF, and CKD, conditions in aggregate affecting 15–25% of the population with type 2 diabetes. While the new evidence supporting the use of particular medications in patients who also have established CVD or are at high risk of CVD is derived from large cardiovascular outcomes trials (CVOTs) demonstrating substantial benefits over 2–5 years, it is important to remember that each trial constitutes a single experiment. Within each drug class, results have been heterogeneous. It is not clear whether there are true drug-class effects with different findings for individual medications due to differences in trial design and conduct, or whether there are real differences between medications within a drug class due to properties of the individual compounds. Where the current evidence is strongest for a specific medication within a class, it is noted. The American Diabetes Association's (ADA) *Standards of Medical Care in Diabetes* will align with this document and will be updated to reflect new evidence as it emerges from ongoing clinical trials.

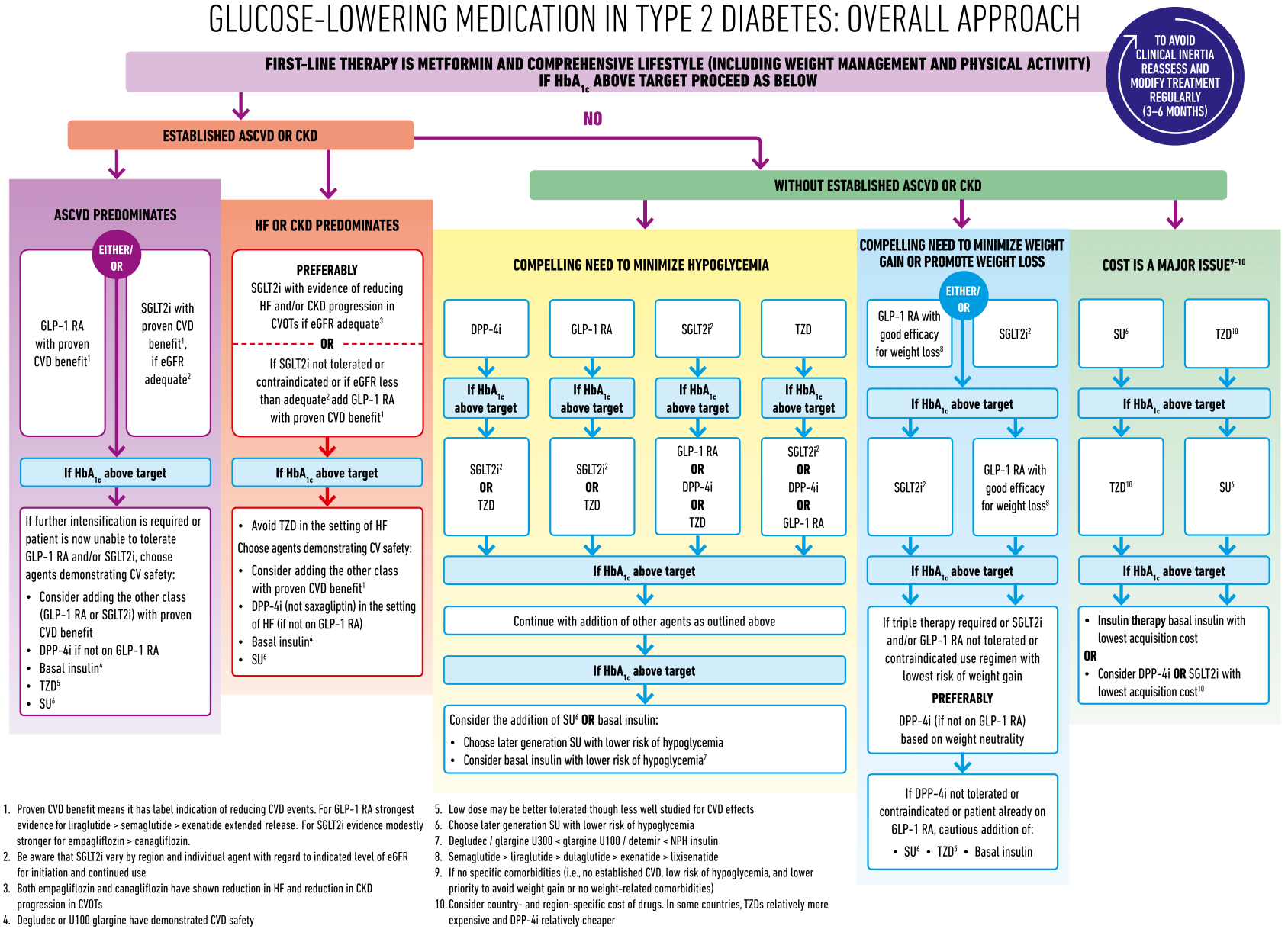
Consensus recommendation

- Among patients with type 2 diabetes who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management (Figs. 2 and 3).

ASCVD is defined somewhat differently across trials, but all trials enrolled individuals with established CVD (e.g., myocardial infarction [MI], stroke, any revascularization procedure) while variably including related conditions compatible with clinically significant atherosclerosis (e.g., transient ischemic attack, hospitalized unstable angina, amputation, congestive heart failure New York Heart Association [NYHA] class II–III, >50% stenosis of any artery, symptomatic or asymptomatic coronary artery disease documented by imaging, CKD with estimated glomerular filtration rate [eGFR] <60 mL min^{-1} [1.73]$^{-2}$). Most trials also included a "risk factor only" group with entry criteria based on age and usually the presence of two or more cardiac risk factors (46). Trials were designed to evaluate cardiovascular safety (i.e., statistical noninferiority compared with placebo), but several showed ASCVD outcome benefit (i.e., statistical superiority compared with placebo), including, in some cases, mortality.

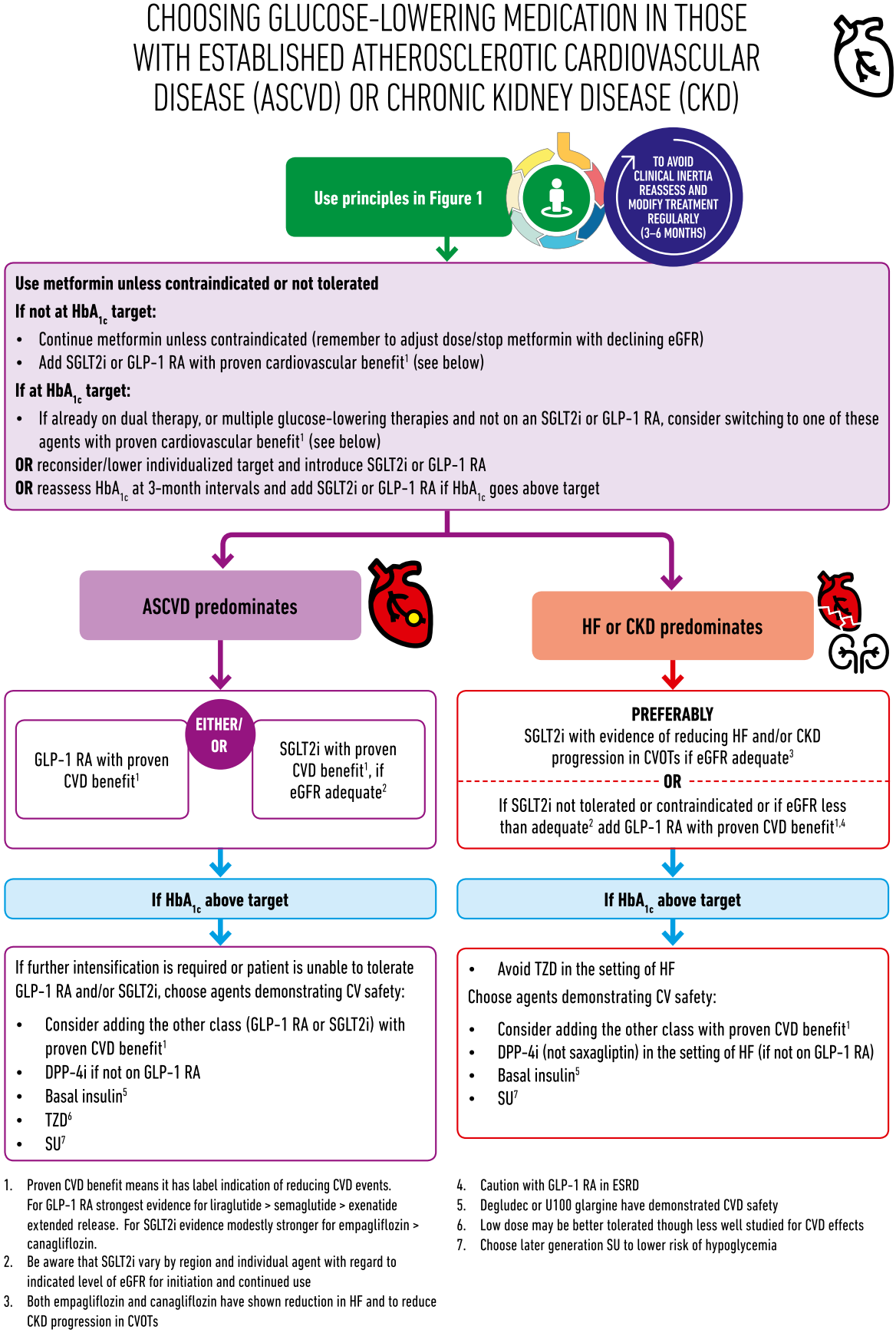
Among GLP-1 receptor agonists, liraglutide, studied in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial ($n = 9,340$), demonstrated an ARR of 1.9% with a hazard ratio (HR) of 0.87 (95% CI 0.78, 0.97; $P = 0.01$ for superiority) for the primary composite outcome of cardiovascular death, nonfatal MI, and nonfatal stroke (major adverse cardiac events [MACE]) compared with placebo over 3.8 years. Each component of the composite contributed to the benefit, and the HR for cardiovascular death was 0.78 (95% CI 0.66, 0.93; $P = 0.007$; ARR 1.7%). The LEADER trial also demonstrated an HR of 0.85 (95% CI, 0.74, 0.97; $P = 0.02$; ARR 1.4%) for all-cause mortality (47). In the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6) ($n = 3,297$), semaglutide compared with placebo demonstrated an ARR of 2.3% with HR 0.74 for MACE (95% CI 0.58, 0.95; $P = 0.02$ for superiority) over 2.1 years, but the reduction in events appeared to be driven by the rate of stroke rather than CVD death (48). The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) compared exenatide extended-release with placebo over 3.2 years in 14,752 participants with type 2 diabetes. While the medication was safe (noninferior), the HR for MACE in the entire trial was 0.91 (95% CI 0.83, 1.0; $P = 0.06$) not reaching the threshold for demonstrated superiority versus placebo; ARR was 0.8% (49). All-cause death was lower in the exenatide arm (ARR 1%, HR 0.86 [95% CI 0.77, 0.97]), but it was not considered to be statistically significant in the hierarchical testing procedure applied. Lixisenatide, a short-acting GLP-1 receptor agonist, did not demonstrate CVD benefit or harm in a trial of patients recruited within 180 days of an acute coronary syndrome admission (50). Taken together, it appears that among patients *with established CVD*, some GLP-1 receptor agonists may provide cardiovascular benefit, with the evidence of benefit strongest for liraglutide, favorable for semaglutide, and less certain for exenatide. There is no evidence of cardiovascular benefit with lixisenatide. Adverse effects for the class are discussed in the section "The Full Range of Therapeutic Options: Lifestyle Management, Medication, and Obesity Management."

Among the SGLT2 inhibitors, empagliflozin compared with placebo was studied in the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) in 7,020 participants with type 2 diabetes and CVD. With a median follow-up of 3.1 years, the ARR was 1.6% and the HR was 0.86 (95% CI 0.74, 0.99; $P = 0.04$ for superiority) for the primary composite end point of nonfatal MI, nonfatal stroke, and cardiovascular death. The ARR was 2.2% and the HR was 0.62 (95% CI 0.49, 0.77; $P < 0.001$) for cardiovascular death (51). The ARR was 2.6% and the HR was 0.68 (95% CI 0.57, 0.82; $P < 0.001$) for death from



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. 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)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

Figure 2—Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.



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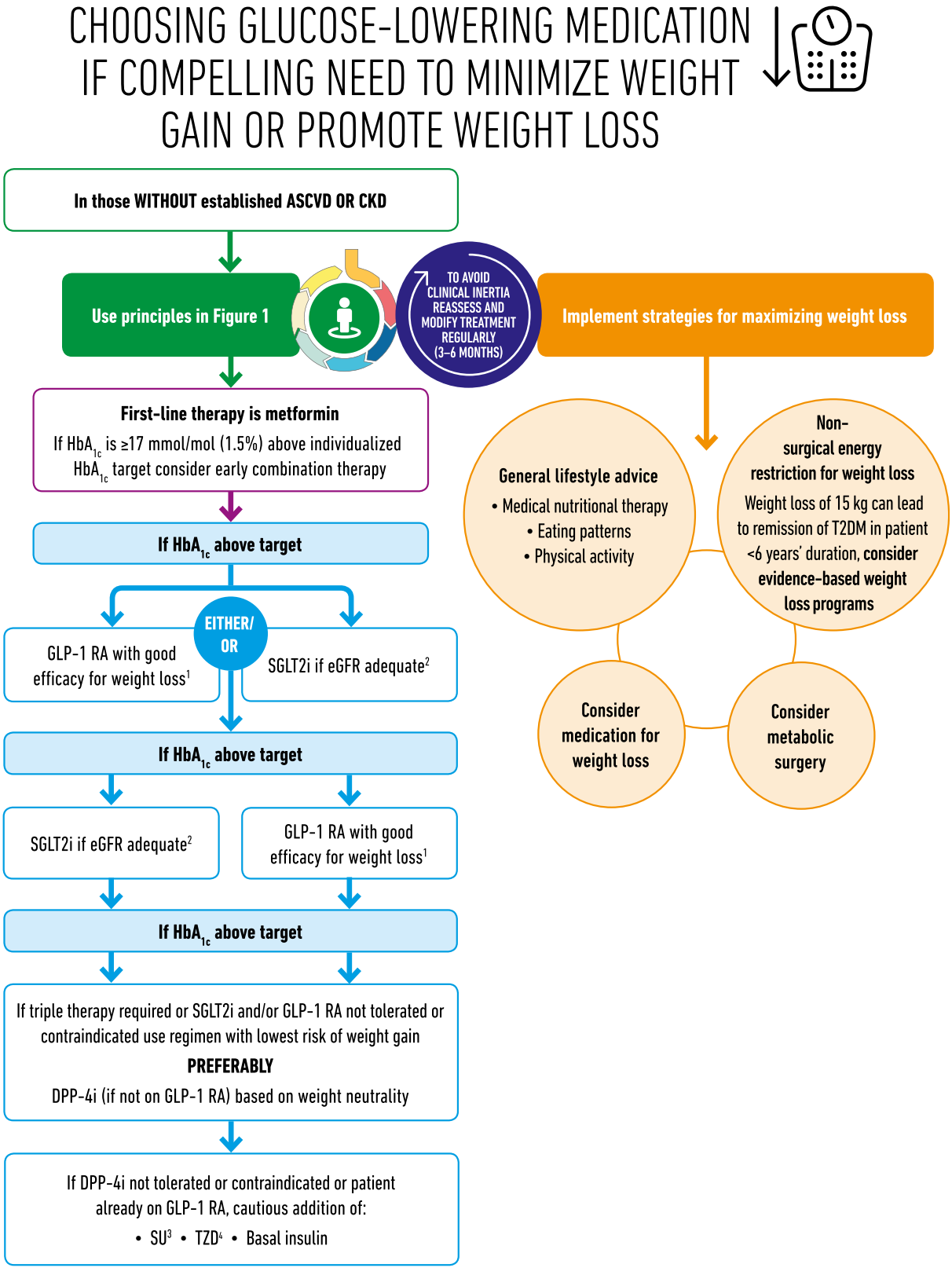
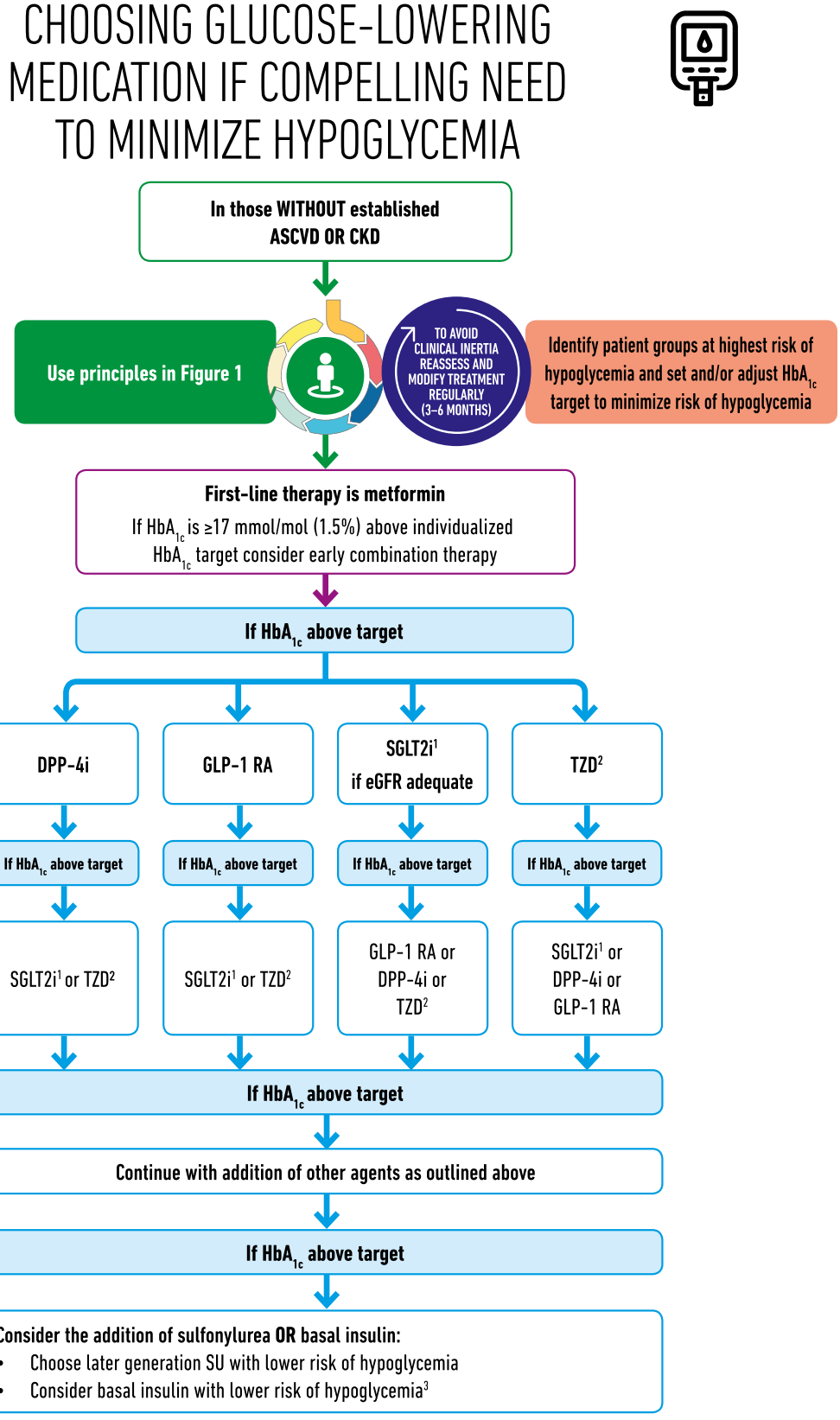
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycemia

Figure 3—Choosing glucose-lowering medication in those with established ASCVD, HF, and CKD. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.



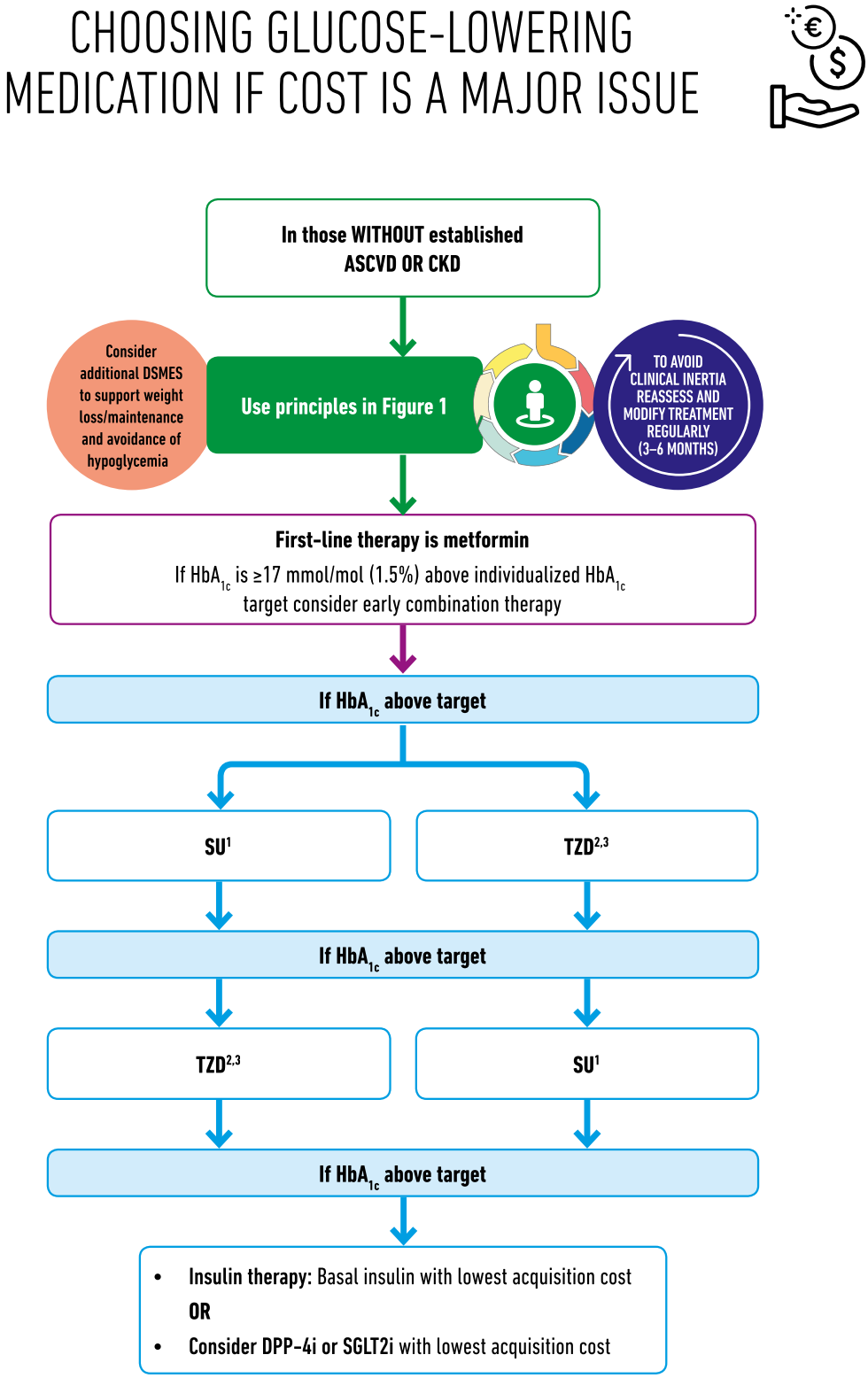
1. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Choose later generation SU with lower risk of hypoglycemia
4. Low dose may be better tolerated though less well studied for CVD effects

Figure 4—Choosing glucose-lowering medication if compelling need to minimize weight gain or promote weight loss. GLP-1 RA, glucagon-like peptide 1 receptor agonist; T2DM, type 2 diabetes; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.



1. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
2. Low dose TZDs are better tolerated
3. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin

Figure 5—Choosing glucose-lowering medication if compelling need to minimize hypoglycemia. DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor.



1. Choose later generation SU to minimize risk of hypoglycemia
2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper
3. Low-dose TZDs are better tolerated

Figure 6—Choosing glucose-lowering medication if cost is a major issue. DPP-4i, dipeptidyl peptidase 4 inhibitor; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

any cause. Canagliflozin compared with placebo was studied in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (comprised of two similar trials, CANVAS and CANVAS-Renal; $n = 10,142$) in participants with type 2 diabetes, 66% of whom had a history of CVD. Participants were followed for a median of 3.6 years. In the combined analysis of the two trials, the primary composite end point of MI, stroke, or cardiovascular death was reduced with canagliflozin (26.9 vs. 31.5 participants per patient-year with placebo; HR 0.86 [95% CI 0.75, 0.97]; $P = 0.02$) for superiority in the pooled analysis, with consistent findings in the component studies. Though there was a trend toward benefit for cardiovascular death, the difference from placebo was not statistically significant in the CANVAS Program (52). For the SGLT2 inhibitors studied to date, it appears that among patients *with established CVD*, there is likely cardiovascular benefit, with the evidence of benefit modestly stronger for empagliflozin than canagliflozin. Adverse effects for the class are discussed in the section "The Full Range of Therapeutic Options: Lifestyle Management, Medication, and Obesity Management."

While the evidence of an ASCVD outcomes benefit for GLP-1 receptor agonists and SGLT2 inhibitors has been demonstrated for people with established ASCVD, the evidence of benefit beyond glucose lowering has not been demonstrated in those without ASCVD. Indeed, in subgroup analyses of these trials, lower-risk individuals have not been observed to have an ASCVD benefit. While this may be due to the short time frame of the studies and the low event rate in those without ASCVD, the finding is consistent across the reported trials. Overall, CVOTs of dipeptidyl peptidase 4 (DPP-4) inhibitors have demonstrated safety, i.e., noninferiority relative to placebo, for the primary MACE end point, but not cardiovascular benefit.

The available evidence for cardiovascular event reduction in patients with type 2 diabetes and clinical CVD is derived from trials in which the participants were not meeting glycemic targets (HbA_{1c} $\geq$53 mmol/mol [$\geq$7%] at baseline). Furthermore, most ($\sim$70% across trials) participants were treated with metformin at baseline. Thus, we recommend that patients with clinical CVD not meeting individualized glycemic targets while treated with metformin (or in whom metformin is contraindicated or not tolerated) should have an SGLT2 inhibitor or GLP-1 receptor agonist with proven benefit for cardiovascular risk reduction added to their treatment program. There are no clinical trial data that support prescribing an SGLT2 inhibitor or GLP-1 receptor agonist with the intent of reducing cardiovascular risk in patients with an HbA_{1c} $<$53 mmol/mol ($<$7%). Limited data suggest that there is no heterogeneity in the cardiovascular benefits of SGLT2 inhibitors or GLP-1 receptor agonists as a function of background glucose-lowering therapy. Thus, background glucose-lowering therapy in patients with clinical CVD arguably is not pertinent in clinical decision making. However, dose adjustment or discontinuation of background medications may be required to avoid hypoglycemia when adding a new agent to a regimen containing insulin, sulfonylurea, or glinide therapy, particularly in patients at or near glycemic goals. Full efforts to achieve glycemic and blood pressure targets and to adhere to lipid, antiplatelet, antithrombotic, and tobacco cessation guidelines (7) should continue after an SGLT2 inhibitor or GLP-1 receptor agonist is added, as such efforts were integral to all studies that have demonstrated cardiovascular benefit of these agents.

Consensus recommendation

- Among patients with ASCVD in whom HF coexists or is of special concern, SGLT2 inhibitors are recommended (Figs. 2 and 3).

Patients with type 2 diabetes are at increased risk of HF (53). In the EMPA-REG OUTCOME and CANVAS CVOT studies testing SGLT2 inhibitors, which enrolled participants with ASCVD, $>$85% of participants did not have symptomatic HF at baseline. Yet, in both trials there was a clinically and statistically significant reduction in hospitalization for HF for the SGLT2 inhibitor as compared with placebo. In the EMPA-REG OUTCOME study with empagliflozin (54), the ARR was 1.4%, and the HR 0.65 (95% CI 0.50, 0.85), and in the CANVAS Program with canagliflozin, the HR was 0.67 (95% CI 0.52, 0.87), with a rate of hospitalized HF of 5.5 vs. 8.7 events per 1,000 patient-years (55). Because HF was neither well characterized at baseline nor as carefully adjudicated as it would have been in a trial specifically designed to evaluate HF outcomes, and because HF was a secondary end point in the trials, further ongoing studies are required to conclusively address the issue. That said, the significant reduction in hospitalization for HF demonstrated in the two study populations and the consistency across two independent trial programs suggest to us that treatment with SGLT2 inhibitors in the setting of clinical HF may provide substantial benefit and should be specifically considered in people with type 2 diabetes and ASCVD and HF.

In the GLP-1 receptor agonist studies LEADER, SUSTAIN 6, and EXSCEL, there was no significant effect on hospitalization for HF with HR 0.86 (95% CI 0.71, 1.06), 1.11 (95% CI 0.77, 1.61), and 0.94 (95% CI 0.78, 1.13), respectively (47–49). Two short-term studies of liraglutide in patients with reduced ejection fraction suggested a lack of benefit in this setting (56,57).

Among the recent cardiovascular safety outcomes trials testing DPP-4 inhibitors, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) study evaluating saxagliptin demonstrated a significant increased risk of HF, with 3.5% risk of hospitalization for HF versus 2.8% for placebo (HR 1.27; 95% CI 1.07, 1.51; $P = 0.007$) (58). In the subsequent Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study of alogliptin there was no statistically significant difference in HF hospitalization (3.9% vs. 3.3% with placebo) (59), and in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), the rate of hospitalization for HF was 3.1% in both sitagliptin- and placebo-treated patients (60).

Consensus recommendation

- For patients with type 2 diabetes and CKD, with or without CVD, consider the use of an SGLT2 inhibitor shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression (Figs. 2 and 3).

Patients with type 2 diabetes and kidney disease are at an increased risk for cardiovascular events. A substantial number of participants with an eGFR of 30–60 mL min^{-1} [1.73 $m]^{-2}$ were included in EMPA-REG OUTCOME, CANVAS, LEADER, and SUSTAIN 6. An important finding in the studies was reduction of the primary ASCVD outcome even among participants with stage 3 CKD (eGFR 30–60 mL min^{-1} [1.73 $m]^{-2}$). For SGLT2 inhibitors, this contrasts with the glucose-lowering effect, which diminishes with declining eGFR.

In addition to the primary cardiovascular end points, most of the SGLT2 inhibitor and GLP-1 receptor agonist CVOTs reported benefit in renal end points, albeit as secondary outcomes. The renal outcome benefit has been most pronounced and consistent for SGLT2 inhibitors. EMPA-REG OUTCOME (empagliflozin) demonstrated an ARR 6.1%, HR of 0.61 (95% CI 0.53, 0.70) for the composite outcome of new or worsening nephropathy (progression to urine albumin/creatinine ratio >33.9 mg/mmol [>300 mg/g], doubling of serum creatinine and ESRD, or death by ESRD). The most prevalent outcome component was the development of sustained albuminuria, but the other components were each significantly reduced relative to placebo (61). CANVAS (canagliflozin) reported an HR of 1.7 (95% CI 1.51, 1.91) for regression of albuminuria and a 40% reduction in risk in the composite outcome of eGFR, ESRD, or renal death (5.5 vs. 9.0 participants per 1,000 patient-years; HR 0.60; 95% CI 0.47, 0.77) (52). Additional trials with primary renal end points are ongoing in high-risk renal populations. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) trial examining canagliflozin in CKD with proteinuria has been stopped at a planned interim analysis for achieving the primary efficacy end point (62).

In LEADER and SUSTAIN 6, the GLP-1 receptor agonist liraglutide was associated with an ARR of 1.5% and an HR of 0.78 (95% CI 0.67, 0.92) for new or worsening nephropathy (63), and semaglutide demonstrated an ARR of 2.3% and an HR of 0.64 (95% CI 0.46, 0.88) for new or worsening nephropathy (48). Progression of albuminuria was the most prevalent component of the composite renal end point, whereas the other components (doubling of serum creatinine, ESRD, or renal death) did not contribute substantially to the benefit. In the DPP-4 inhibitor CVOTs, the DPP-4 inhibitors have been shown to be safe from a renal perspective, with modest reduction in albuminuria (64).

THE FULL RANGE OF THERAPEUTIC OPTIONS: LIFESTYLE MANAGEMENT, MEDICATION, AND OBESITY MANAGEMENT

This section summarizes the lifestyle, medication, and obesity management therapies that lower glucose or improve other outcomes in patients with type 2 diabetes. A more comprehensive discussion of these issues is available elsewhere (3,21,65). For more details on weight loss medications and metabolic surgery, see the section "Obesity Management Beyond Lifestyle Intervention." Basic information about specific options in each category of therapy is summarized in Table 2.

Lifestyle interventions, including MNT and physical activity, are effective and safe for improving glucose control in type 2 diabetes. For these reasons, they are recommended as first-line therapies from the time of diagnosis and as cotherapy for patients who also require glucose-lowering medications or metabolic surgery. Lifestyle management should be part of the ongoing discussion with individuals with type 2 diabetes at each visit.

Lifestyle Management

Consensus recommendation

- An individualized program of MNT should be offered to all patients.

Medical Nutrition Therapy

MNT comprises education and support to help patients adopt healthy eating patterns. The goal of MNT is to manage blood glucose and cardiovascular risk factors to reduce risk for diabetes-related complications while preserving the pleasure of eating (21). Two basic dimensions of MNT include dietary quality and energy restriction. Strategies directed at each dimension can improve glycemic control.

Dietary Quality and Eating Patterns. There is no single ratio of carbohydrate, proteins, and fat intake that is optimal for every person with type 2 diabetes. Instead, there are many good options and professional guidelines usually recommend individually selected eating patterns that emphasize foods of demonstrated health benefit, that minimize foods of demonstrated harm, and that accommodate patient preference and metabolic needs, with the goal of identifying healthy dietary habits that are feasible and sustainable. Three trials of a Mediterranean eating pattern reported modest weight loss and improved glycemic control (66–68). In one of these, people with new-onset diabetes assigned to a low-carbohydrate Mediterranean eating pattern were 37% less likely to require glucose-lowering medications over 4 years compared with patients assigned to a low-fat diet (HR 0.63 [95% CI 0.51, 0.86]). A meta-analysis of RCTs in patients with type 2 diabetes showed that the Mediterranean eating pattern reduced HbA_{1c} more than control diets (mean difference −3.3 mmol/mol, 95% CI −5.1, −1.5 mmol/mol [−0.30%, 95% CI −0.46%, −0.14%]) (69). Low-carbohydrate, low glycemic index, and high-protein diets, and the Dietary Approaches to Stop Hypertension (DASH) diet all improve glycemic control, but the effect of the Mediterranean eating pattern appears to be the greatest (70–72). Low-carbohydrate diets (<26% of total energy) produce substantial reductions in HbA_{1c} at 3 months (−5.2 mmol/mol, 95% CI −7.8, −2.5 mmol/mol [−0.47%, 95% CI −0.71%, −0.23%]) and 6 months (4.0 mmol/mol, 95% CI −6.8, −1.0 mmol/mol [−0.36%, 95% CI −0.62%, −0.09%]), with diminishing effects at 12 and 24 months; no benefit of moderate carbohydrate restriction (26–45%) was observed (73). Vegetarian eating patterns have been shown to lower HbA_{1c}, but not fasting glucose, compared with nonvegetarian ones (74). Very recent trials of different eating patterns in type 2 diabetes have typically also included weight reduction, hindering firm conclusions regarding the distinct contribution of dietary quality.

Consensus recommendation

- All overweight and obese patients with diabetes should be advised of the health benefits of weight loss and encouraged to engage in a program of intensive lifestyle management, which may include food substitution.

Nonsurgical Energy Restriction for Weight Loss. If a patient wishes to aim for remission of type 2 diabetes, particularly

Table 2—Glucose-lowering medications and therapies available in the U.S. or Europe and specific characteristics that may guide individualized treatment choices in nonpregnant adults with type 2 diabetes

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Lifestyle					
Diet quality	• Mediterranean type • DASH • Low carbohydrate • Vegetarian • Others	• Depends on diet	• Inexpensive • No side effects	• Requires instruction • Requires motivation • Requires lifelong behavioral change • Social barriers may exist	Intermediate
Physical activity	• Running, walking • Bicycling (including stationary) • Swimming • Resistance training • Yoga • Tai chi • Many others	• Energy expenditure • Weight management • ↑ Insulin sensitivity	• Inexpensive • ↓ Fall risk by increasing balance/strength • ? Improves mental health • ↑ Bone density • ↓ Blood pressure • ↓ Weight • Improves ASCVD risk factors	• Risk of musculoskeletal injury • Requires motivation • Risk of foot trauma in patients with neuropathy • Requires lifelong behavioral change	Intermediate
Energy restriction	• Individual energy restriction with or without energy tracking • Programs with counseling • Food substitution programs	• Energy restriction • Weight management • ↓ Hepatic and pancreatic fat • ↑ Insulin sensitivity	• Lowers glycemia • Reduces need for diabetes and other medications • No serious side effects • Improves ASCVD risk factors	• Requires motivation • Requires lifelong behavioral change	Variable, with potential for very high efficacy; often intermediate
Oral medications					
Biguanides	• Metformin	• ↓ Hepatic glucose production • Multiple other non-insulin-mediated mechanisms	• Extensive experience • No hypoglycemia • Inexpensive	• GI symptoms • Vitamin B_{12} deficiency • Use with caution or dose adjustment for CKD stage 3B (eGFR 30–44 mL min^{-1} [1.73 m]$^{-2}$) • Lactic acidosis (rare)	High
SGLT2 inhibitors	• Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	• Blocks glucose reabsorption by the kidney, increasing glucosuria • ? Other tubulo-glomerular effects	• No hypoglycemia • ↓ Weight • ↓ Blood pressure • Effective at all stages of T2DM with preserved glomerular function • ↓ MACE, HF, CKD with some agents (see text)	• Genital infections • UTI • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Creatinine (transient) • Dose adjustment/avoidance for renal disease • ↑ Risk for amputation (canagliflozin) • ↑ Risk for fracture (canagliflozin)	Intermediate–high (dependent on GFR)

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Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
				• ↑ Risk for DKA (rare) • Fournier's gangrene (rare) • Expensive	
DPP-4 inhibitors	• Sitagliptin • Vildagliptin[a] • Saxagliptin • Linagliptin • Alogliptin	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion	• No hypoglycemia • Weight neutral • Well tolerated	• Rare urticaria/angioedema • ↑ HF hospitalization (saxagliptin) • Dose adjustment/avoidance for renal disease depending on agent • ? Pancreatitis • ? Arthralgia • ? Bullous pemphigoid • Expensive (U.S.); variable in Europe	Intermediate
Sulfonylureas	• Glibenclamide/glyburide • Glipizide • Gliclazide[a] • Glimepiride	• ↑ Insulin secretion	• Extensive experience • ↓ Microvascular risk (UKPDS) • Inexpensive	• Hypoglycemia • ↑ Weight • Uncertain cardiovascular safety • Dose adjustment/avoidance for renal disease • High rate of secondary failure	High
TZDs	• Pioglitazone • Rosiglitazone[b]	• ↑ Insulin sensitivity	• Low risk for hypoglycemia • Durability • ↑ HDL-C • ↓ Triacylglycerols (pioglitazone) • ↓ ASCVD events (pioglitazone: in a poststroke insulin-resistant population and as secondary end point in a high-risk-of-CVD diabetes population) • Lower cost	• ↑ Weight • Edema/heart failure • Bone loss • ↑ Bone fractures • ↑ LDL-C (rosiglitazone) • ? Bladder cancer • ? Macular edema	High
Meglitinides (Glinides)	• Repaglinide • Nateglinide	• ↑ Insulin secretion	• ↓ Postprandial glucose excursions • Dosing flexibility • Safe in advanced renal disease with cautious dosing (especially repaglinide) • Lower cost	• Hypoglycemia • ↑ Weight • Uncertain cardiovascular safety • Frequent dosing schedule	Intermediate–high
α-Glucosidase inhibitors	• Acarbose • Miglitol	• Slows carbohydrate digestion/absorption	• Low risk for hypoglycemia • ↓ Postprandial glucose excursions • Nonsystemic mechanism of action • Cardiovascular safety • Lower cost	• Frequent GI side effects • Frequent dosing schedule • Dose adjustment/avoidance for renal disease	Low–intermediate
Bile acid sequestrants	• Colesevelam[b]	• ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• No hypoglycemia • ↓ LDL-C	• Constipation • ↑ Triacylglycerols • May ↓ absorption of other medications • Intermediate expense	Low–intermediate

Continued on p. 2683

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
Dopamine-2 agonists	• Quick-release bromocriptine[b]	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• No hypoglycemia • ? ↓ ASCVD events	• Headache/dizziness/syncope • Nausea • Fatigue • Rhinitis • High cost	Low–intermediate
Injectable medications					
Insulins					
Long acting (basal)	• Degludec (U100, U200) • Detemir • Glargine (U100, U300)	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Once-daily injection	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost	Very high
Intermediate acting (basal)	• Human NPH	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Less expensive than analogs	• Hypoglycemia • Weight gain • Training requirements • Often given twice daily • Frequent dose adjustment for optimal efficacy	Very high
Rapid acting	• Aspart (conventional and fast acting) • Lispro (U100, U200) • Glulisine	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose	• Hypoglycemia • Weight gain • Training requirements • May require multiple daily injections • Frequent dose adjustment for optimal efficacy • High cost	Very high
Inhaled rapid acting	• Human insulin inhalation powder[b]	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • ↓ Postprandial glucose • More rapid onset and shorter duration than rapid-acting analogs	• Spirometry (FEV_1) required before initiating, after 6 months, and annually • Contraindicated in chronic lung disease • Not recommended in smokers • Hypoglycemia • Weight gain • Training requirements • May require multiple inhalations daily	High

Continued on p. 2684

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
				• Frequent dose adjustment for optimal efficacy; limited options in dosing interval • High cost • Respiratory side effects (e.g., bronchospasm, cough, decline in FEV_1)	
Short acting	• Human regular (U100, U500)	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • ↓ Postprandial glucose • Less expensive than analogs	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • May require multiple daily injections	Very high
Premixed	• Many	• Activates insulin receptor • ↑ Glucose disposal • ↓ Glucose production	• Nearly universal response • Theoretically unlimited efficacy • Fewer injections than basal/bolus before every meal • Recombinant human analogs are less expensive	• Hypoglycemia • Weight gain • Training requirements • Frequent dose adjustment for optimal efficacy • High cost (except human insulin premix) • Can lead to obligate eating	Very high
GLP-1 RA					
Shorter acting	• Exenatide • Lixisenatide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• No hypoglycemia as monotherapy • ↓ Weight • Excellent postprandial glucose efficacy for meals after injections • Improves cardiovascular risk factors	• Frequent GI side effects that may be transient • Modestly ↑ heart rate • Training requirements • Dose adjustment/avoidance in renal disease • Acute pancreatitis (rare/uncertain) • Very high cost	Intermediate–high
Longer acting	• Dulaglutide • Exenatide extended-release • Liraglutide • Semaglutide	• Glucose dependent: ↑ Insulin secretion ↓ Glucagon secretion • ↑ Satiety	• No hypoglycemia as monotherapy • ↓ Weight • ↓ Postprandial glucose excursions • Improves cardiovascular risk factors • ↓ MACE with some agents (see text) • ↓ Albuminuria with some agents (see text)	• GI side effects, including gallbladder disease • Greater ↑ heart rate • Training requirements • Dose adjustment/avoidance for some agents in renal disease • Acute pancreatitis (rare/uncertain)	High–very high

Continued on p. 2685

Table 2—Continued

Class	Medications/therapies in class	Primary physiological action(s)	Advantages	Disadvantages/adverse effects	Efficacy
			• Greater lowering of fasting glucose vs. short-acting preparations • Once-weekly dosing (except liraglutide, which is daily)	• C-cell hyperplasia/medullary thyroid tumors (rare/uncertain; observed in animals only) • Very high cost	
Other injectables					
Amylin mimetics	• Pramlintide[b]	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • ↓ Weight	• Hypoglycemia • Frequent dosing schedule • Training requirements • Frequent GI side effects • Very high cost	Intermediate
Fixed-dose combination of GLP-1 RA and basal insulin analogs	• Liraglutide/degludec • Lixisenatide/glargine	• Combined activities of components	• Enhanced glycemic efficacy vs. components • Reduced adverse effects (e.g., GI, hypoglycemia) vs. components	• Less weight loss than GLP-1 receptor agonist alone • Very high cost	Very high
Weight loss medications	• Lorcaserin[b] • Naltrexone/bupropion • Orlistat • Phentermine/topiramate[b] • Liraglutide 3 mg	• Reduced appetite • Fat malabsorption (orlistat)	• Mean 3–9 kg weight loss vs. placebo	• High discontinuation rates from side effects • <50% achieve ≥5% weight loss • Drug-specific side effects • Limited durability • High cost	Intermediate
Metabolic surgery	• VSG • RYGB • Adjustable gastric band • BPD	• Restriction of food intake (all) • Malabsorption (RYGB, BPD) • Changes in hormonal and possibly neuronal signaling (VSG, RYGB, BPD)	• Sustained weight reduction • ↑ Rate of remission of diabetes • ↓ Number of diabetes drugs • ↓ Blood pressure • Improved lipid metabolism	• High initial cost • ↑ Risk for early and late surgical complications • ↑ Risk for reoperation • ↑ Risk for dumping syndrome • ↑ Nutrient and vitamin malabsorption • ↑ Risk for new-onset depression • ↑ Risk for new-onset opioid use • ↑ Risk for gastroduodenal ulcer • ↑ Risk for hypoglycemia • ↑ Risk for alcohol use disorder	Very high

More details available in ADA's *Standards of Medical Care in Diabetes—2018* (3). Glucose-lowering efficacy of drugs by change in HbA_{1c}: >22 mmol/mol (2%) very high, 11–22 mmol/mol (1–2%) high, 6–11 mmol/mol (0.5–1.5%) intermediate, <6 mmol/mol (0.5%) low. [a]Not licensed in the U.S. for type 2 diabetes. [b]Not licensed in Europe for type 2 diabetes. BPD, biliopancreatic diversion; DKA, diabetic ketoacidosis; FEV_1, forced expiratory volume in 1 s on pulmonary function testing; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastroplasty; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

within 6 years of diagnosis, evidence-based weight management programs are often successful.

The most effective nonsurgical strategies for weight reduction involve food substitution and intensive, sustained counseling (e.g., 12–26 individual counseling sessions over 6–12 months). Among adults with type 2 diabetes, meal replacement (825–853 kcal/day [3,450–3,570 kJ/day] formula diet for 3–5 months) followed by gradual reintroduction of food and intensive counseling resulted in 9-kg placebo-adjusted weight loss at 1 year and high rates of diabetes remission (46% vs. 4%; odds ratio [OR] 19.7 [95% CI 7.8, 49.8]) compared with best usual practice (75). In terms of intensive behavioral interventions, the Action for Health in Diabetes (Look AHEAD) trial (76) randomized 5,145 overweight or obese patients with type 2 diabetes to an intensive lifestyle program that promoted energy restriction, incorporating meal replacements to induce and sustain weight loss, along with increased physical activity compared with standard diabetes education and support in the control group. After 9.6 years, weight loss was greater in the intervention group (8.6% vs. 0.7% at 1 year; 6.0% vs. 3.5% at study end; both $P < 0.05$). HbA_{1c} also fell in the intervention group despite less use of glucose-lowering medications. Cardiovascular event rates were not reduced, but there were numerous other benefits. In a 12-month trial, 563 adults with type 2 diabetes who were randomized to Weight Watchers compared with standard care had a 2.1% net weight loss (−4.0% vs. −1.9%; $P < 0.001$), a 5.3 mmol/mol (−3.5 vs. +1.8 mmol/mol; $P = 0.020$) net absolute improvement in HbA_{1c} (0.48% [−0.32% vs. +0.16%]), and a greater reduction in use of glucose-lowering medications (−26% vs. +12%; $P < 0.001$) (77). Similar programs have resulted in a net 3-kg weight loss over 12–18 months (78–80).

Physical Activity

Consensus recommendation

- Increasing physical activity improves glycemic control and should be encouraged in all people with type 2 diabetes.

Aerobic exercise, resistance training, and the combination of the two are effective in reducing HbA_{1c} by about 6.6 mmol/mol (0.6%) (81–84). Of these modalities, some evidence suggests that aerobic exercise and the combination of aerobic exercise and resistance training may be more effective than resistance training alone (85), but this remains controversial. When considering exercise interventions, special considerations are required for individuals with CVD, uncontrolled retinopathy or nephropathy, and severe neuropathy. A wide range of physical activity, including leisure time activities (e.g., walking, swimming, gardening, jogging, tai chi, and yoga) can significantly reduce HbA_{1c} (86–90). In general, supervision of exercise and motivational strategies, such as monitoring using a step counter, can improve the effect of exercise on HbA_{1c} compared with advice alone (84,91). The combination of dietary change for weight reduction and physical exercise improves hyperglycemia and reduces cardiovascular risk factors more than dietary interventions or physical activity alone (92).

Medications for Lowering Glucose

Metformin

Metformin is an oral medication that reduces plasma glucose via multiple mechanisms. It is available as an immediate-release formulation that is typically administered twice a day and as extended-release formulations for once-daily or twice-daily administration. The formulations are equally effective with no consistent differences in side effect profile (93). Dosages of immediate-release metformin start at 500 mg once or twice a day with meals and should be increased as tolerated to a target dosage of 1,000 mg twice a day. The maximum daily dose is 2,550 mg in the U.S. and 3,000 mg in the European Union, though doses above 2,000 mg are generally associated with little additional efficacy and poorer tolerability (94). Gastrointestinal symptoms are common and dose dependent, and may improve over time or with dose reduction. Metformin should not be used in patients with an eGFR <30 mL min^{-1} [1.73 m]$^{-2}$ and dose reduction should be considered when the eGFR is <45 mL min^{-1} [1.73 m]$^{-2}$ (95–97). Caution should be taken when conditions are present that may reduce eGFR. Advantages of metformin include its high efficacy, low cost, minimal hypoglycemia risk when used as monotherapy, and the potential for some weight loss. Some studies have suggested a benefit for preventing CVD (98), but this has not been supported by the results of a recent meta-analysis (99). However, metformin may lower risk for cardiovascular mortality compared with sulfonylurea therapy (100). Rare cases of lactic acidosis have been reported, usually in the setting of severe illness or acute kidney injury. Therefore, metformin should be omitted in the setting of severe illness, vomiting, or dehydration. Metformin may result in lower serum vitamin B_{12} concentration; therefore, periodic monitoring and supplementation is generally recommended if levels are deficient, particularly in those with anemia or neuropathy (101). Because of its high efficacy in lowering HbA_{1c}, good safety profile, and low cost, metformin remains the first-line medication for management of type 2 diabetes.

SGLT2 Inhibitors

SGLT2 inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose (102). The glucose-lowering efficacy of these medications is dependent on renal function. Initiation and continuation of SGLT2 inhibitors are restricted by eGFR and require intermittent monitoring of renal function (refer to European Medicines Agency and U.S. Food and Drug Administration prescribing information for current recommendations). These medications are of high efficacy in lowering glucose in the setting of normal renal function (51,52,103). All SGLT2 inhibitors are associated with a reduction in weight and blood pressure. Alone or with metformin, they do not increase the risk for hypoglycemia. Empagliflozin and canagliflozin have cardiac and renal benefits in patients with established or at high risk of ASCVD. Cardiac and renal benefits have been demonstrated down to an eGFR of 30 mL min^{-1} [1.73 m]$^{-2}$, though currently none of the SGLT2 inhibitors have been approved for use by regulators at an eGFR below 45 mL min^{-1} [1.73 m]$^{-2}$ (see the section "Recommended Process for Glucose-Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcomes Trials Fit In?") (51,52,61). The class is associated with increased risk for mycotic genital infections (mostly vaginitis in women, balanitis in men) (51,

52,104,105). Case reports of diabetic ketoacidosis with SGLT2 inhibitors in type 2 diabetes continue to raise concern, though increased rates have not been confirmed in large trials (102,106). Therefore, the SGLT2 inhibitors should be used with caution and appropriate patient education should be provided for those with insulin deficiency. SGLT2 inhibitors have been associated with an increased risk of acute kidney injury, dehydration, and orthostatic hypotension; caution should be taken when SGLT2 inhibitors are used in combination with diuretics and/or ACE inhibitors and angiotensin receptor blockers. Canagliflozin has been associated with increased risk for lower-limb amputation (6.3 canagliflozin vs. 3.4 per 1,000 patient-years with placebo after 3.1 years; HR 1.97 [95% CI 1.41, 2.75]) (52). Similarly, fracture risk has been reported with canagliflozin (15.4 vs. 11.9 participants with fracture per 1,000 patient-years; HR 1.26 [95% CI 1.04, 1.52]) (52). It is uncertain whether amputation and fractures are class effects.

GLP-1 Receptor Agonists

GLP-1 receptor agonists are currently delivered by subcutaneous injection. These medications stimulate insulin secretion and reduce glucagon secretion in a glucose-dependent manner, improve satiety, and promote weight loss (107,108). Structural differences among GLP-1 receptor agonists affect duration of action, and their formulation and dosing may affect efficacy for glucose-lowering and weight reduction as well as side effect profile and cardiovascular effects (109). Dulaglutide, exenatide extended-release, and semaglutide are administered once weekly (108,109). Liraglutide and lixisenatide are administered once daily, and exenatide is available in a twice-daily formulation. GLP-1 receptor agonists have high glucose-lowering efficacy, but with variation within the drug class (110,111). Evidence suggests that the effect may be greatest for semaglutide once weekly, followed by dulaglutide and liraglutide, closely followed by exenatide once weekly, and then exenatide twice daily and lixisenatide (110,112–116). The short-acting medications exenatide twice daily and lixisenatide have greater postprandial effects, at least after the meals with which they are administered. All GLP-1 receptor agonists reduce weight (110); the reduction ranges from about 1.5 kg to 6.0 kg over about 30 weeks of therapy (110,117). Liraglutide and semaglutide have been shown to improve cardiovascular outcomes (47,48) (see the section "Recommended Process for Glucose-Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcomes Trials Fit In?"). The most common side effects of GLP-1 receptor agonists are nausea, vomiting, and diarrhea, though these tend to diminish over time. GLP-1 receptor agonists have minimal risk for hypoglycemia, but may increase the hypoglycemic potential of insulin and sulfonylureas when combined with those medications (118). Contrary to early signals, GLP-1 receptor agonists do not seem to substantially increase risk for pancreatitis, pancreatic cancer, or bone disease (119). They are associated with increased risk of gallbladder events (120). Semaglutide was associated with increased retinopathy complications in the SUSTAIN 6 trial (HR 1.76, 95% CI 1.11, 2.78), largely among those with baseline retinopathy who had rapid improvement of glycemic control (48). While this observation remains unexplained, this is also a recognized effect of intensification of glycemic control with insulin.

DPP-4 Inhibitors

DPP-4 inhibitors are oral medications that increase insulin secretion and reduce glucagon secretion in a glucose-dependent manner. They have moderate glucose-lowering efficacy (121,122). DPP-4 inhibitors are well tolerated, have a neutral effect on weight, and have minimal risk of hypoglycemia when used as monotherapy (123). When added to sulfonylurea therapy, however, the risk for hypoglycemia is increased 50% compared with sulfonylurea therapy alone (124). The recommended dose for each DPP-4 inhibitor is determined and needs to be adjusted based on renal function; linagliptin is the exception as it has minimal renal excretion. Rare but increased rates of pancreatitis (125) and musculoskeletal side effects have been reported (126). CVOTs demonstrated the cardiovascular safety but no cardiovascular benefit of three DPP-4 inhibitors (saxagliptin, alogliptin, and sitagliptin) as well as imbalances regarding HF for saxagliptin and alogliptin (127,128) (see the section "Recommended Process for Glucose-Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcomes Trials Fit In?").

Thiazolidinediones

Thiazolidinediones (TZDs) (pioglitazone and rosiglitazone) are oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy (129–131). TZDs increase HDL-cholesterol (132,133), and pioglitazone has been shown to reduce cardiovascular end points (132,134–138) and hepatic steatohepatitis (139), but without conclusive evidence for benefit. TZDs are associated with the best evidence among glucose-lowering medications for glycemic durability (140). However, these notable benefits must be balanced with safety concerns regarding fluid retention and congestive heart failure (136,140,141), weight gain (132,136,140–142), bone fracture (143,144), and, possibly, bladder cancer (145). Lower-dose therapy (e.g., pioglitazone 15–30 mg) mitigates weight gain and edema, but the broader benefits and harms of low-dose TZD therapy have not been evaluated.

Sulfonylureas

Sulfonylureas are oral medications that lower glucose by stimulating insulin secretion from pancreatic β-cells. They are inexpensive, widely available, and have high glucose-lowering efficacy (146). Sulfonylureas were used as part of the glucose-lowering regimen in the UK Prospective Diabetes Study (UKPDS) (147) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (148) trials, which both demonstrated reductions in microvascular complications. Sulfonylureas are associated with weight gain and risk for hypoglycemia and down titration of dose to reduce the risk of hypoglycemia results in higher HbA_{1c} (146,149,150). Sulfonylureas are known to be associated with a lack of durable effect on glucose lowering (144,151). The weight gain associated with sulfonylureas is relatively modest in large cohort studies and the incidence of severe hypoglycemia is lower than with insulin (152). Important differences among sulfonylureas affect both safety and efficacy. Glibenclamide (known as glyburide in the U.S. and Canada) has a higher risk

of hypoglycemia compared with other sulfonylureas (153). Glipizide, glimepiride, and gliclazide may have a lower risk for hypoglycemia compared with other sulfonylureas (152,154). Adverse cardiovascular outcomes with sulfonylureas in some observational studies have raised concerns, although findings from recent systematic reviews have found no increase in all-cause mortality compared with other active treatments (152). As newer-generation sulfonylureas appear to confer a lower risk of hypoglycemia and have favorable cost, efficacy, and safety profiles, sulfonylureas remain a reasonable choice among glucose-lowering medications, particularly when cost is an important consideration. Patient education and use of low or variable dosing with later generation sulfonylureas may be used to mitigate the risk of hypoglycemia. Greatest caution in this regard is warranted for people at high risk of hypoglycemia, such as older patients and those with CKD.

Insulin

Numerous formulations of insulin are available with differing durations of action. Human insulins (NPH, regular [R], and premixed combinations of NPH and R) are recombinant DNA-derived human insulin, while insulin analogs have been designed to change the onset or duration of action. The main advantage of insulin over other glucose-lowering medications is that insulin lowers glucose in a dose-dependent manner over a wide range, to almost any glycemic target as limited by hypoglycemia. Older formulations of insulin have also demonstrated reduction in microvascular complications and with long-term follow-up, all-cause mortality, and diabetes-related death (147,155). Beyond hypoglycemia, the disadvantages of insulin include weight gain and the need for injection, frequent titration for optimal efficacy, and glucose monitoring (156).

The effectiveness of insulin is highly dependent on its appropriate use; patient selection and training; adjustment of dose for changes in diet, activity, or weight; and titration to acceptable, safe glucose targets. Formulations of intermediate- and long-acting insulin have different timings of onset, durations of action, and risks of hypoglycemia. However, the way in which insulin is administered, including the dose, timing of injection, and glycemic targets, has a greater impact on the adverse effects of insulin than differences among insulin formulations.

Basal Insulin. Basal insulin refers to longer-acting insulin that is meant to cover the body's basal metabolic insulin requirement (regulating hepatic glucose production), in contrast to bolus or prandial insulin, which is meant to reduce glycemic excursions after meals. Basal insulin is the preferred initial insulin formulation in patients with type 2 diabetes. Options include once- or twice-daily administration of intermediate-acting NPH or detemir insulin and the once-daily administration of glargine (U100 or U300) or degludec (U100 or U200). Long-acting insulin analogs (degludec [U100 or U200], glargine [U100 and U300], detemir) have a modestly lower absolute risk for hypoglycemia compared with NPH insulin, but cost more (157–160). However, in real-world settings where patients are treated to conventional treatment targets, initiation of NPH compared with determir or glargine U100 did not increase hypoglycemia-related emergency department visits or hospital admissions (161). When comparing human and analog insulins, cost differences can be large while differences in hypoglycemia risk are modest and differences in glycemic efficacy minimal.

Degludec is associated with a lower risk of severe hypoglycemia compared with glargine U100 insulin when targeting intensive glycemic control in patients with long-standing type 2 diabetes at high risk of CVD; absolute incidence difference of 1.7% over 2 years (rate ratio 0.60; $P < 0.001$ for superiority; OR 0.73; $P < 0.001$ for superiority) (162). Biosimilar formulations are now available for glargine with similar efficacy profile and lower cost (163). No insulin has been shown to reduce risk for CVD (156), but data suggest that glargine U100 and degludec do not increase risk for MACE (162,164).

Concentrated formulations of degludec (U200) and glargine (U300) are available that allow injection of a reduced volume, a convenience for patients on higher doses. Glargine U300 is associated with a lower risk of nocturnal hypoglycemia compared with glargine U100 but requires a 10–14% higher dose of glargine for equivalent efficacy (165–167).

Not all patients have their blood glucose adequately controlled with basal insulin. In particular, patients with higher pretreatment HbA_{1c}, higher BMI, longer duration of disease, and a greater number of oral glucose-lowering medications are more likely to require intensified therapy (168).

Other Insulin Formulations. Short- and rapid-acting insulin formulations administered at mealtime are generally used to intensify basal insulin therapy in patients not meeting glycemic targets. Options include human regular insulin, various analogs (aspart, glulisine, and lispro), formulations (faster insulin aspart, lispro U200), biosimilars (lispro), and insulins with different routes of administration (inhaled). Rapid-acting insulin analogs have a modestly lower risk for hypoglycemia compared with human regular insulin but at a higher cost. Various premixed formulations of human and analog insulins are available and continue to be widely used in some regions, though they tend to have an increased risk of hypoglycemia as compared with basal insulin alone (Table 2 and Fig. 7).

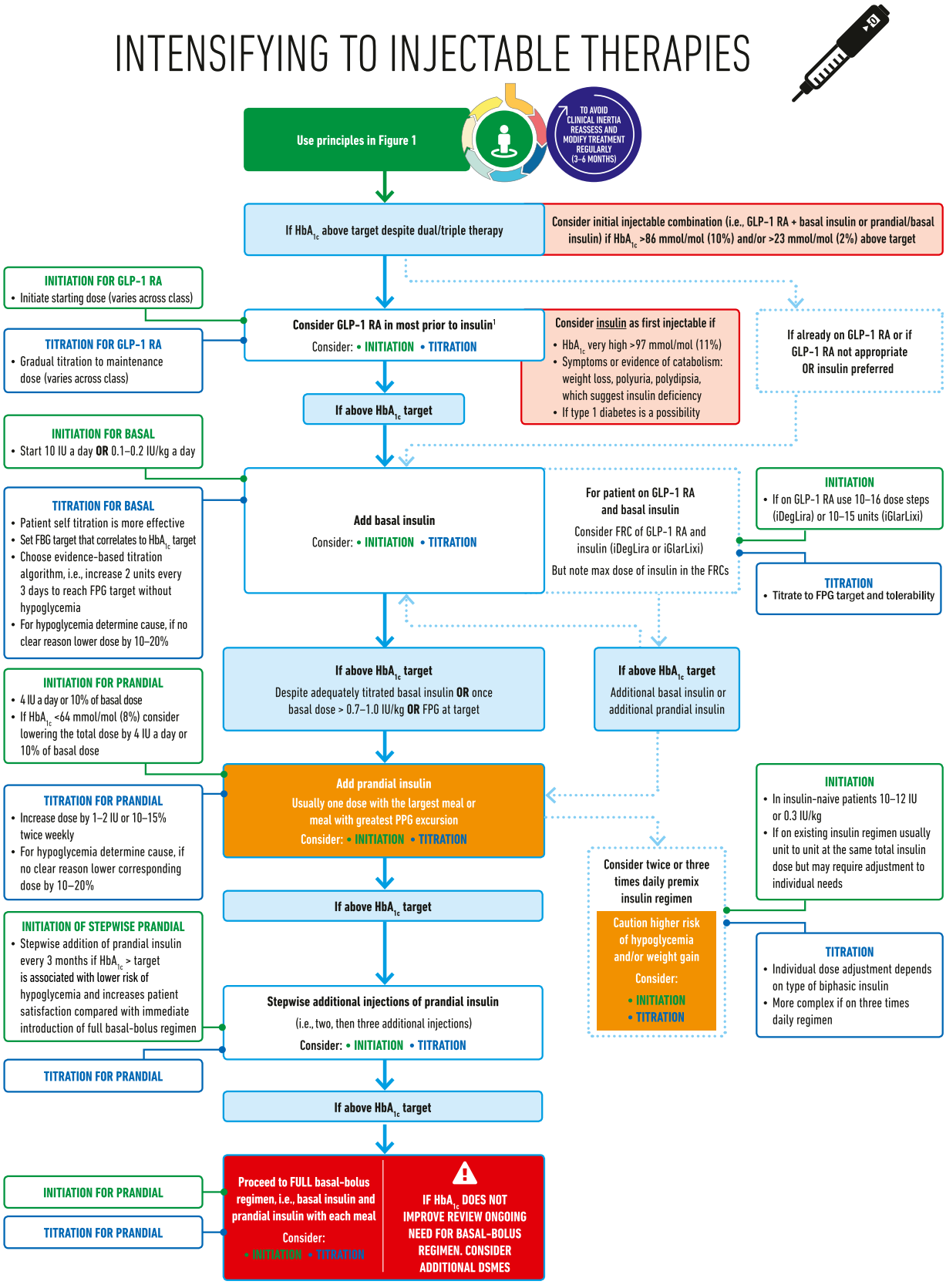
Other Glucose-Lowering Medications

Other oral glucose-lowering medications (i.e., meglitinides, α-glucosidase inhibitors, colesevelam, quick-release bromocriptine, pramlintide) are not used commonly in the U.S. and some are not licensed at all in Europe. No major new scientific information on these medications has emerged in recent years. Their basic characteristics are listed in Table 2.

Obesity Management Beyond Lifestyle Intervention

Medications for Weight Loss

Several clinical practice guidelines recommend weight-loss medications as an optional adjunct to intensive lifestyle management for patients with obesity, particularly if they have diabetes (169–171). Others do not (172). Several medications and medication combinations approved in the U.S. or Europe for weight loss have been found to improve glucose control in people with diabetes (173,174). One glucose-lowering medication, liraglutide, is also approved for the treatment of obesity



1. Consider choice of GLP-1 RA considering: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

Figure 7—Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide 1 receptor agonist; FBG, fasting blood glucose; FPG, fasting plasma glucose; max, maximum; PPG, postprandial glucose.

at a higher dose (175). Cost, side effects, and modest efficacy limit the role of pharmacotherapy in long-term weight management.

Metabolic Surgery

Consensus recommendation

- Metabolic surgery is a recommended treatment option for adults with type 2 diabetes and *1*) a BMI $\geq$40.0 kg/m^2 (BMI $\geq$37.5 kg/m^2 in people of Asian ancestry) or *2*) a BMI of 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods.

Metabolic surgery is highly effective in improving glucose control (176–178) and often produces disease remission (179–182). The effects can be sustained for at least 5 years (177,182). Benefits include a reduction in the number of glucose-lowering medications needed to achieve glycemic targets (178,179).

Several clinical practice guidelines and position statements recommend consideration of metabolic surgery as a treatment option for adults with type 2 diabetes and *1*) a BMI $\geq$40.0 kg/m^2 (BMI $\geq$37.5 kg/m^2 in people of Asian ancestry) or *2*) a BMI of 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods (65,183). Because baseline BMI does not predict surgical benefits on glycemia or hard outcomes and the improvement in glycemic control occurs early through weight-independent mechanisms (183), metabolic surgery may be considered for those with a BMI of 30.0–34.9 kg/m^2 (27.5–32.4 in people of Asian ancestry) who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods.

Adverse effects of bariatric surgery, which vary by procedure, include surgical complications (e.g., anastomotic or staple line leaks, gastrointestinal bleeding, intestinal obstruction, the need for reoperation), late metabolic complications (e.g., protein malnutrition, mineral deficiency, vitamin deficiency, anemia, hypoglycemia), and gastroesophageal reflux (184,185). Patients who undergo metabolic surgery may be at risk for substance use, including drug and alcohol use and cigarette smoking (186). People with diabetes presenting for metabolic surgery also have increased rates of depression and other major psychiatric disorders (187). These factors should be assessed preoperatively and during follow-up. Metabolic surgery should be performed in high-volume centers with multidisciplinary teams that are experienced in the management of diabetes and gastrointestinal surgery. Long-term lifestyle support and routine monitoring of micronutrient and nutritional status must be provided to patients after surgery (188,189).

PUTTING IT ALL TOGETHER: STRATEGIES FOR IMPLEMENTATION

For an increasing number of patients, presence of specific comorbidities (e.g., ASCVD, HF, CKD, obesity), safety concerns (e.g., risk of hypoglycemia), or health care environment (e.g., cost of medications) mandate a specific approach to the choice of glucose-lowering medication. These are considered in Figs. 2–6. For patients not reaching their target HbA_{1c}, it is important to re-emphasize lifestyle measures, assess adherence, and arrange timely follow-up (e.g., within 3–6 months) (Fig. 1).

Initial Monotherapy

Consensus recommendation

- Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes.

Metformin remains the preferred option for initiating glucose-lowering medication in type 2 diabetes and should be added to lifestyle measures in newly diagnosed patients. This recommendation is based on the efficacy, safety, tolerability, low cost, and extensive clinical experience with this medication. Results from a substudy of UKPDS (n = 342) showed benefits of initial treatment with metformin on clinical outcomes related to diabetes, with less hypoglycemia and weight gain than with insulin or sulfonylureas (98).

Initial Combination Therapy Compared With Stepwise Addition of Glucose-Lowering Medication

Consensus recommendation

- The stepwise addition of glucose-lowering medication is generally preferred to initial combination therapy.

In most patients, type 2 diabetes is a progressive disease, a consequence generally attributed to a steady decline of insulin secretory capacity. The practical impact of gradual loss of β-cell function is that achieving a glycemic target with monotherapy is typically limited to several years. Stepwise therapy (i.e., adding medications to metformin to maintain HbA_{1c} at target) is supported by clinical trials (3). While there is some support for initial combination therapy due to the greater initial reduction of HbA_{1c} than can be provided by metformin alone (190,191), there is little evidence that this approach is superior to sequential addition of medications for maintaining glycemic control or slowing the progression of diabetes. However, since the absolute effectiveness of most oral medications rarely exceeds an 11 mmol/mol (1%) reduction in HbA_{1c}, initial combination therapy may be considered in patients presenting with HbA_{1c} levels more than 17 mmol/mol (1.5%) above their target. Fixed-dose formulations can improve medication adherence when combination therapy is used (192), and may help achieve glycemic targets more rapidly (100). Potential benefits of combination therapy need to be weighed against the exposure of patients to multiple medications and potential side effects, increased cost, and, in the case of fixed combination medications, less flexibility in dosing.

Choice of Glucose-Lowering Medication After Metformin

Consensus recommendation

- The selection of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific adverse medication effects, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost (Figs. 2–6).

As detailed in the "Medications for Lowering Glucose" section, the glucose-lowering medications that can be added to metformin have distinct profiles of

action, efficacy, and adverse effects (100,193). The early introduction of basal insulin is well established, in particular when HbA_{1c} levels are very high (>97 mmol/mol [>11%]), symptoms of hyperglycemia are present, or there is evidence of ongoing catabolism (e.g., weight loss). This constellation of symptoms can occur in type 2 diabetes but suggest insulin deficiency and raise the possibility of autoimmune (type 1) or pancreatogenic diabetes in which insulin would be the preferred therapy. While this remains the usual strategy for patients when HbA_{1c} levels are very high, SGLT2 inhibitors (194) and GLP-1 receptor agonists (195) have demonstrated efficacy in patients with HbA_{1c} levels exceeding 75 mmol/mol (9%), with the additional benefits of weight reduction and reduced risk of hypoglycemia.

Evidence from clinical trials supports the use of several of the SGLT2 inhibitors and GLP-1 receptor agonists as add-on therapy for people with type 2 diabetes with an HbA_{1c} >53 mmol/mol (>7%) and established CVD (48,51,52). However, since only 15–20% of patients with type 2 diabetes conform to the characteristics of patients in these trials, other clinical features need to be considered in the majority when selecting second medications to add to metformin (Figs. 2–6) (149,196–204).

Sulfonylureas and insulin are associated with an increased risk for causing hypoglycemia and would not be preferred for patients in whom this is a concern. Furthermore, hypoglycemia is distressing and so may reduce treatment adherence (Fig. 5). For patients prioritizing weight loss or weight maintenance (Fig. 4), important considerations include the weight reduction associated with SGLT2 inhibitors and GLP-1 receptor agonists, the weight neutrality of DPP-4 inhibitors, and the weight gain associated with sulfonylureas, basal insulin, and TZDs. An important consideration for society in general and for many patients in particular is the cost of medications; sulfonylureas, pioglitazone, and recombinant human insulins are relatively inexpensive, although their cost may vary across regions. Short-term acquisition costs, longer-term treatment cost, and cost-effectiveness should be considered in clinical decision making when data are available (Fig. 6).

Intensification Beyond Two Medications

Consensus recommendation

- Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.

The lack of a substantial response to one or more noninsulin therapies should raise the issue of adherence and, in those with weight loss, the possibility that the patient has autoimmune (type 1) or pancreatogenic diabetes. However, it is common in people with long-standing diabetes to require more than two glucose-lowering agents, often including insulin. Compared with the knowledge base guiding dual therapy of type 2 diabetes, there is less evidence guiding these choices (205). In general, intensification of treatment beyond two medications follows the same general principles as the addition of a second medication, with the assumption that the efficacy of third and fourth medications will be generally less than expected. No specific combination has demonstrated superiority except for those that include insulin and GLP-1 receptor agonists that have broad ranges of glycemic efficacy. As more medications are added, there is an increased risk of adverse effects. It is important to consider medication interactions and whether regimen complexity may become an obstacle to adherence. Finally, with each additional medication comes increased costs, which can affect patient burden, medication-taking behavior, and medication effectiveness (193,205–211).

While most patients require intensification of glucose-lowering medications, some require medication reduction or discontinuation of medication, particularly if the therapy is ineffective or is exposing patients to a higher risk of side effects such as hypoglycemia or when glycemic goals have changed due to a change in clinical circumstances (e.g., development of comorbidities or even healthy aging). A guiding principle is that for all therapies the response should be reviewed at regular intervals, including the impact on efficacy (HbA_{1c}, weight) and safety; the therapy should be stopped or the dose reduced if there are minimal benefits or if harm outweighs any benefit. In particular, ceasing or reducing the dose of medications that have an increased risk of hypoglycemia is important when any new glucose-lowering treatment (lifestyle or medication) is started (Fig. 7) (40). HbA_{1c} levels below 48 mmol/mol (6.5%) or substantially below the individualized glycemic target should prompt consideration of stopping or reducing the dose of medications with risk of hypoglycemia or weight gain.

Addition of Injectable Medications

Consensus recommendation

- In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended (Fig. 7).

See the "Insulin" and "Basal Insulin" sections in "Medications for Lowering Glucose" for more medication details.

Patients often prefer combinations of oral medications to injectable medications. The range of combinations available with current oral medications allows many people to reach glycemic targets safely. However, there is currently no evidence that any single medication or combination has durable effects and, for many patients, injectable medications become necessary within 5–10 years of diabetes diagnosis.

Evidence from trials comparing GLP-1 receptor agonists and insulin (basal, premixed, or basal-bolus) shows similar or even better efficacy in HbA_{1c} reduction (212,213). GLP-1 receptor agonists have a lower risk of hypoglycemia and are associated with reductions in body weight compared with weight gain with insulin (212,214). Some GLP-1 receptor agonists allow for once-weekly injections, as opposed to daily or more often for insulin. Based on these considerations, a GLP-1 receptor agonist is the preferred option in a patient with a definite diagnosis of type 2 diabetes who needs injectable therapy. However, the tolerability and high cost of GLP-1 receptor agonists are important limitations to their use. If additional glucose lowering is needed despite therapy with a long-acting GLP-1 receptor agonist, the addition of basal insulin is a reasonable option (215,216).

Alternatively, the addition of insulin to oral medication regimens is well established. In particular, using basal insulin in combination with oral medications is effective, and has less hypoglycemia and weight gain than combinations using premixed insulin formulations or prandial insulin (217). A standard approach for optimizing basal insulin regimens is to titrate the dose based on a target fasting glucose concentration, which is a simple index of effectiveness. Either NPH insulin or long-acting insulin analogs are efficacious for controlling fasting glucose, although basal analog formulations show reduced risks of hypoglycemia, particularly overnight, when titrated to the same fasting glucose target as NPH insulin (157,218).

Beyond Basal Insulin

Consensus recommendation

- Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin (Figs. 7 and 8).

It has become common practice to approach insulin use in people with type 2 diabetes by following the established paradigms developed for those with type 1 diabetes. This includes multiple daily injections with doses of insulin analogs before meals that are adjusted based on ambient blood glucose and meal constituents. While this is reasonable for people with type 2 diabetes who are lean, insulinopenic, and sensitive to exogenous insulin, it ignores the substantial differences in pathophysiology between most people with type 2 diabetes and type 1 diabetes. Most people with type 2 diabetes are obese and insulin resistant, requiring much larger doses of insulin and experiencing lower rates of hypoglycemia than those with type 1 diabetes. In patients with type 2 diabetes, weight gain is a particularly problematic side effect of insulin use. Recent evidence supports the effectiveness of combinations of insulin with glucose-lowering medications that do not increase body weight. For example, SGLT2 inhibitors can be added to insulin regimens to lower blood glucose levels without increasing insulin doses, weight gain, or hypoglycemia (219–221). In a meta-analysis that studied the combination of either SGLT2 inhibitors or DPP-4 inhibitors with insulin, the SGLT2 inhibitor–insulin combination was associated with a greater reduction in HbA_{1c}, an advantage in terms of body weight and no increase in the rates of hypoglycemia (222,223). Depending on baseline HbA_{1c}, glycemic profile, and individual response, the insulin dose may need to be reduced to prevent hypoglycemia when adding an SGLT2 inhibitor.

The combination of basal insulin and a GLP-1 receptor agonist has high efficacy, with recent evidence from clinical trials demonstrating the benefits of this combination to lower HbA_{1c} and limit weight gain and hypoglycemia compared with intensified insulin regimens (224,225). Most data come from studies in which a GLP-1 receptor agonist is added to basal insulin. However, there is evidence that insulin added to a GLP-1 receptor agonist can also effectively lower HbA_{1c}, although some weight gain results (215). Fixed-ratio combinations of insulin and GLP-1 receptor agonists are available and can decrease the number of injections compared with administering the medications separately (226–228).

A final approach to glycemic management when basal insulin plus oral medications is insufficient to achieve HbA_{1c} targets is intensified insulin regimens (Figs. 7 and 8). DSMES focused on insulin therapy is particularly helpful when intensified insulin therapy is considered. Referral to a diabetes specialist team should be considered in cases where the provider is uncomfortable or unfamiliar with intensification, poor outcomes continue despite intensification, or patients have other issues that complicate intensification. Intensified insulin regimens include *1*) one or more daily injections of rapid- or short-acting insulin before meals (prandial insulin) or *2*) switching to one to three daily administrations of a fixed combination of short- and long-acting insulin (premixed or biphasic insulins) (229,230). When adding prandial insulin, giving one injection with the largest meal of the day is a simple and safe approach (231). Over time, if glycemic targets are not met with one dose of prandial insulin daily, additional prandial injections can be added to other meals (232). Results of meta-analyses suggest a modestly greater reduction in HbA_{1c} with basal-prandial regimens compared with biphasic insulin regimens, but at the expense of greater weight gain (233–235). While still commonly used, we do not generally advocate premixed insulin regimens, particularly those administered three times daily, for routine use when intensifying insulin regimens (Fig. 7).

Continuous insulin infusion using insulin pumps may have a role in a small minority of people with type 2 diabetes (236).

Access and Cost

Consensus recommendation

- Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications.

The availability of glucose-lowering medications, patient support systems, and blood glucose-monitoring devices can differ worldwide, depending on a region's economy, culture, and health care system. Cost of and access to newer medications and insulin remain important issues throughout the world. Although the economics of diabetes care is complex and broadly includes the costs to society of diabetic complications and long-term outcomes, the cost of drugs and the affordability of treatment are often the primary basis for decision making. Within health care systems, variance in medication coverage is based on different assessments of cost-effectiveness. This results in huge disparities in the cost of new and old glucose-lowering medications in some countries, limiting access to the full range of diabetes therapies in large segments of the population, and creating a two-tiered system of treatment. Since glycemic management remains a cornerstone of the prevention of diabetes complications, these disparities raise questions of fairness, equity, and overall public health. Nonetheless, the use of less expensive agents, such as metformin, sulfonylureas, and human insulin, remain effective options (Figs. 2 and 6). Redoubling lifestyle management efforts can also have great impact, but behavioral intervention and support can also be costly, and socioeconomic barriers to improving lifestyle are well described (237).

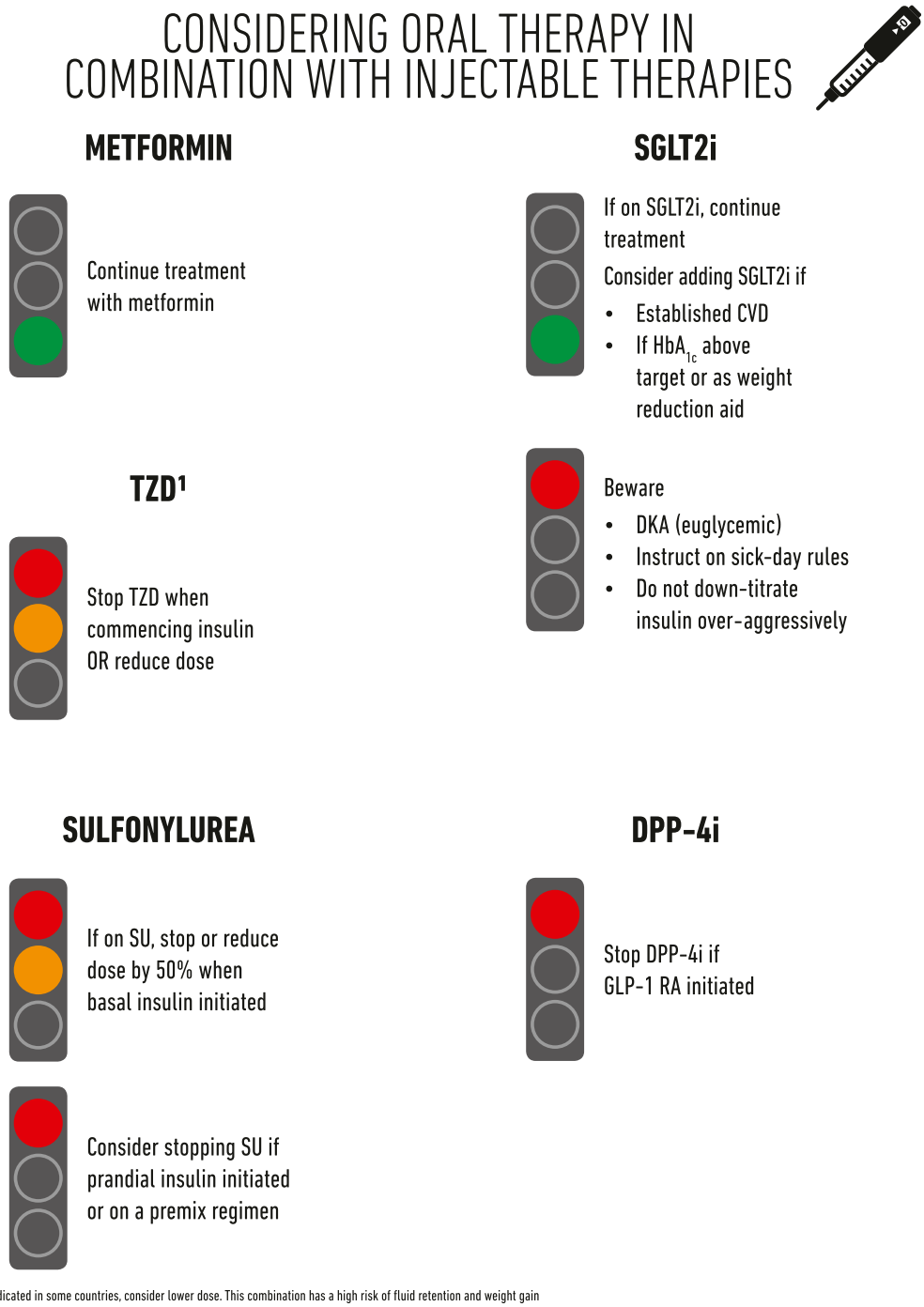


Figure 8—Considering oral therapy in combination with injectable therapies. DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea.

Emerging Technology

There is an increasing call for the use of technology and telemedicine to improve patients' health (238). Many types of inputs can be digitalized, such as blood glucose levels, time spent exercising, steps walked, energy ingested, medication doses administered, blood pressure, and weight. Patterns in these variables can be identified by software, leading to specific treatment recommendations supported by real-time algorithms. Telemedicine incorporates multiple types of communication services, such as two-way video, e-mail, texting, smartphones, tablets, wireless monitors, decision support tools, and other forms of telecommunication technologies. Results overall suggest a modest improvement in glycemic control (239,240).

KEY KNOWLEDGE GAPS

Despite over 200 years of research on lifestyle management of diabetes and more than 50 years of comparative-effectiveness research in diabetes, innumerable unanswerecd questions regarding the management of type 2 diabetes remain. In the context of our current consensus recommendations, the following is an incomplete

discussion of vexing issues that must be addressed.

Evolving areas of current investigation will provide improvements in diabetes care and hold great hope for new treatments.

- Implementation science. The tools available to prevent and treat diabetes are vastly improved. However, implementation of effective innovation has lagged behind.
- Basic science. Our understanding of the basic mechanisms of diabetes, the development of complications, and the treatment of both, though continuously advancing, has highlighted how much we do not know.
- Personalized/precision medicine. Though promising, these –omics and big data approaches addressing both personal and environmental factors and their interaction are largely unrealized in diabetes care and will require large investments and coordination to have impact.
- Informatics. The benefits and role of enhanced monitoring of glucose and other variables leveraged with real-time informatics-based approaches to adapt treatment on an individual basis has great potential but has not been elucidated.
- Overweight/obesity. Current therapy is clearly inadequate. Innovation in methods and implementation would transform diabetes prevention and care. Understanding the biology, psychology, and sociology of obesity to identify pharmacological, behavioral, and political approaches to preventing and treating this principal cause of type 2 diabetes is essential.
- Lifestyle management and DSMES. Though the benefits of these approaches are clear, better paradigms on how to target, individualize, and sustain the effects are needed.
- β-Cell function. Preserving and enhancing β-cell function is perceived as the holy grail of diabetes and yet effective techniques are inadequately developed.
- Translational research. There is a huge gap between the knowledge gained from clinical trials and application of that information in clinical practice. This gap should be filled with pragmatic studies and other designs that include costs, measures of patient preference, and other patient-recorded outcome measures. Patients and other stakeholders should have more input into trial designs and outcomes. Pragmatic designs will enhance generalizability of results and reduce cost. Better application of "real-world evidence" will complement randomized trial evidence.
- Drug development. New medications will require demonstration of broad efficacy for glucose, comorbidities and/or complications, as well as safety and tolerability to compete in the marketplace.
- Complications. Steatohepatitis, HF, nonalbuminuric CKD, chronic mental illness, and other emerging issues are complications in diabetes that may supplant classical microvascular and macrovascular disease in importance and impact. Understanding optimal diagnostic, screening, and treatment strategies is urgently needed.

Other areas of importance include better segmentation of "type 2 diabetes," as well as appropriate diagnosis of secondary diabetes, which should allow more informed individualization of care. Better data on optimal approaches to diabetes management in frail and older adult patients is urgently required considering the controversy around glycemic targets and the benefits and harms of specific treatments from lifestyle management to medications. Current approaches to the management of type 2 diabetes in adolescents and young adults do not seem to alter the loss of β-cell function and most individuals in this age-group quickly transition to insulin therapy. Studies to guide optimal therapy in this emerging population with a terrifyingly high risk of early disability is an immediate need.

There are enduring questions that continue to challenge guideline development. For example, does metformin provide cardiovascular benefit in patients with type 2 diabetes early in the natural history of diabetes, as suggested by the UKPDS? Is metformin's role as first-line medication management truly evidence-based or a quirk of history? Though the rationale for early combination therapy targeting normal levels of glycemia in early diabetes is seductive, clinical trial evidence to support specific combinations and targets is essentially nonexistent. As the cost implications for these approaches is enormous, evidence is desperately needed. Different models of care are being implemented globally. Defining optimal cost-effective approaches to care, particularly in the management of patients (multimorbidity), is essential.

New questions arise from the recent cardiovascular outcomes studies. Do the cardiovascular and renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists demonstrated in patients with established CVD extend to lower-risk patients? Is there additive benefit of use of GLP-1 receptor agonists and SGLT2 inhibitors for prevention of cardiovascular and renal events? If so, in what populations?

Addressing these and other vital clinical questions will require additional investment in basic, translational, clinical, and implementation research. More time- and cost-efficient research paradigms to address patient-centered end points will need to be developed through regulatory reform and leveraging informatics and coordinated learning health care systems. The increasing burden of cardiorenal metabolic disease in terms of incidence, prevalence, and cost is an existential threat to society. Urgent attention to improve prevention and treatment is of the essence.

The management of hyperglycemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available. Patient-centered decision making and support and consistent efforts to improve diet and exercise remain the foundation of all glycemic management. Initial use of metformin, followed by addition of glucose-lowering medications based on patient comorbidities and concerns is recommended as we await answers to the many questions that remain.

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