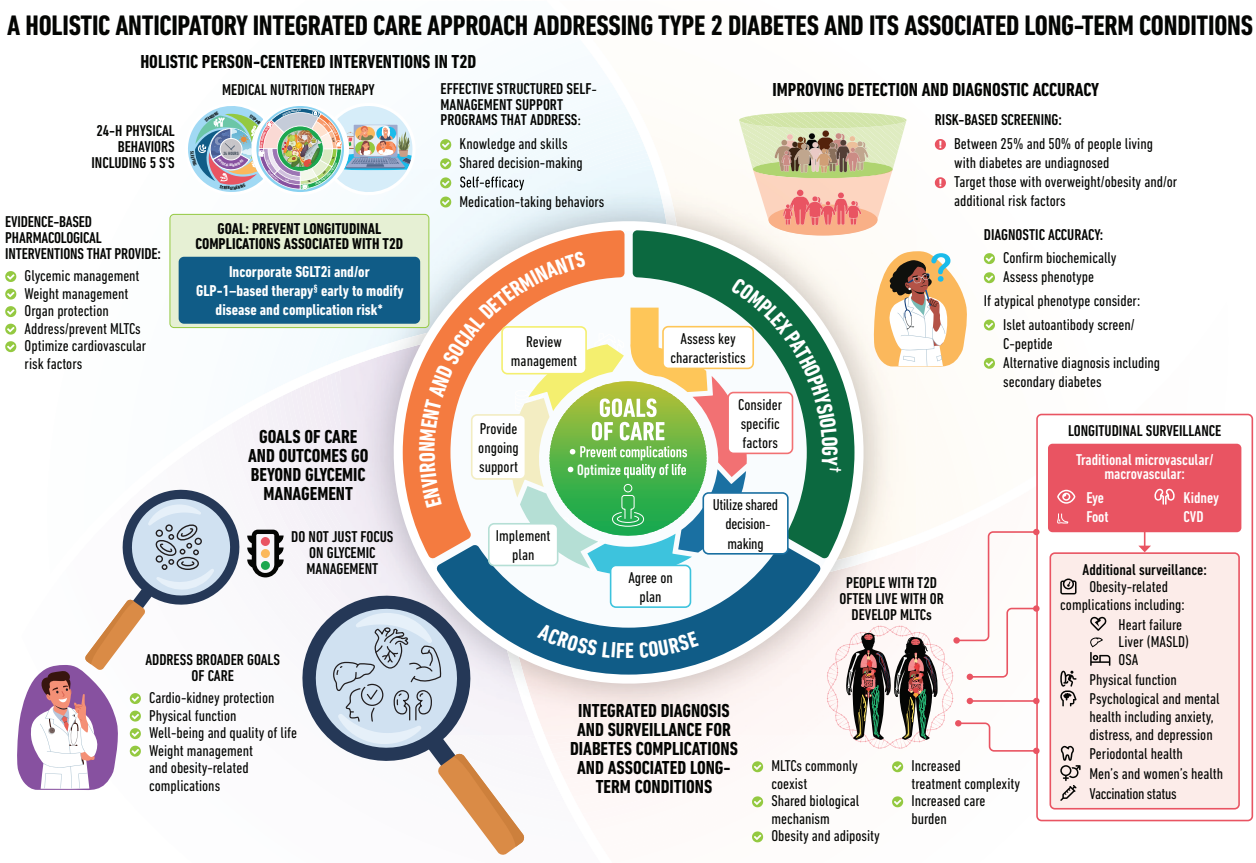
Diabetes Care

American Diabetes Association

Management of Type 2 Diabetes, 2026. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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Diabetes Care 2026;49(00):1–45 | https://doi.org/10.2337/dci26-0141



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Management of Type 2 Diabetes, 2026. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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https://doi.org/10.2337/dci26-0141

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The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the consensus statement on the management of type 2 diabetes in nonpregnant adults, published since 2006 and last updated in 2022. The target audience is the multidisciplinary health care team providing diabetes care in the U.S. and Europe. A systematic examination of publications since 2022 informed new recommendations. This update has broadened the focus from the management of hyperglycemia to the holistic management of type 2 diabetes and its risk of associated multiple long-term conditions. Fundamental aspects of diabetes care include promoting healthy lifestyle behaviors (healthy eating, 24-h physical behaviors including sleep, and avoiding tobacco and substance use), alongside the provision of psychological support and weight management interventions. For the management of people living with type 2 diabetes, earlier use, potentially from diagnosis, of sodium–glucose cotransporter 2 (SGLT2) inhibitors and/or glucagon-like peptide 1 (GLP-1)-based therapies to offer organ protection and improve long-term outcomes in type 2 diabetes is advocated. Furthermore, earlier combination use of SGLT2 inhibitors and GLP-1–based therapies should be considered in people with concomitant cardiovascular disease, chronic kidney disease, and heart failure. Finally, the ability to transform outcomes for people living with type 2 diabetes is within our grasp through the consistent, equitable, and systematic implementation of strategies and therapies that are already available.

Type 2 diabetes is a chronic complex disease, and management requires multifactorial behavioral and pharmacological treatments to prevent or delay complications and maintain quality of life (Fig. 1). This includes management of blood glucose levels, weight, cardiovascular and kidney disease risk factors, and associated multiple long-term conditions (MLTCs) and complications. This necessitates that care be delivered in an organized and structured way, such as described in the chronic care model, and includes a person-centered approach to enhance engagement in self-care activities, ideally delivered in a multidisciplinary setting. Careful consideration of clinical characteristics, social determinants of health (SDOH), and the preferences of people living with diabetes must inform individualization of treatment goals and

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CONSENSUS REPORT
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strategies, with consideration of the available therapeutic options to prevent or diminish the impact of MLTCs and complications.

DATA SOURCES, SEARCHES, AND STUDY SELECTION

This report follows the Accurate Consensus Reporting Document (ACCORD) principles (1). The 16-member writing group was appointed by the European Association for the Study of Diabetes (EASD) Committee on Clinical Affairs on behalf of the EASD Board and by the American Diabetes Association's (ADA's) scientific leadership on behalf of its board based on their clinical and research expertise in type 2 diabetes. The group included equal representation from both organizations across different clinical disciplines and was cochaired by Melanie Davies (EASD) and John Buse (ADA). Two or four members of the writing group were assigned to be the primary authors of each section. These individuals had specific knowledge of the relevant area and were tasked with reviewing and summarizing the available literature.

The group largely worked virtually, with regular recorded video conferences (April 2025–June 2026) and a 2-day face-to-face workshop in February 2026. The writing group accepted prior editions of this consensus report as a starting point (2,3). To identify newer evidence, a search was conducted on PubMed for randomized controlled trials (RCTs), systematic reviews, and meta-analyses published in English between 1 May 2022 and 31 December 2025. Eligible publications examined the efficacy or safety of pharmacological or nonpharmacological interventions in adults with type 2 diabetes. Reference lists in eligible reports were scanned to identify additional relevant articles. Additional references were identified by writing group members outside the PubMed search strategy by forward and backward citation chasing. Details of the keywords and the search strategy are available at https://doi.org/10.17605/osf.io/pu93h. Publications were grouped according to subject matter, and the writing group members reviewed this new evidence. Up-to-date meta-analyses evaluating the effects of therapeutic interventions across clinically important subgroup populations were assessed using relevant guidance (4,5). Evidence appraisal was informed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines on the formulation of clinical practice recommendations (6,7). Based on this evidence, writing group members collaboratively identified the topic areas and sections that needed to be updated in a nonanonymous setting. Topic areas and questions were posed to the full group by the chairs and other writing group members during meetings. Discussions were carried out in detail to clarify the meaning, resolve questions, and bring forth new ideas. Consensus was sought through discussion among writing group members. Where consensus could not be achieved, final decisions were determined by majority vote. Qualitative meeting summaries were shared with writing group members and allowed reflection and the opportunity to air discussion points throughout the development of the report until consensus was reached. All writing group members collectively reviewed all sections to verify scientific rigor, language, and utility to the intended readership. Each section, in turn, was revised and approved by the entire working group.

The draft consensus recommendations were presented for public comments at the ADA meeting in New Orleans in 2026, and the report was evaluated by external peer review, leading to subsequent revisions. Although evidence based with stakeholder input, the recommendations presented herein reflect the values and preferences of the consensus group, acknowledging limitations in the evidence base. The dualities of interests of the authors were tracked throughout the development of this statement and are reported at the end of the article. The document was reviewed and approved by the ADA's Professional Practice Committee (PPC) and the EASD's Committee on Clinical Affairs (CCA).

THE RATIONALE, IMPORTANCE, AND CONTEXT OF TYPE 2 DIABETES TREATMENT

Fundamental aspects of diabetes care include promoting healthy behaviors through medical nutrition therapy (MNT), 24-h physical behaviors (the five S's: standing, stepping, sweating, strengthening, and sleep) (2,3), and psychological support, as well as weight management and tobacco/substance use disorder counseling as needed. This should be delivered in the context of diabetes self-management education and support (DSMES). The expanding number of interventions (from behavioral interventions to pharmacological interventions, devices, use of technology, and surgery) and growing information about their benefits and risks provide more options for people with diabetes and providers but complicate decision-making (8). This complexity is compounded by increased information from online sources and social media that can sometimes be incomplete or misleading (9–11).

In the last iteration of this consensus (2022), a focus on holistic care of the individual with diabetes was recommended and practical strategies addressed. People with type 2 diabetes often live with MLTCs and exhibit accelerated aging,

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Received 3 June 2026 and accepted 30 July 2026

This article contains supplementary material online at https://doi.org/10.2337/figshare.33260637.

This article is being simultaneously published in Diabetologia *(https://doi.org/10.1007/s00125-026-06855-7) and* Diabetes Care *(https://doi.org/10.2337/dci26-0141) by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA).*

This article underwent external peer review. Following this, the report was assessed for EASD by its Committee on Clinical Affairs and approved by its Executive Board and for ADA by its Professional Practice Committee.

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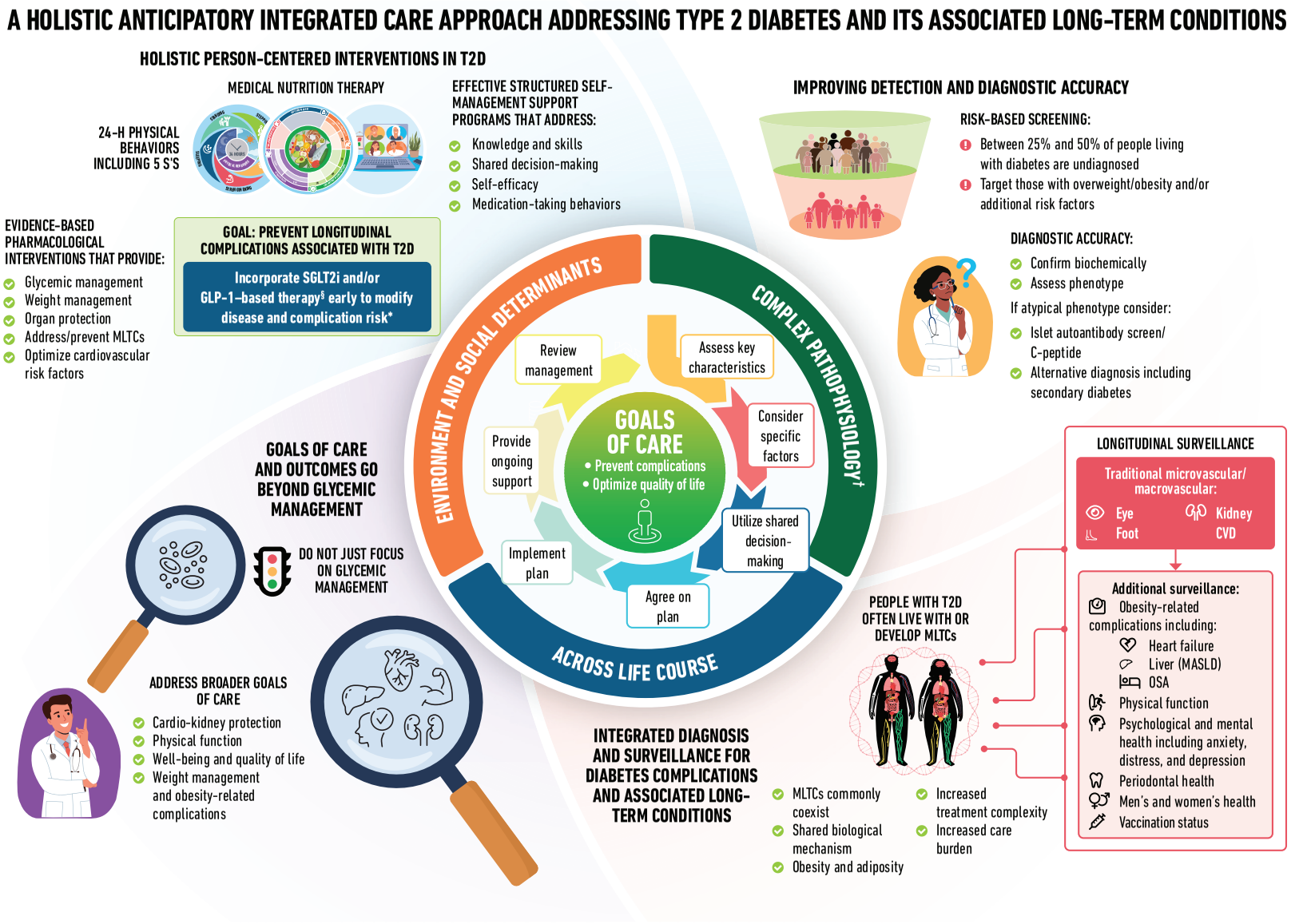


Figure 1—A holistic anticipatory integrated care approach addressing type 2 diabetes and its associated long-term conditions. *Use combination therapy based on target achievement and individual CVD and CKD risk. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. †Dominantly driven by excess adiposity. MASLD, metabolic dysfunction–associated steatotic liver disease; MLTCs, multiple long-term conditions; OSA, obstructive sleep apnea; T2D, type 2 diabetes.

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often driven by consequences of excess adiposity (12,13). The health care team should strive to achieve optimal outcomes with regard to cardiovascular, kidney, liver, and pulmonary outcomes, physical function, well-being, cognitive outcomes, and more. They should also address wider care needs associated with SDOH (14). This effort must take a long view of optimizing outcomes across the life course, accounting for the complex pathophysiology, dominantly driven by excess adiposity, underpinning type 2 diabetes (15) and seizing opportunities to achieve disease prevention, modification, and remission, particularly through efforts to achieve 10–15% weight loss. A growing body of evidence identifies chronic low-grade inflammation as a mechanism behind type 2 diabetes and its associated cardio-kidney complications. Consequently, reducing residual inflammatory risk is increasingly recognized as a complementary therapeutic goal alongside optimization of glucose levels, body weight, and traditional cardiovascular risk factors, with the potential to modify disease progression and improve long-term outcomes (16,17). Interventions applied need to be reviewed and adjusted over time.

At diagnosis of type 2 diabetes and at regular intervals, alternative diagnoses such as type 1 diabetes, monogenic diabetes, and hypercortisolism (among others) should be considered based on clinical context and in particular the response of individuals to treatment (18–22).

Attaining recommended glucose targets yields substantial and enduring reductions in the onset and progression of microvascular complications, and early intervention is essential. Recent recommendations suggest screening for type 2 diabetes in all adults aged ≥35 years and all adults with overweight or obesity at any age with any additional risk factor for diabetes to make the diagnosis early and afford the opportunity for treatment (23).

With regard to hyperglycemia, the greatest absolute risk reduction for microvascular complications comes from improving very elevated glucose levels, and a more modest reduction results from near normalization of plasma glucose levels. The impact of glucose management on macrovascular complications is less certain but is supported by multiple meta-analyses and epidemiological studies. Because the benefits of intensive glucose management emerge slowly while the harm can be immediate, people with longer life expectancy have more to gain from early intensive glycemic management. A reasonable HbA_{1c} target for most nonpregnant adults with sufficient life expectancy to see microvascular benefits (generally ∼10 years) is around 48–53 mmol/mol (6.5–7%) or lower (24). A target of 48 mmol/mol (6.5%) or lower may be more appropriate for adults with type 2 diabetes who are managed with lifestyle/diet alone or in combination with medication that is not associated with hypoglycemia and for people with early-onset type 2 diabetes (diagnosis aged <40 years) (25,26). 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 (27). Continuous glucose monitoring (CGM) provides more information than blood glucose monitoring and can be useful for some people with type 2 diabetes (28). Increasingly, CGM is viewed as an alternative method to assess and target glucose levels, with a general target of time in range (TIR) 3.9–10.0 mmol/L (70–180 mg/dL) >70% (24). Aiming for a lower target HbA_{1c} or more stringent CGM metrics, such as time in tight range (TITR) 3.9–7.8 mmol/L (70–140 mg/dL), may have value if these aims can be achieved safely. Less stringent targets can be appropriate in individuals with limited life expectancy or advanced complications or if other factors such as frailty are present (24).

Other targets are relevant to minimizing risks of complications of diabetes, including those for blood pressure (BP) and lipid management. Recent trials have demonstrated benefits of lower targets and more intensive strategies in people with type 2 diabetes (29–32). The recommended general BP goal is <130/80 mmHg, though a systolic BP goal <120 mmHg should be encouraged in individuals with high cardiovascular or kidney risk (29). For most people with type 2 diabetes aged >40 years, statin therapy is recommended. In those aged 20–39 years with type 2 diabetes and additional atherosclerotic cardiovascular disease (ASCVD) risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy. For those with multiple CVD risk factors whose LDL-cholesterol remains ≥1.8 mmol/L (70 mg/dL) despite maximum tolerated statin therapy, it may be reasonable to add ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (29). The European Society of Cardiology suggests a risk-based approach with a range of LDL-cholesterol target values. For example, in those at very high risk, a target LDL-cholesterol of <1.4 mmol/L (<55 mg/dL) is suggested (32).

Early diagnosis and intervention for diabetes MLTCs and complications afford best opportunities to slow progression. Thus, systematic screening for these should begin at the diagnosis of type 2 diabetes and should go beyond the traditional screening for microvascular complications (Fig. 1). Preventive care paradigms should include a comprehensive medical evaluation, immunization review, assessment of oral health habits, attention to bone health, screening and intervention for substance abuse, and assessing sexual health and adequacy of contraception (33). Considering the increases in risk for specific cancers, such as colon, breast, and endometrial cancer, in those living with obesity, specific attention should be paid to screening guidelines. Sex-specific factors beyond contraception should also be considered (34), including hypogonadism, erectile dysfunction, and reduced fertility in men (35,36) and menstrual cycle irregularities, polycystic ovary syndrome (PCOS), urinary stress incontinence, and cardiometabolic risk across the reproductive life course in women (37,38). Regular (usually annual) assessment of diabetes complications, including a comprehensive eye and foot examination, the staging of chronic kidney disease (CKD), and the assessment of cardiovascular symptoms (29,33,39,40), remains an essential part of diabetes care. More recent statements have recommended needs-based screening and assessment of heart failure (29), metabolic dysfunction–associated steatotic liver disease (MASLD) (33,41), and psychological well-being (33).

The demonstrated broad benefits of both glucagon-like peptide 1 (GLP-1)-based therapies and/or sodium–glucose cotransporter 2 (SGLT2) inhibitors for high-risk individuals with ASCVD, heart failure, CKD, MASLD, obstructive sleep apnea (OSA), and other obesity-related diseases and complications are largely independent of their glucose-lowering effects. In the present consensus report, "GLP-1–based" therapies refer to both GLP-1 receptor agonists (GLP-1 RAs) and the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP)

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Table 1—Medications for lowering glucose: summary of characteristics

Medication	Efficacy	Hypoglycemia (520)	Weight change (521)	Effects on cardiovascular outcomes		Effects on kidney outcomes		Effects on MASH outcomes	Route of administration	Cost	Clinical considerations
				MACE[a]	Heart failure[a]	Progression of CKD[a]	Dosing/use considerations[b]				
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m^2	Neutral	Oral	Low	• GI side effects common: to mitigate GI side effects, consider slow dose titration, extended-release formulations, and administration with food • Potential for vitamin B_{12} deficiency: monitor at regular intervals and replace as appropriate
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for dose considerations for kidney function of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Unknown	Oral	High	• DKA risk, rare in T2D: discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days), during critical illness, or during prolonged fasting to mitigate potential risk; reinitiate treatment again as early as possible according to physicians' recommendation • Increased risk of genital mycotic infections: mitigate risk with genital hygiene and avoid use in high-risk individuals • Necrotizing fasciitis of the perineum (Fournier's gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, BP: adjust other volume-contracting agents as applicable

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Table 1—Continued

Medication	Efficacy	Hypoglycemia (520)	Weight change (521)	Effects on cardiovascular outcomes: MACE[a]	Effects on cardiovascular outcomes: Heart failure[a]	Effects on kidney outcomes: Progression of CKD[a]	Effects on kidney outcomes: Dosing/use considerations[b]	Effects on MASH outcomes	Route of administration	Cost	Clinical considerations
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (s.c. and oral) Neutral: exenatide once weekly, lixisenatide	Benefit: semaglutide (s.c.)	Benefit for kidney end points in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (s.c.) Benefit for CKD progression: semaglutide (s.c.)	• See labels for dose considerations for kidney function of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor kidney function when initiating or escalating doses in people with kidney impairment reporting severe adverse GI reactions	Benefit: semaglutide (s.c.)	s.c.; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel individuals on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for people experiencing GI challenges • Pancreatitis has been reported in postmarketing surveillance but causality has not been established; discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis are suspected • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and duration of T2D >10 years) • NAION has been reported (very rare incidence) but causality has not been established: monitor for NAION during eye examinations • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration

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Table 1—Continued

Medication	Efficacy	Hypoglycemia (520)	Weight change (521)	Effects on cardiovascular outcomes: MACE[a]	Effects on cardiovascular outcomes: Heart failure[a]	Effects on kidney outcomes: Progression of CKD[a]	Dosing/use considerations[b]	Effects on MASH outcomes	Route of administration	Cost	Clinical considerations
Dual GLP-1/GIP agonists	Very high	No	Loss (very high)	Benefit: tirzepatide	Benefit: tirzepatide	Benefit for kidney end points in CVOTs: tirzepatide	• See label for dose considerations for kidney function • No dose adjustment • Monitor kidney function when initiating or escalating doses in people with kidney impairment reporting severe adverse GI reactions	Potential benefit	s.c.	High	• Risk of thyroid C cell tumors in rodents but human relevance not determined • Counsel people on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for people experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals, duration of T2D >10 years, established retinopathy)
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Dose adjustment required based on kidney function (sitagliptin, saxagliptin, alogliptin); can be used in kidney impairment • No dose adjustment required for linagliptin	Unknown	Oral	High	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain • Bullous pemphigoid (postmarketing): discontinue if suspected

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Table 1—Continued

Medication	Efficacy	Hypoglycemia (520)	Weight change (521)	Effects on cardiovascular outcomes		Effects on kidney outcomes		Effects on MASH outcomes	Route of administration	Cost	Clinical considerations
				MACE[a]	Heart failure[a]	Progression of CKD[a]	Dosing/use considerations[b]				
TZDs	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in kidney impairment due to potential for fluid retention	Potential benefit	Oral	Low	• Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (edema; heart failure) • Benefit in MASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and edema
Sulfonylureas (second-generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glibenclamide (known as glyburide in the U.S. and Canada): generally not recommended in CKD Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	Unknown	Oral	Low	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be safe (see text) • Use with caution in people at risk for hypoglycemia
Insulin (human insulin and analogs)	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	Unknown	• s.c.; inhaled (human insulin) • s.c. (analogs)	• Low (s.c.) (human insulin) • High (analogs)	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs • Risk of hypoglycemia and duration of activity increases with severity of impaired kidney function

[a]Medications listed in alphabetical order. [b]For agent-specific dosing recommendations, please refer to manufacturers' prescribing information. CV, cardiovascular; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; T2D, type 2 diabetes.

agonist tirzepatide. Although these treatments were initially introduced as glucose-lowering agents, they are now increasingly prescribed for other indications and used for glycemic and weight management and organ protection. As highly effective weight loss therapies have evolved, preservation of muscle mass and physical function are emerging as important considerations (42,43).

There is increasing recognition of global threats to metabolic and mental health, including lack of access to care, poverty, food and employment insecurity, deportation, discrimination, stigmatization, disinformation, climate change, water and air quality, societal strife, and personal isolation and loneliness (44,45). The potential impact of these global issues is likely greater on people living with type 2 diabetes compared with the general population (44,46). Although beyond the scope of this consensus statement, the authors strongly endorse global collaboration to stem these trends.

The importance of the principles of care as elucidated in the previous version of this consensus statement (2,3) remains undiminished. For brevity, these critical issues are addressed in the section "Putting It All Together: Strategies for Implementation," which encompasses communication between health care providers and people living with type 2 diabetes (language matters), DSMES, individualized approaches, treatment behaviors, persistence, weight reduction, use of diabetes technology, and therapeutic inertia.

THERAPEUTIC OPTIONS: HEALTHY LIFESTYLE BEHAVIORS, WEIGHT MANAGEMENT, AND PHARMACOTHERAPY FOR THE TREATMENT OF TYPE 2 DIABETES

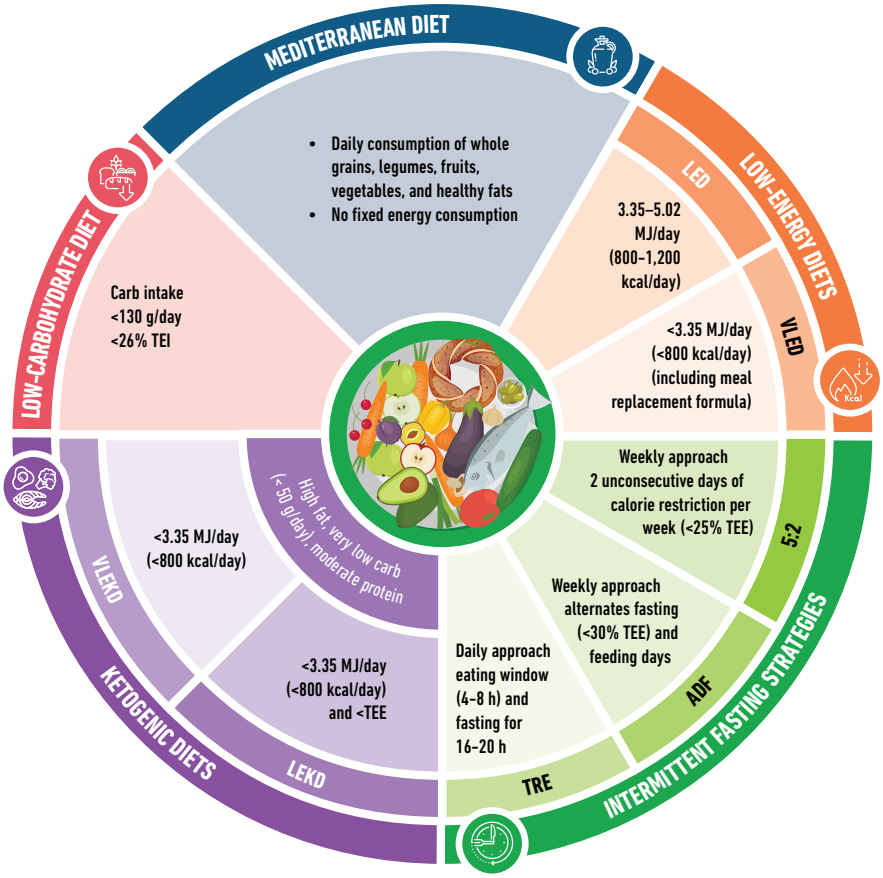
This section summarizes the lifestyle and behavioral therapy, weight management interventions, and pharmacotherapy that support the management of people with type 2 diabetes. Specific pharmacological treatment options are summarized in Table 1. Additional details are available in the previous ADA/EASD consensus report (2,3) and the ADA's 2026 "Standards of Care in Diabetes" (47,48).

MNT

MNT refers to a personalized dietary intervention (49). This is integral to type 2 diabetes management, with evidence supporting

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DIETARY PATTERNS AND METABOLIC EFFECTS IN PEOPLE LIVING WITH TYPE 2 DIABETES



MEDITERRANEAN DIET	
• **Mediterranean diet**	• Sustainable long-term metabolic and CV benefits, even in the absence of substantial weight loss • Modulation of gut microbiota, improving insulin sensitivity, inflammation, oxidative status, and overall metabolic health
LOW-ENERGY DIETS	
• **Low-energy diet (LED)**	• Effective strategy for weight loss and glycemic management in T2D with obesity • Can lead to T2D remission in the long term if implemented early in disease course (DiRECT 5-year follow-up), athough prolonged remission is infrequent
• **Very-low-energy diet (VLED)**	• VLED and formula meal replacement – highly effective approaches for weight management in T2D in the short term • VLED with total diet replacement induction phase – highly effective for T2D remission, with most of the evidence restricted to 1 year or less • Adherence challenges; of limited long-term sustainability; and may require medical supervision
INTERMITTENT FASTING STRATEGIES	
With focus on energy restriction: • **5:2 fasting** • **Alternate-day fasting (ADF)**	• 5:2 intermittent fasting leveraging formula meal replacement over 12–16 weeks provides greater benefit for HbA_{1c}, weight reduction, and other metabolic outcomes than oral glucose-lowering medications or lifestyle therapy
With focus on timing: • **Time-restricted eating (TRE)**	• Beneficial effect on HbA_{1c}, body weight loss, lipids in the short term • More effective for weight loss than energy restriction, with similar reduction in HbA_{1c} • Adherence challenges, especially with prolonged fasting; individual variability in response
KETOGENIC DIETS	
• **Low-energy ketogenic diet (LEKD)** • **Very-low-energy ketogenic diet (VLEKD)**	• Significant improvement in blood glucose, HbA_{1c}, body weight, waist circumference, lipids vs. non-ketogenic diets • Offers rapid metabolic benefits • Concerns over adherence and safety; may require medical support/supervision, particularly in patients taking SGLT2 inhibitors
LOW-CARBOHYDRATE DIETS	
• **Low-carbohydrate diets (LCD)**	• Beneficial effect on glucose management, insulin resistance, body weight, waist circumference, lipids, and blood pressure vs. control diets • Decreased requirement for glucose-lowering medications over the intermediate to long term • Low-carbohydrate breakfast – significantly lower glycemic variability and higher TIR vs. a low-fat breakfast

Figure 2—Dietary patterns and metabolic effects in people living with type 2 diabetes. CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2; TEE, total energy expenditure; TEI, total energy intake; TIR, time in range; T2D, type 2 diabetes.

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its key role in improving glucose levels and reducing diabetes-related complications in individuals with and without obesity. Core dimensions of MNT include energy intake restriction and diet quality, with weight loss often being the primary objective.

Diet Quality and Eating Patterns

There is no single ratio of carbohydrate, protein, and fat intake that is optimal for every person with type 2 diabetes. Instead, we recommend tailoring personalized eating patterns that emphasize foods with demonstrated health benefits, minimize foods shown to be harmful, and accommodate individual preferences with the goal of developing healthy dietary habits that are feasible and sustainable. Both the quality and the quantity of foods are crucially important (Fig. 2).

The Mediterranean diet has consistently demonstrated metabolic and cardiovascular benefits, along with improved glucose levels, even in the absence of substantial weight reduction (50–52). This diet provides greater benefit than a low-fat diet for preserving kidney function in people with type 2 diabetes and obesity and for reducing cardiovascular events in people with coronary heart disease (53,54). Other diets have demonstrated short-term metabolic benefits, but long-term safety and efficacy remain an area of question and interest (55).

Ketogenic diets encompass a broad range of nutritional interventions that vary both in the degree of carbohydrate restriction and in their energy composition. Ketogenic diets have shown some short-term benefits on glucose levels, insulin sensitivity, and other metabolic outcomes, often preceding substantial weight loss. However, these diets should be balanced by the need to consider safety concerns and consider medication adjustment to mitigate both risk of hypoglycemia and ketoacidosis risk, particularly with concomitant SGLT2 inhibitor use (50,56,57).

Dietary interventions providing different amounts of carbohydrates have been proposed as a means of achieving improved glycemic management and weight loss in people living with type 2 diabetes. Low-carbohydrate diets have demonstrated beneficial effects on glucose management and body weight in people living with type 2 diabetes and overweight or obesity in the short term, decreasing the requirement for glucose-lowering medications (58–60).

There has been increasing interest in time-restricted eating and intermittent fasting strategies, such as alternate-day fasting or the 5:2 model in which weekly eating is normal for 5 days and daily energy intake is reduced to 2.09–2.51 MJ (500–600 kcal) on two nonconsecutive days (61–65). Intermittent fasting is relatively safe and effective in people with type 2 diabetes, although caution in the setting of specific glucose-lowering medications, such as insulin, is required. Such interventions can be challenging to sustain in the long term, particularly prolonged fasting, and individual variability in response must be acknowledged (50). A 5:2 intermittent fasting meal replacement strategy demonstrated greater HbA_{1c} reduction and weight loss over 16 weeks compared with metformin or an SGLT2 inhibitor (66). Time-restricted eating has been associated with greater weight loss compared with restriction of daily energy intake, with similar reduction in HbA_{1c} (67). The long-term efficacy and safety of these approaches require further investigation.

A meta-analysis of 22 trials has demonstrated that both Mediterranean diet and intermittent fasting effectively improve glycemic management, lipid profiles, and anthropometric measurements in people with type 2 diabetes, with the former offering more consistent and sustainable long-term benefits (51). A network meta-analysis of 42 RCTs, comprising 4,809 people with type 2 diabetes, comparing ten dietary approaches, has demonstrated that ketogenic, Mediterranean, moderate-carbohydrate, and low-glycemic-index diets have promising effects for lowering HbA_{1c} significantly related to weight loss (68).

Nonsurgical Energy Restriction for Weight Loss

An overall healthy eating plan that results in an energy deficit, in conjunction with medications and/or metabolic surgery, supports glycemic and weight management goals in adults with type 2 diabetes. Structured medical nutrition and lifestyle programs may be considered for glycemic benefit and can be adapted for specific cultural indications (2,3). Very-low-energy diets and formula meal replacement are highly effective for weight loss in the short term, with limited evidence on long-term sustainability (69). They offer a method of achieving clinically meaningful weight loss and improvements in microvascular and macrovascular outcomes (70), particularly when access to medications is limited. The greatest improvements in outcomes are achieved through sustained weight loss and lifestyle change rather than dietary composition itself.

The Diabetes Remission Clinical Trial (DiRECT) demonstrated that a structured low-energy diet, involving total diet replacement formula followed by stepped food reintroduction and behavioral support for weight loss maintenance, delivered in primary care, resulted in type 2 diabetes remission in 46% of participants at 1 year (71,72) and sustained remission at 2 years correlated with the extent of sustained weight loss. At 5 years, participants who continued to receive low-intensity support maintained a mean weight loss of 6.1 kg, with 13% (7% of the original intervention group) achieving type 2 diabetes remission (73). Thus, long-term sustainability of remission with this approach remains challenging (73).

Intensive lifestyle intervention in the Look AHEAD trial led to broad improvements in health outcomes but no reductions in cardiovascular events (74). However, in those with evidence of hyperglycemia remission at a single point in time there was a 33% lower rate of CKD and 40% lower rate of composite CVD, with the greatest effect being seen in those with longer-term remission (75).

Several determinants of diabetes remission have been identified, including younger age, shorter diabetes duration, higher β-cell function, greater weight loss, and greater energy deficit (76–78).

Dietary Supplements

Numerous dietary supplements, including pre-/pro- and synbiotics, berberine, curcumin, fenugreek, okra, propolis and resveratrol, have been studied for their potential role in managing type 2 diabetes and its complications. The evidence of benefit is inconclusive (79–84). Studies of vitamin D in type 2 diabetes have been completed, with very modest effects seen on HbA_{1c}. Current evidence does not support its use for glycemic management (85–88).

Consensus Recommendations

- An overall healthy eating plan that results in an energy deficit, in conjunction with medications and/or metabolic surgery as individually appropriate, should be considered to support glycemic and weight management goals in adults with type 2 diabetes and overweight or obesity.

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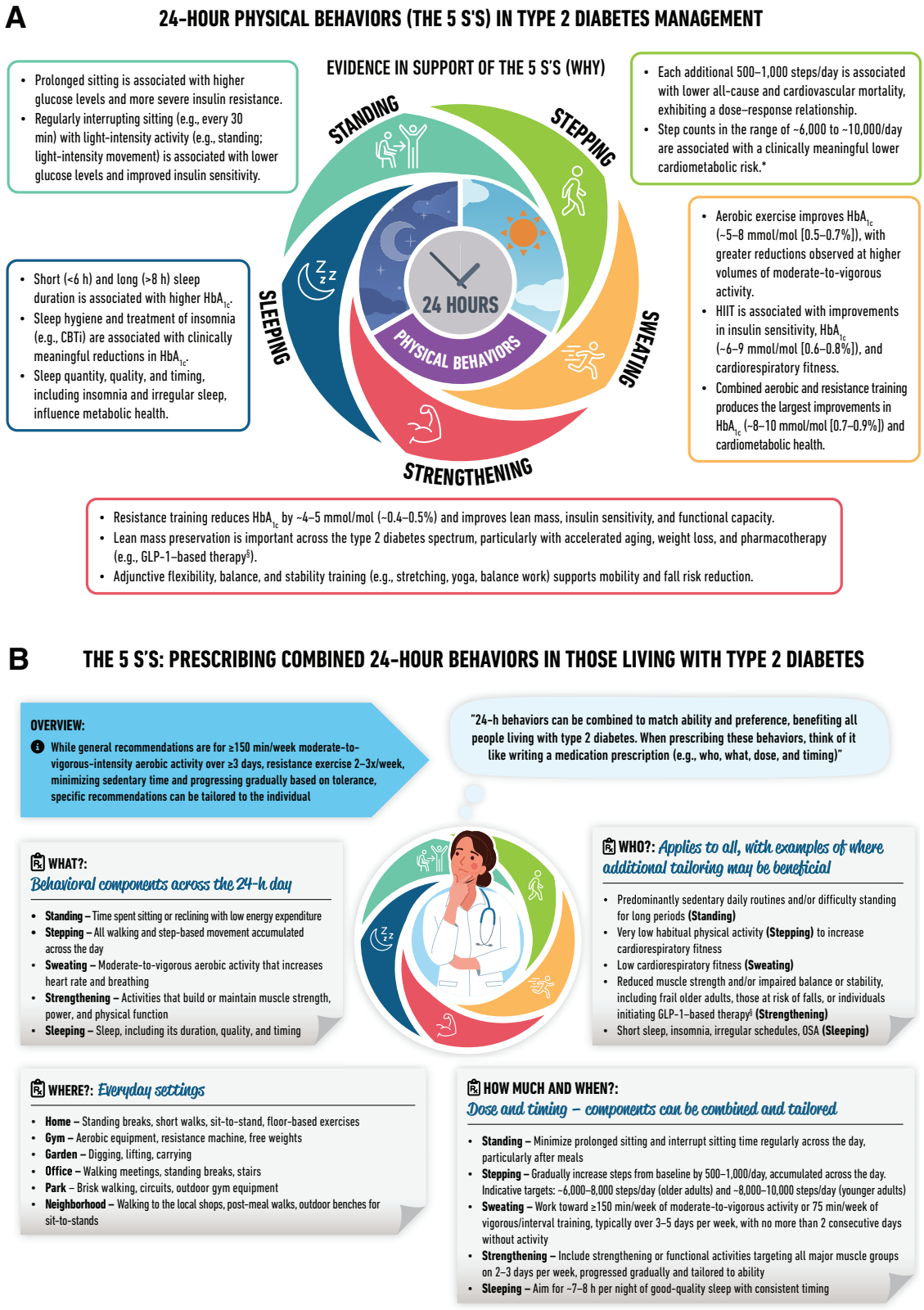


Figure 3—*A*: Behaviors (the five S's) in type 2 diabetes management. *Evidence specific to established type 2 diabetes is limited; step targets are therefore inferred from population-level meta-analyses. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. CBTi, cognitive behavioral therapy for insomnia; HIIT, high-intensity interval training. *B*: The five S's: prescribing combined 24-h behaviors in those living with type 2 diabetes. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. OSA, obstructive sleep apnea.

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- MNT focused on identifying healthy dietary habits that are feasible and sustainable is recommended.
- Structured medical nutrition and lifestyle programs should be adapted for specific cultural context.
- Consider offering intensive lifestyle therapy aiming for 10% or greater weight loss with the possibility of remission. Achieving remission of type 2 diabetes at any time may have long-term benefits.
- A Mediterranean dietary pattern should be preferentially considered in people with type 2 diabetes and established ASCVD, where feasible and acceptable to the individual.
- Specific dietary supplements are not recommended for glycemic management in people with type 2 diabetes.

Physical Activity Behaviors

The management of type 2 diabetes is increasingly guided by a 24-h behavioral approach, in which the five S's (standing, stepping, sweating, strengthening, and sleep) provide a practical, evidence-informed framework that brings together daily movement and rest patterns to support cardiometabolic health. This perspective emphasizes that improvements in glucose levels, cardiovascular risk, functional capacity, and cognitive health arise not only from structured exercise but also from the distribution of sedentary time, light movement, and sleep across the day. Embedding behavioral care within the five S's supports personalized recommendations that reflect real-world patterns of activity, rest, and circadian rhythm, helping people living with type 2 diabetes to translate small, sustainable adjustment into meaningful cardiometabolic benefit. With growing evidence for "lifestyle as medicine" in type 2 diabetes, this framework supports shared, person-centered decision-making across 24-h behaviors (Fig. 3).

Within this framework, structured exercise ("sweating") remains pivotal, with widespread benefits across physiological (e.g., fitness, adiposity, and cardiovascular risk factors) and psychological (e.g., quality of life and depressive symptoms) markers of health (89,90). Meta-analyses of exercise training trials in people living with type 2 diabetes consistently demonstrate that regular moderate-to-vigorous aerobic activity produces clinically meaningful reductions in HbA_{1c} (~5–8 mmol/mol [~0.5–0.7%]) (91–93), with greater improvements observed at higher volumes of activity (94–96). High-intensity interval training also improves HbA_{1c}, insulin sensitivity, and fitness, supporting its role as a time-efficient modality, particularly when higher-volume training is impractical (92,93,95,97).

Extending beyond aerobic modalities alone, evidence consistently shows that programs combining aerobic and resistance exercise produce the largest overall improvements in HbA_{1c} (~8–10 mmol/mol [~0.7–0.9%]) and broader cardiometabolic health (91,92,98), with adjunctive flexibility, stability, and mind-body modalities (e.g., yoga) supporting functional capacity and balance (89,90). Resistance exercise independently improves insulin sensitivity, HbA_{1c} (~4–5 mmol/mol [~0.4–0.5%]), preserves lean mass, and supports functional capacity, reinforcing "strengthening" as a core therapeutic lever in type 2 diabetes, particularly in phenotypes at risk for muscle loss (91,92,95,98,99). This priority becomes even more pressing in the context of weight loss (12,42,100). Recent body composition analyses from large pharmacotherapy trials, including SURMOUNT-1, indicate that approximately 25–40% of total weight loss achieved with GLP-1–based therapies reflects lean mass loss (101,102), highlighting the importance of embedding both "strengthening" and "sweating" activities to preserve function and mitigate accelerated skeletal muscle ageing.

Beyond structured sessions, sedentary behavior represents an independent, modifiable risk factor. RCTs demonstrate that breaking up prolonged sitting with brief bouts of walking or simple resistance activities lowers postprandial glucose and insulin levels (103–105). These findings are supported by recent systematic reviews and network meta-analysis, which identify regular sitting interruptions, particularly involving light-intensity movement, as effective strategies for improving acute glucose and insulin regulation across the day (106–108).

"Stepping" behaviors provide an additional scalable target within the same 24-h behavioral framework. Evidence drawn predominantly from large population-based cohort studies and meta-analyses demonstrates a consistent dose-response association between daily step count and cardiometabolic outcomes, with each additional 500–1,000 steps/day associated with lower all-cause mortality and cardiovascular events (109). Step counts in the range of ~6,000–10,000/day are associated with a clinically meaningful lower cardiometabolic risk (110–112), and while diabetes-specific evidence remains more limited, these population-based findings support gradual progression in daily steps in people with type 2 diabetes.

Finally, "sleep" completes the 24-h behavioral cycle. Both sleep quantity and quality show U-shaped or graded associations with HbA_{1c}, while observational evidence suggests that irregular sleep timing and later chronotype are associated with less favorable metabolic profiles (113–118). Clinical trials of behavioral sleep interventions, including cognitive behavioral therapy for insomnia, further indicate that improving sleep quantity and quality can lead to clinically meaningful reductions in HbA_{1c} (119). Improvements in sleep quality and duration and reductions in HbA_{1c} can also be achieved through simple changes to sleep hygiene (e.g., consistent sleep schedule, limiting exposure to bright light and screens in the evenings, and avoiding consumption of caffeine in the afternoon and evening) (120). Together, these findings support a personalized approach that considers sleep duration, quality, and timing alongside other physical activity behaviors.

Consensus Recommendations

- The five S's (increasing standing, increasing stepping, incorporating sweating [aerobic] physical activity and strengthening [resistance exercise], and ensuring adequate quality, quantity, and timing of sleep) are fundamental to glycemic management and holistic care in type 2 diabetes.
- Counsel and support adults with type 2 diabetes to progressively increase physical activity volume and intensity beyond minimum thresholds when feasible and safe, given the dose-related benefits on glucose levels, cardiometabolic outcomes, and overall well-being. It is important to consider the presence of MLTCs and frailty status.
- A combination of aerobic and resistance/strength activity, aiming for a minimum of 150 min/week of moderate-to-vigorous-intensity aerobic activity (or 75 min vigorous) accumulated over ≥3 days per week, with sessions typically lasting ~30 min, is recommended.

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- Resistance exercise should be included 2–3 times per week, with intensity and progression adjusted according to individual tolerance and functional capacity, and in the context of individual MLTCs and frailty status.
- Resistance exercise should be encouraged during weight loss interventions to help preserve skeletal muscle mass and strength.
- Alongside regular structured exercise, reductions in sedentary time, increases in daily movement, and optimization of sleep should be recognized and supported.

Medications for Lowering Glucose

Cardio-Kidney–Protective Glucose-Lowering Medications

SGLT2 Inhibitors. SGLT2 inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose. They have high glucose-lowering efficacy, with lower efficacy at lower estimated glomerular filtration rates (eGFR). However, their scope of use has significantly expanded based on cardiovascular and kidney outcome studies (2,3,121). Cardiovascular and kidney outcome trials have demonstrated their efficacy in the following outcomes:

- reducing the risk of composite major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, hospitalization for heart failure (HHF), and all-cause mortality in individuals with type 2 diabetes with an established/high risk of CVD
- improving kidney outcomes, including reducing the risk of significant loss of kidney function, development of kidney failure, and kidney and cardiovascular mortality, in individuals with type 2 diabetes with established CKD.

This is discussed further in the section "Personalized Approach to Treatment Based on Individual Characteristics and MLTCs" below. Evidence supporting their use is summarized in Table 1. Although the different SGLT2 inhibitors have not been compared in randomized studies, target trial emulation studies have suggested similar cardiovascular benefit (122).

Recent data have increased confidence in the safety of the SGLT2 inhibitor class (121,123). Their use is associated with increased risk for mycotic genital infections, which are reported to be typically mild and treatable. While SGLT2 inhibitor use can increase the risk of diabetic ketoacidosis (DKA) even with euglycemia, the incidence is low in type 2 diabetes (123). SGLT2 inhibitor cardiovascular outcome trials (CVOTs) have reported DKA rates of 0.1–0.6% compared with rates of <0.1–0.3% for placebo (124–128), with very low rates in the heart failure (129–132) and CKD (133–135) outcome studies. Guidelines suggest that risk may be mitigated with education and guidance, including education on signs and symptoms of DKA, and temporary discontinuation of the medication in clinical situations that predispose to DKA (e.g., prolonged fasting or carbohydrate restriction, surgery, acute illness, infection, insulin omission, or dose reduction) (48,136–141).

While early studies brought attention to several safety-related areas of interest (acute kidney injury [AKI], dehydration, orthostatic hypotension, amputation and fractures), longer-term studies that have prospectively assessed and monitored these events have not seen a significant imbalance in risks (142,143). Analyses based on those included in heart failure and CKD studies suggested similar benefit regardless of frailty among study participants (144,145). Recent register-based studies suggest the benefit can be extended to older people (aged >70 years) (146). Analyses of SGLT2 inhibitor outcome trial data also suggest that people with type 2 diabetes and peripheral arterial disease (PAD) derive greater absolute outcome benefits from SGLT2 inhibitor therapy than those without PAD, with no increase in risk of major adverse limb events (MALE) (147). In post hoc analyses, SGLT2 inhibitor use has been associated with reduced incidence of serious and nonserious kidney-related adverse events in people with type 2 diabetes and CKD and greater full recovery from AKI (148).

GLP-1 RAs. GLP-1 RAs augment glucose-dependent insulin secretion and glucagon suppression, decelerate gastric emptying, curb postmeal glycemic increments, and reduce appetite, energy intake, and body weight (149). In addition to their physiological effects, GLP-1 RAs have been shown to influence health behaviors, such as shifting food-purchasing patterns toward minimally processed foods (150). Beyond improving HbA_{1c} in adults with type 2 diabetes, specific GLP-1 RAs have received regulatory approval for the following:

- reducing risk of MACE in adults with type 2 diabetes with established CVD (dulaglutide, liraglutide, and subcutaneous [s.c.] as well as oral semaglutide) or multiple CVD risk factors (dulaglutide)
- reducing the risk of progression of CKD in adults with type 2 diabetes and CKD (s.c. semaglutide) (Table 1)
- improving heart failure symptoms in individuals with heart failure with preserved ejection fraction (HFpEF), type 2 diabetes, and obesity (s.c. semaglutide) (151)
- improving liver histological findings in people with MASLD and moderate or advanced liver fibrosis (s.c. semaglutide) (152)
- chronic weight management (s.c. liraglutide 3.0 mg once daily; s.c. semaglutide 1.7 mg, 2.4 mg, or 7.2 mg once weekly; oral semaglutide 25 mg daily; and oral orforglipron [a GLP-1 RA now licensed in the U.S. for weight management] 17.2 mg daily) (153).

Whereas initial GLP-1 RAs were injectable peptides (s.c. injection), oral formulations of semaglutide are available (154). Orforglipron is a small-molecule GLP-1 RA without food or water dosing restrictions. It has demonstrated greater reductions in HbA_{1c} and body weight than oral semaglutide (7–14 mg) but is currently only indicated for weight management (155). Higher doses of dulaglutide (3.0 and 4.5 mg) have been approved for glycemic management, and subcutaneous (s.c.) semaglutide (7.2 mg) and oral semaglutide (25 mg) for weight management. Studies have demonstrated incremental benefits of these higher doses for both glycemic and weight management (156–159).

Dual GLP-1/GIP Agonists. Many nutrient-stimulated hormone-based medications and combinations are currently in development beyond GLP-1 RAs. The first of these, the dual GLP-1/GIP agonist tirzepatide, is approved for once-weekly s.c. administration to improve glucose levels in adults with type 2 diabetes and for weight management as an adjunct to healthy eating and exercise. Mechanistically, GLP-1 and GIP have overlapping and distinct effects (160) and, clinically, tirzepatide appears to be more effective than GLP-1 RAs for HbA_{1c} and weight reduction. Across the SURPASS program, tirzepatide demonstrated superior glucose-lowering efficacy to placebo, s.c. semaglutide 1.0 mg,

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insulin degludec, and insulin glargine. For HbA_{1c}, placebo-adjusted reductions of ~22 mmol/mol (~2%) and mean weight reductions of 7–9.5 kg were seen across doses. Up to 62% of those treated with tirzepatide reached an HbA_{1c} of <39 mmol/mol (5.7%) and up to 68% lost more than 10% of their baseline body weight (161).

Additional metabolic benefits included the following:

- improvements in liver fat content and reduced visceral and subcutaneous abdominal adipose tissue volume (162)
- improved symptoms in individuals with OSA and obesity (163) and HFpEF and obesity (164)
- in the SURPASS-CVOT, participants with type 2 diabetes and ASCVD were randomized to tirzepatide or the GLP-1 RA dulaglutide, which was previously proven to reduce the risk of MACE. Tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke (hazard ratio [HR] 0.92 [95.3% CI 0.83, 1.01]) and had similar incidence of serious adverse events but more gastrointestinal side effects (165)
- in an analysis comparing putative placebo from the REWIND study and participants from SURPASS-CVOT for an indirect treatment effect comparison, tirzepatide versus putative placebo was associated with lower three-point MACE (HR 0.72 [95% CI 0.55, 0.94]), death from cardiovascular cause or heart failure events (HR 0.70 [95% CI 0.51, 0.96]), and all-cause death (HR 0.61 [95% CI 0.45, 0.82]), suggesting cardiovascular benefit of tirzepatide in this indirect comparison (166). Tirzepatide received regulatory approval to reduce the risk of MACE in adults with type 2 diabetes at high risk for these events.

GLP-1–Based Therapies (Both GLP-1 RAs and the Dual GLP-1/GIP Agonist Tirzepatide): Safety and Tolerability. The most common side effects of GLP-1–based therapies are gastrointestinal in nature (nausea, vomiting, diarrhea, and constipation), tending to occur during initiation and dose escalation and diminish over time. Education should be provided when initiating GLP-1–based therapy. Slower or flexible dose escalations can be considered in the setting of gastrointestinal intolerance (167,168).

Data from CVOTs on other safety areas of interest (pancreatitis, pancreatic cancer, medullary thyroid cancer, retinopathy, and suicide) indicate that there is no increase in these risks with GLP-1 RAs in the populations studied (169). Gallbladder and biliary events occur at higher rates (27/10,000 person-years) with GLP-1 RAs versus placebo or non–GLP-1 RA medications, particularly at higher doses, longer duration, and when used for weight loss rather than glycemic management (170). GLP-1–based therapies (except lixisenatide and twice-daily exenatide) are contraindicated in people at risk for the rare medullary thyroid cancer (i.e., those with a history or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2); this is related to rodent studies in which thyroid C cell tumors were more common with GLP-1 RA treatment than with placebo. GLP-1–based therapies may increase the risk of progression of diabetic retinopathy, perhaps related to rapid improvement in glucose levels, so baseline and ongoing retinal monitoring is recommended. An excess of nonarteritic anterior ischemic optic neuropathy (NAION) was reported in people with obesity or type 2 diabetes treated with semaglutide compared with non–GLP-1 RA treatment (HR 4.28 [95% CI 1.62, 11.29]) (171). Subsequent studies demonstrated that NAION is associated with obesity and diabetes and is very rare (1 case per 10,000 person-years of semaglutide exposure), although its relationship to semaglutide remains unclear (172).

Metformin

Because of its high efficacy in lowering HbA_{1c}, minimal hypoglycemia risk when used as monotherapy, weight neutrality with the potential for modest weight loss, good safety profile, and low cost, metformin has traditionally been recommended as first-line glucose-lowering therapy for the management of type 2 diabetes. However, there is increasing evidence that other approaches may be appropriate in some populations. Notably, the benefits of GLP-1 RAs and SGLT2 inhibitors for cardiovascular and kidney outcomes have been found to be independent of metformin use and, thus, these agents should be used in people with established or high risk of CVD, heart failure, or CKD, independent of metformin use (173–175). That said, these data come from subgroup analyses not protected by randomization, so the evidence is not definitive, and some may prefer to continue metformin when initiating GLP-1–based therapies or SGLT2 inhibitors. Metformin should not be used in people with an eGFR <30 mL/min per 1.73 m^2, and dose reduction should be considered when the eGFR is <45 mL/min per 1.73 m^2 (176). Metformin use may result in lower serum vitamin B_{12} concentrations and worsening of symptoms of neuropathy; therefore, periodic monitoring and supplementation are generally recommended if levels are deficient (177,178).

Other Glucose-Lowering Medications

Dipeptidyl Peptidase 4 Inhibitors. Dipeptidyl peptidase 4 (DPP-4) inhibitors are oral medications that inhibit the enzymatic inactivation of endogenous incretin hormones (GLP-1 and GIP), resulting in glucose-dependent insulin release and a decrease in glucagon secretion. They have moderate glucose-lowering efficacy, are generally considered to be weight neutral (179), and are well tolerated with minimal risk of hypoglycemia. CVOTs have demonstrated the cardiovascular safety, without cardiovascular risk reduction, of the DPP-4 inhibitors saxagliptin, alogliptin, sitagliptin, and linagliptin (180). As a class, DPP-4 inhibitors are associated with modest reduction in urine albumin-creatinine ratio (UACR) without significant effect on eGFR (181).

DPP-4 inhibitors have a favorable safety profile with minimal side effects. A meta-analysis suggests an increased risk of composite gallbladder/biliary disease and cholecystitis versus placebo or other glucose-lowering medications (relative risk [RR] 1.38 [95% CI 1.08, 1.75]), with higher risk seen in older adults and with longer duration of use (182). An increased risk of HHF was found with saxagliptin versus placebo, and there have been rare reports of arthralgia and hypersensitivity reactions with the DPP-4 inhibitor class (183). The high tolerability and modest efficacy of DPP-4 inhibitors may mean that they are suitable for specific populations, such as in older adults with mild hyperglycemia or in individuals with high risk of hypoglycemia. They are also an oral option in those with low eGFR (Table 1).

Sulfonylureas. Sulfonylureas have high glucose-lowering efficacy, are inexpensive,

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and are broadly accessible, but they lack a durable effect and increase the risk for hypoglycemia and weight gain (184). Use of sulfonylureas or insulin for early, more intensive blood glucose management in the UK Prospective Diabetes Study (UKPDS) significantly decreased the risk of microvascular complications (185). Findings from systematic reviews and real-world studies suggest no increase in all-cause mortality rates with sulfonylureas compared with other active treatments (184,186). There may be heterogeneity across the class; specifically, glimepiride has demonstrated cardiovascular safety in comparison with the DPP-4 inhibitor linagliptin (187).

Thiazolidinediones. Thiazolidinediones (TZDs) are oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy (188–191). TZDs have a high durability of glucose response, most likely through an effect on preservation of β-cell function (192). In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) in adults with type 2 diabetes and macrovascular disease, a reduction in secondary cardiovascular end points was seen, although significance was not achieved for the primary outcome (193). In the Insulin Resistance Intervention After Stroke (IRIS) study in adults without diabetes but with insulin resistance and recent history of stroke or transient ischemic attack, there was a lower risk of stroke or myocardial infarction with pioglitazone versus placebo (194,195). Beneficial effects on MASLD and metabolic dysfunction–associated steatohepatitis (MASH) have been seen with pioglitazone (196,197). However, these benefits must be balanced against the possible side effects of fluid retention and congestive heart failure (192,193,198), weight gain (192–194,198,199), and bone fracture (200,201) and possible increased risk of bladder cancer (202). Side effects can be mitigated by using lower doses and combining TZD therapy with other medications (SGLT2 inhibitors and GLP-1–based therapies) that promote weight loss and sodium excretion (203).

Insulin

The primary advantage of insulin therapy is that it lowers glucose in a dose-dependent manner and thus can address almost any level of blood glucose. However, its efficacy and safety are largely dependent on the education and support provided to facilitate self-management (188–191). Careful consideration should be given to the pharmacokinetic and pharmacodynamic profiles of the available insulins as well as the matching of the dose and timing to an individual's physiological requirements (Supplementary Fig. 1).

Detailed descriptions of different insulins have been given in previous reports (188–191). The preferred way of initiating insulin in people with type 2 diabetes is to give basal insulin (Supplementary Fig. 1). A modest but significant reduction in HbA_{1c} and the risk of total and nocturnal hypoglycemia has been observed for basal insulin analogs versus intermediate-acting (NPH) insulin (204). Rapid- and ultra-rapid-acting insulin can be added to basal insulin to intensify therapy to address prandial blood glucose levels. Premixed insulins combine basal insulin with mealtime insulin (short- or rapid-acting) in the same vial or pen. Premixed insulin may offer convenience for some but reduces treatment flexibility. Analog-based mixtures may be timed in closer proximity to meals. Education on the impact of dietary nutrients on glucose levels to reduce the risk of hypoglycemia while using mixed insulin is important. Insulins with different routes of administration (inhaled, bolus-only insulin delivery patch pump) are also available (205–207).

Once-weekly insulins have now been developed, with once-weekly insulin icodec being approved for type 2 diabetes in some regions, including the U.S. and Europe. Once-weekly insulin icodec was found to reduce HbA_{1c} significantly more than glargine U-100 in insulin-naive adults with type 2 diabetes (estimated between-group difference [ETD] −0.19% [95% CI −0.36, −0.03]) (208). While overall rates of hypoglycemia were low, rates of combined clinically significant or severe hypoglycemia were higher with insulin icodec than with insulin glargine U100 (208). In a participant-level meta-analysis of the ONWARDS program, icodec had greater glucose-lowering efficacy compared with daily basal insulin comparators (ETD −0.10 to −0.29%); the incidence of clinically significant hypoglycemia was similar, although with higher event rates, equating to approximately one extra clinically significant hypoglycemic episode per person every 7 years (209).

Once-weekly insulin efsitora alfa has completed its phase III clinical development program in type 2 diabetes but is not approved as of June 2026. Insulin efsitora alfa was found to be noninferior to insulin glargine and insulin degludec, with similar reductions in HbA_{1c} in QWINT-1 and QWINT-2, respectively (210,211). QWINT-4 evaluated once-weekly insulin efsitora alfa compared with insulin glargine U100 in the treatment context of basal-bolus insulin therapy, demonstrating noninferiority for glucose-lowering efficacy, with no difference in hypoglycemia (212).

Combination GLP-1 RA–Insulin Therapy. Two fixed-ratio combinations of GLP-1 RA with daily basal insulin analog are available: insulin degludec plus liraglutide (IDegLira) and insulin glargine plus lixisenatide (iGlarLixi). In addition, a once-weekly formulation of insulin icodec plus semaglutide is available in Europe, based on the COMBINE trials in adults with type 2 diabetes (213–215). The combination of basal insulin with GLP-1 RA results in greater glucose-lowering efficacy than the monocomponents, with less weight gain and lower rates of hypoglycemia than with intensified insulin regimens and better gastrointestinal tolerability than with GLP-1 RA alone (213,214,216,217).

Less Commonly Used Glucose-Lowering Medications

α-Glucosidase inhibitors improve glucose levels by reducing postprandial glucose excursions and may provide specific benefits in those with high carbohydrate consumption or reactive hypoglycemia (218,219). Other glucose-lowering medications (i.e., meglitinides, colesevelam, quick-release bromocriptine, and pramlintide) are not commonly used in the U.S. for type 2 diabetes, and most are not licensed in Europe. There was no new evidence that impacts clinical practice.

Combination of Glucose-Lowering Therapies

The underlying pathophysiology of type 2 diabetes is complex, with multiple contributing abnormalities resulting in a naturally progressive disease and increasing HbA_{1c} over time in many individuals with the disease. Increasing data suggest benefits of combination approaches early on in diabetes care.

Combination of SGLT2 Inhibitors and GLP-1–Based Therapies

Studies of concomitant SGLT2 inhibitors and GLP-1–based therapy show benefits for HbA_{1c}, BP, and weight (220,221).

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Prespecified and post hoc subgroup analyses demonstrate that adding an SGLT2 inhibitor to background GLP-1–based therapy or vice versa may further reduce cardiovascular risk (220,222–225). Therefore, the use of a combination of SGLT2 inhibitor and GLP-1–based therapy can be considered to improve glucose levels (especially adding GLP-1–based therapy to an SGLT2 inhibitor) and cardiovascular and kidney outcomes (226).

Other Considerations

Hypercortisolism. Hypercortisolism may be associated with hyperglycemia in approximately one-quarter of individuals with inadequate glycemic management despite multiple medications (20). Baseline characteristics that increase the odds of having hypercortisolism include older age, lower BMI, higher medication burden for hypertension, taking analgesics or fibrates, and taking SGLT2 inhibitors, tirzepatide, and high-dose GLP-1 RAs. In individuals with an HbA_{1c} of above 58 mmol/mol (7.5%) despite multiple glucose-lowering medications and non–ACTH-dependent hypercortisolism, cortisol-directed medical therapy with mifepristone reduced HbA_{1c} substantially and may be beneficial for the management of hyperglycemia (227). However, treatment was associated with high rates of adverse events and withdrawal symptoms; these should be managed proactively and by employing mineralocorticoid receptor antagonists (MRAs) to avoid hypokalemia, as appropriate. Mifepristone is currently only approved in the U.S. Other cortisol-directed therapies are available but have not been tested in this context.

Nonsteroidal MRAs. For decades, mineralocorticoid receptor agonists (MRAs) (spironolactone and eplerenone) have been used in heart failure with reduced ejection fraction (HFrEF) and in resistant hypertension. In CKD, these agents have not been used due to side effects including high risk for hyperkalemia. Recently, nonsteroidal MRAs have been tested in type 2 diabetes with CKD, with most data available on finerenone. Two phase III trials in type 2 diabetes with CKD (FIGARO-DKD and FIDELIO-DKD) included participants with eGFR 25–90 mL/min per 1.73 m^2 and UACR >3.0 mg/mmol (>30 mg/g) on maximal tolerated renin-angiotensin system inhibitors and with potassium <4.8 mmol/L at screening (228,229). Studies were combined in a patient-level analysis, FIDELITY, and among 13,026 people with a median follow-up of 3.0 years. The composite cardiovascular outcome was reduced with finerenone compared with placebo (HR 0.86 [95% CI 0.78, 0.95], P = 0.0018). The composite kidney outcome was also reduced (HR 0.77 [95% CI 0.67, 0.88], P = 0.0002). Overall safety outcomes were generally similar between treatment arms. Hyperkalemia leading to permanent treatment discontinuation occurred more frequently in people receiving finerenone (1.7%) than placebo (0.6%) (230).

Colchicine. It has been discussed for many years whether chronic low-grade inflammation should be targeted in individuals with ASCVD. An old and affordable drug, colchicine, has been tested in six trials including 21,000 participants for secondary prevention of MACE in established ASCVD. A recent meta-analysis suggested that it achieved a 25% relative reduction in MACE (231), with no interaction with diabetes (23% of the participants). In COLCOT, conducted in people with type 2 diabetes and a recent myocardial infarction, low-dose colchicine (0.5 mg daily) reduced cardiovascular events (232). The heterogeneity between trials, populations, and doses, as well as rare but serious side effects, calls for caution.

Weight and Body Composition Management Beyond Lifestyle Interventions

Medications for Weight Loss in Type 2 Diabetes

Weight loss medications are effective adjuncts to lifestyle interventions and healthy behaviors for the management of weight and have also been found to improve glucose levels in people with type 2 diabetes (233). Semaglutide and tirzepatide are the most effective agents, with tirzepatide showing superiority for weight reduction (234). Orforglipron, an oral small-molecule GLP-1 RA (17.2 mg oral daily), as well as higher-dose semaglutide (7.2 mg s.c. and 25 mg orally) have not been specifically compared with tirzepatide but are unlikely to be more efficacious (156,157,235,236).

Metabolic Surgery

Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates (233,237). In the Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (ARMSS-T2D) study, the rate of remission was 37.5% in the metabolic surgery group versus 2.6% in the medical/lifestyle group at 3 years; at 7 years the rate of remission was 18% in the metabolic surgery group and 6% in the medical/lifestyle group. Surgery produced improved health-related quality of life and health utility in individuals with type 2 diabetes and obesity compared with medical therapy up to 12 years after intervention. Anemia, fractures, and gastrointestinal adverse events were more common after metabolic surgery (238–240). In a meta-analysis of seven studies in individuals with type 2 diabetes and BMI <35 kg/m^2 (n = 544), metabolic surgery was more effective than nonsurgical treatment in achieving diabetes remission (odds ratio 25.06; 64% vs. 2.8%) (241). However, it is important to note that many of these estimates of benefit included data from nonrandomized studies and compared outcomes with medical treatments for obesity that were less effective than those available today (242).

In individuals with a BMI <35 kg/m^2, those with younger age, short diabetes duration, higher levels of obesity, better glucose levels, and better β-cell function were more likely to achieve diabetes remission after metabolic surgery (243). Gastric bypass is superior to sleeve gastrectomy regarding long-term remission of type 2 diabetes, weight loss, and cardiovascular risk factors, albeit at the expense of a higher frequency of symptomatic postprandial hypoglycemia (244).

Reductions in CVD, CVD mortality, and all-cause mortality among individuals with type 2 diabetes have been seen in observational and matched-cohort studies of metabolic surgery (245,246). Furthermore, metabolic surgery is also associated with a lower risk of nephropathy (245,247) and retinopathy (245) versus treatment with GLP-1 RAs and can improve liver outcomes among individuals with biopsy-proven MASH (248,249). Metabolic surgery for people with type 2 diabetes and a BMI ≥30 kg/m^2 (or ≥27.5 kg/m^2 for Asian American individuals) (250) is recommended by The American Society for Metabolic and Bariatric Surgery (251), although the European Association for the Study of Obesity framework considers metabolic surgery in

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people with a BMI ≥35 kg/m^2 with an obesity-related disease or complication or with BMI ≥30 kg/m^2 with poorly managed glucose levels despite optimal medical therapy (252).

Consensus Recommendation

- Metabolic surgery could be considered for people with type 2 diabetes and a BMI ≥30 kg/m^2 (or ≥27.5 kg/m^2 for people of Asian ancestry) and should be considered for people with a BMI ≥35 kg/m^2 (or ≥32.5 kg/m^2 for people of Asian ancestry).

Skeletal Muscle and Body Composition

Type 2 diabetes with obesity is often characterized by excess adiposity and low muscle mass/function and is referred to as sarcopenic obesity, a condition increasingly recognized for its clinical and functional features that negatively influence important person-centered outcomes (253–256).

Both obesity pharmacotherapy and metabolic surgery reduce body weight by lowering fat mass and fat-free mass. This has raised concern about the loss of fat-free mass (particularly skeletal muscle and bone) and its potential long-term consequences on strength, physical function, resting energy expenditure, and longer-term risks of frailty, sarcopenia, and sarcopenic obesity. Reported changes in lean mass vary: some studies show lean mass accounting for 40–60% of weight lost, while other studies report reductions closer to 15% (43,101,102,257–259). A recent meta-analysis in individuals living with type 2 diabetes reported a nonsignificant mean reduction in muscle mass measures with GLP-1–based therapies, despite reductions in fat mass (260). In the SURPASS-3 MRI substudy, tirzepatide improved body weight and fat distribution and was associated with favorable changes in muscle fat infiltration, and reductions in muscle volume generally aligned with the expected changes relative to weight loss (256). GLP-1–based therapy has also been linked to improvements in self-reported outcomes of physical function (261,262).

Overall, MRI-based and clinical data suggest that skeletal muscle changes with GLP-1–based therapies are largely adaptive: reductions in muscle volume appear proportionate with aging, disease status, and the degree of weight loss achieved, while improvements in insulin sensitivity and muscle fat infiltration may enhance muscle quality, lowering the probability for loss in strength and function (256,263).

Engagement in structured exercise before and after metabolic surgery can improve muscle strength (264,265), reduce weight regain (266,267), enhance insulin sensitivity (268), and improve body composition outcomes (269). Similarly, combining structured exercise with obesity pharmacotherapy appears to yield complementary effects, including improved glycemic and inflammation profiles, reduced abdominal adiposity, and more favorable body composition (47,270–273).

PERSONALIZED APPROACH TO TREATMENT BASED ON INDIVIDUAL CHARACTERISTICS AND MLTCs: RECOMMENDED PROCESS FOR GLUCOSE-LOWERING MEDICATION SELECTION

Use of agents such as SGLT2 inhibitors and GLP-1–based therapies in the care of individuals with or at high risk for cardio-kidney complications is of proven benefit in improving outcomes. New evidence continues to support the care of at-risk individuals, independent of their need for additional glucose lowering (274–277). For feasibility reasons, most trials have focused upon the effects of therapies in people with established CVD or kidney disease; however, people with type 2 diabetes are fundamentally at increased risk of such MLTCs compared with the general population (278). This risk is not always appreciated early in the course of type 2 diabetes, a problem that is compounded by low rates of screening for complications such as kidney disease (279). This provides a greater impetus for the use of beneficial agents from the time of diabetes diagnosis (Fig. 4).

People With Cardio-Kidney MLTCs

Established ASCVD

A recent meta-analysis of ten RCTs (169), including the most recent trials SOUL and FLOW, showed that the GLP-1 RA class reduces MACE by 14% in people with type 2 diabetes and CVD or at high cardiovascular risk. In SOUL, conducted in people with established ASCVD and/or CKD, oral semaglutide (14 mg) significantly reduced the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 14% compared with placebo (280). A post hoc analysis showed that this benefit occurred regardless of concomitant SGLT2 inhibitor use (281). In people with type 2 diabetes and ASCVD, the dual GLP-1/GIP agonist tirzepatide was also found to be cardioprotective, as noninferiority to dulaglutide with respect to a composite of death from cardiovascular causes, myocardial infarction, or stroke was demonstrated in the dedicated SURPASS-CVOT (165), together with superiority over an imputed placebo in an indirect prespecified exploratory comparison (166). The protective effects of GLP-1 RAs on cardio-kidney outcomes may be dose dependent (282,283). A meta-analysis demonstrates that the cardio-kidney benefits of GLP-1 RAs are consistent, regardless of SGLT2 inhibitor use (284).

The salutary effect of GLP-1 RAs on ASCVD appears to extend to PAD, as shown by STRIDE, in which semaglutide increased walking distance in people with symptomatic type 2 diabetes and PAD (285), and SOUL, in which MALE were reduced 29% by semaglutide (280). GLP-1 RAs were associated with fewer PAD-related clinical events and a reduced need for revascularization in three meta-analyses of RCTs (286–288).

Further evidence of the cardioprotective effects of glucose-lowering therapies has emerged from secondary analyses and evidence syntheses. In a post hoc analysis of CANVAS and CREDENCE, canagliflozin reduced MACE and other cardiovascular and kidney outcomes regardless of baseline PAD, with greater absolute benefits in those with PAD and without increasing the risk of MALE (147). A meta-regression analysis suggested that SGLT2 inhibitor therapy was more effective in reducing three-point MACE in people with eGFR <60 mL/min per 1.73 m^2 and albuminuria than in those with normal kidney function, whereas age, sex, BMI, HbA_{1c}, and preexisting CVD or heart failure did not modify SGLT2 inhibitor efficacy (289).

For GLP-1 RAs, no differences were shown in MACE and mortality outcomes (290–292) in metformin users compared with nonusers. Similarly, for SGLT2 inhibitors, no differences were observed in MACE, cardiovascular death or HHF,

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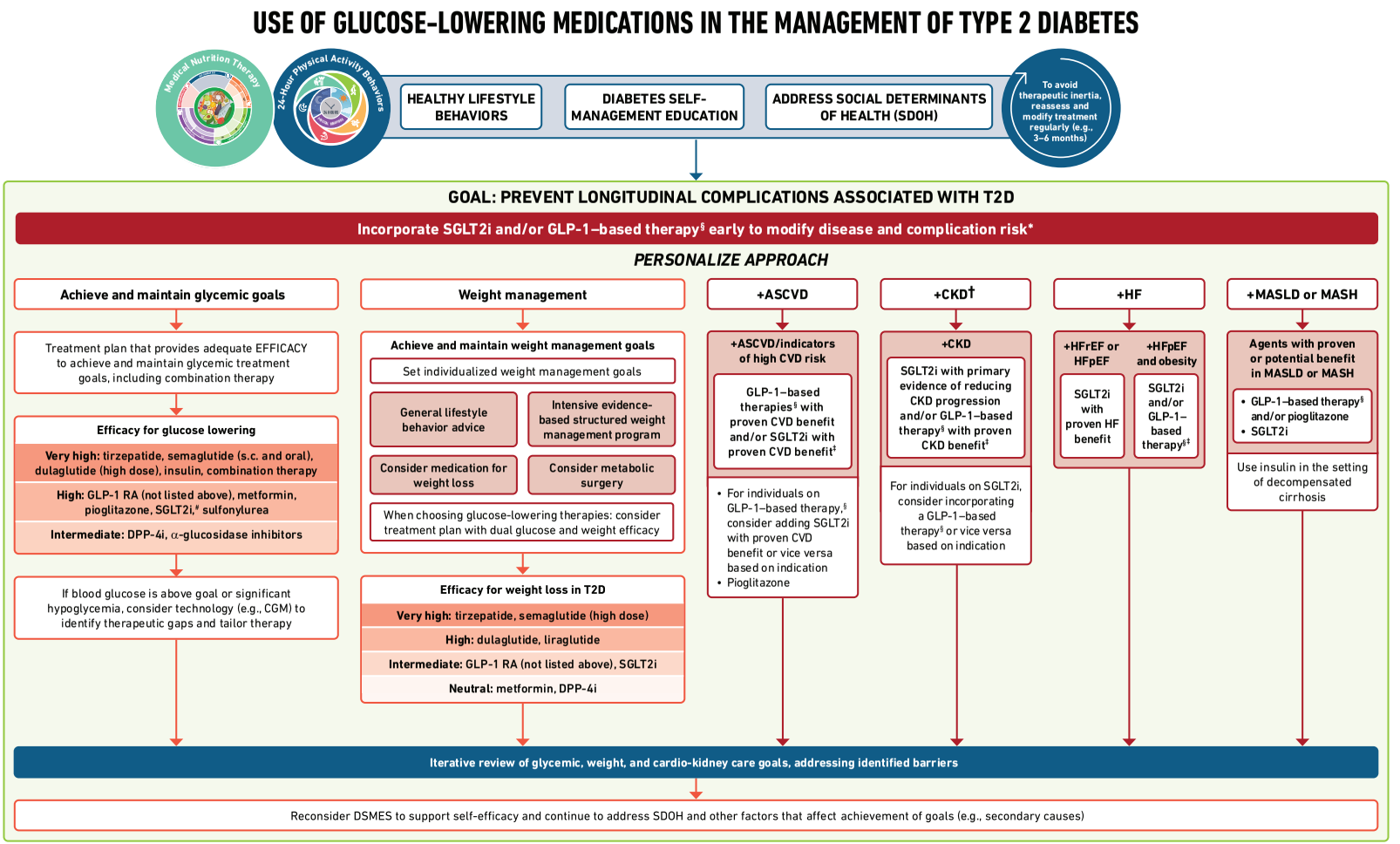


Figure 4—Use of glucose-lowering medications in the management of type 2 diabetes. *Use combination therapy based on target achievement and individual CVD and CKD risk. †eGFR <60 mL/min per 1.73 m^2 and/or albuminuria (UACR ≥3.0 mg/mmol [30 mg/g]). Repeat measurement is required to confirm CKD. ‡While evidence does not suggest simultaneous introduction of a GLP-1–based therapy with SGLT2i, evidence indicates that each will have benefit toward outcome risk reduction. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. #Glucose-lowering efficacy is intermediate to high, dependent on eGFR. ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitor; CKD, chronic kidney disease; DSMES, diabetes self-management education and support; DPP-4i, dipeptidyl peptidase 4 inhibitor; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; OSA, obstructive sleep apnea; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

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major kidney outcomes, or mortality rates in those using versus not using metformin (174). These data support the use of GLP-1 RAs and SGLT2 inhibitors in individuals with compelling indications, independent of metformin use.

Regarding non–glucose-lowering therapies, a meta-analysis of 18 RCTs showed that both steroidal and nonsteroidal MRAs significantly reduced MACE by 19%, cardiovascular mortality by 14%, and HHF by 23% (293).

Heart Failure

Dedicated heart failure outcome trials (DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved and SOLOIST-WHF) support a consistent class benefit of SGLT2 inhibitors on heart failure outcomes, including cardiovascular death, HHF, or urgent hospital visits for heart failure, across left ventricular ejection fraction ranges (294). Updated meta-analyses confirm that SGLT2 inhibitors reduce heart failure events and cardiovascular death in cohorts with varying combinations of heart failure, type 2 diabetes, and CKD (295,296) and in people with type 2 diabetes aged >65 years or with frailty (297). A meta-analysis of DAPA-HF and DELIVER suggests that dapagliflozin may lead to larger risk reductions in cardiovascular death and HHF in people with type 2 diabetes and heart failure who have concomitant neuropathy than in those who do not (298).

Recent evidence is refining the role of GLP-1–based therapies in HFpEF, particularly in people with type 2 diabetes and/or obesity. In STEP-HFpEF DM, semaglutide 2.4 mg improved heart failure health status and exercise capacity in people with type 2 diabetes, obesity, and HFpEF (151). A prespecified pooled individual participant data analysis of STEP-HFpEF and STEP-HFpEF DM showed consistent benefits across key subgroups (299). Beyond symptoms and function, analyses suggest potential reductions in clinical heart failure events with semaglutide in higher-risk settings: in a secondary analysis of FLOW in people with type 2 diabetes and CKD, semaglutide reduced heart failure events or cardiovascular death, with effects independent of prior heart failure history (300); a pooled analysis showed that semaglutide reduced the composite of cardiovascular death and worsening heart failure in HFpEF, driven mainly by fewer worsening heart failure events rather than cardiovascular death (301). Similarly, in a subgroup analysis of SUMMIT, tirzepatide reduced time to first cardiovascular death or worsening heart failure event and improved Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS), with similar effects in individuals with HFpEF but without type 2 diabetes (302). However, not all GLP-1 RA data are positive for heart failure outcomes: in a post hoc analysis from REWIND, dulaglutide was not associated with a reduction in heart failure events (303). A systematic review/meta-analysis focusing on people with type 2 diabetes without preexisting heart failure suggested that GLP-1 RAs may decrease the risk of new-onset heart failure independent of HbA_{1c} or weight reduction but correlated with protective effects on MACE, as heart failure prevention effects were more pronounced in studies restricted to people with ASCVD (304).

Recent analyses clarify the cardio-kidney profile of finerenone across heart failure and CKD phenotypes. In FINEARTS-HF, conducted in people with heart failure and mildly reduced or preserved ejection fraction (46.2% with diabetes at baseline), finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and cardiovascular death when compared with placebo (305); these effects were not modified by glycemic status (306). Furthermore, in a prespecified participant-level pooled analysis integrating FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF, finerenone reduced HHF and improved a broad range of outcomes, including cardiovascular events, kidney outcomes, and all-cause mortality (307). A prespecified analysis from FIDELIO-DKD also demonstrated that finerenone improved cardio-kidney outcomes in people with type 2 diabetes and CKD regardless of prior heart failure (308).

Consensus Recommendations

- Both SGLT2 inhibitors and GLP-1–based therapy confer cardiovascular benefits independent of metformin and should be first-line therapeutic considerations.
- In people with established CVD, GLP-1–based therapies with proven benefit should be used to reduce MACE and all-cause mortality, or an SGLT2 inhibitor with proven benefit should be used to reduce MACE, heart failure, and all-cause mortality and to improve kidney outcomes.
- As benefits may be additive, combination therapy with SGLT2 inhibitors and GLP-1–based therapy could be considered in those at high risk for CVD or with established CVD or kidney disease irrespective of HbA_{1c} levels.
- In people with PAD, semaglutide can be used to improve symptoms.
- In individuals without established CVD but with multiple cardiovascular risk factors (e.g., age ≥55 years, obesity, hypertension, smoking, dyslipidemia, or albuminuria) a GLP-1–based therapy with proven benefit could be used to reduce MACE and improve kidney outcomes, or an SGLT2 inhibitor with proven benefit could be used to reduce MACE and heart failure and improve kidney outcomes. The level of certainty in this recommendation is lower for this subgroup, because some CVOTs recruited exclusively people with established CVD, and fewer events were recorded among those with cardiovascular risk factors only in trials that enrolled both subgroups. In addition, definitions of risk factors were not identical across CVOTs but generally comprised age ≥55 years plus two or more additional risk factors, including obesity, hypertension, smoking, dyslipidemia, or albuminuria. Furthermore, in terms of absolute effects, cardiovascular benefits of GLP-1 RAs and SGLT2 inhibitors were less pronounced in people with three or more cardiovascular risk factors than in those with established CVD (309).
- In people with heart failure (with or without reduced ejection fraction), SGLT2 inhibitors should be used to improve heart failure and kidney outcomes.
- In people with obesity and HFpEF, semaglutide or tirzepatide should be used to improve heart failure symptoms.
- In people with HFpEF or heart failure with mildly reduced ejection fraction, a nonsteroidal MRA with proven benefit should be used to improve heart failure and mortality.
- To reduce progression of CKD and CVD in type 2 diabetes with albuminuria, addition of a nonsteroidal MRA with proven benefit is recommended when eGFR >25 mL/min per 1.73 m^2.

Atrial Arrhythmias

Growing evidence suggests that GLP-1–based therapies and SGLT2 inhibitors

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may confer clinical benefits on atrial arrhythmias, particularly atrial fibrillation, in people with type 2 diabetes and related cardiometabolic disease. Across randomized and observational evidence, GLP-1 RAs appear to be associated with a lower risk of atrial arrhythmias, effects that may be more pronounced in higher-risk subgroups such as individuals with type 2 diabetes and prior myocardial infarction (310). In a secondary analysis of STEP-HFpEF and STEP-HFpEF DM, semaglutide improved heart failure–related symptoms regardless of the presence of atrial fibrillation and across atrial fibrillation subtypes (311). A systematic review/meta-analysis of 30 RCTs reported that semaglutide was associated with a 27% reduction in atrial fibrillation risk and a 78% reduction in complete atrioventricular block in people with type 2 diabetes (312). Real-world evidence also suggests benefit with tirzepatide (313).

In parallel, evidence syntheses support antiarrhythmic benefits with SGLT2 inhibitors. In people with diabetes undergoing catheter ablation, SGLT2 inhibitors were associated with a significant reduction in atrial fibrillation recurrence (314,315). Evidence combining RCTs and observational studies indicates that SGLT2 inhibitors reduce the risk of new-onset atrial fibrillation in people with type 2 diabetes when compared with GLP-1 RAs, DPP-4 inhibitors, and placebo (316–318).

Consensus Recommendation

- In people at high risk for atrial arrhythmias, semaglutide or SGLT2 inhibitors with proven benefit could be considered to reduce atrial fibrillation incidence.

CKD

Lifestyle and multiple glucose-lowering and cardio-kidney–protective drug classes have been evaluated for prevention or slowing of CKD in type 2 diabetes. In older adults with type 2 diabetes (aged ≥60 years), an intensive lifestyle intervention in Look AHEAD was associated with reduced kidney disease progression (319). Consistent with the importance of durable weight and metabolic improvement, in a systematic review/meta-analysis of 25 RCTs, bariatric surgery was associated with lower odds of kidney complications (320).

A large body of evidence supports the use of SGLT2 inhibitors as foundational kidney-protective therapy across CKD risk strata. A systematic review/meta-analysis reported that SGLT2 inhibitors are consistently beneficial for eGFR slope improvement and composite kidney outcomes, regardless of CKD at baseline (321). Network meta-analyses and comparative evidence suggest that SGLT2 inhibitors provide the largest combined kidney/cardiovascular risk reductions in type 2 diabetes with CKD, followed by GLP-1 RAs and MRAs (322), and may be particularly well suited to complement metabolic management in preventing progression of kidney composite outcomes compared with GLP-1 RAs and finerenone (323). Additional evidence suggests that SGLT2 inhibitors significantly reduce AKI risk in people with CKD, CVD, and type 2 diabetes, with greater efficacy in those with higher baseline eGFR (324), and provide consistent kidney benefits across MLTCs (325). Post hoc analyses from CVOTs suggest SGLT2 inhibitor kidney benefit across CKD phenotypes and background therapies and across type 2 diabetes subgroups, including those with nonalbuminuric CKD (326). DECLARE–TIMI 58 post hoc analyses showed that dapagliflozin mitigated kidney function decline in individuals with type 2 diabetes at high cardiovascular risk, including in those at low Kidney Disease: Improving Global Outcomes (KDIGO) risk (327). A post hoc analysis suggested that SGLT2 inhibitor effects on kidney composite outcomes did not differ by baseline use of renin-angiotensin-aldosterone system inhibitors, diuretics (including loop diuretics), or MRAs (328).

Multiple levels of evidence support kidney-relevant benefits of GLP-1–based therapies, particularly in higher-risk CKD. In FLOW, conducted in people with type 2 diabetes and albuminuric CKD, semaglutide 1 mg reduced the risk of adverse kidney outcomes by 24% and cardiovascular death by 29% versus placebo (329). Post hoc analyses of FLOW also indicated that semaglutide reduced MACE across KDIGO categories (330). Across post hoc analyses from PIONEER and SUSTAIN-6, semaglutide improved eGFR slope and reduced a composite kidney outcome irrespective of baseline UACR strata and across KDIGO categories, alongside reduced risk of developing CKD and reduced MACE (274,331,332). A systematic review/meta-analysis reported that semaglutide reduced major kidney-related adverse events (333). In the SOUL trial in participants with type 2 diabetes and ASCVD and/or CKD but mostly preserved eGFR, oral semaglutide slowed eGFR decline versus placebo, although it did not significantly reduce adverse kidney outcomes (334). In a post hoc analysis of REWIND, dulaglutide reduced the hazard of a kidney function–related outcome compared with placebo (335). In SURPASS-CVOT, tirzepatide was noninferior to dulaglutide with respect to change in eGFR over time (165). A prespecified exploratory analysis of SURPASS-CVOT also showed that tirzepatide was associated with a reduced risk of major kidney events, compared with dulaglutide, primarily driven by a reduction in new-onset macroalbuminuria in people with low-to-moderate risk of CKD and slowed decline in kidney function in people at high risk of CKD (336). Overall, evidence syntheses show that GLP-1 RAs reduce a composite kidney outcome by ∼17–24% (169,337,338). In a retrospective cohort study of kidney transplant recipients with type 2 diabetes, GLP-1 RA use was associated with better graft and patient survival (339). The salutary effects of GLP-1 RAs on kidney outcomes may be additive to those of SGLT2 inhibitors and MRAs, as benefits occur regardless of background SGLT2 inhibitor or MRA use (284,340,341).

In people with type 2 diabetes and CKD, finerenone has demonstrated broad kidney benefits across kidney risk strata. In the FIDELITY prespecified analysis of two phase 3 trials, finerenone reduced a CKD-associated composite outcome, as well as cardiovascular events and first and recurrent heart failure events (230). Cardiovascular and heart failure benefits were observed consistently across eGFR and/or UACR categories (342,343). Additional FIDELITY post hoc analyses reported reductions in all-cause, sudden, and cardiovascular death across a broad range of CKD stages (344). Cardio-kidney benefits of finerenone were observed irrespective of background SGLT2 inhibitor use (345); a mediation analysis suggested that early albuminuria reduction predicted kidney benefit more strongly than cardiovascular benefit (346).

Combination approaches are also emerging in type 2 diabetes with CKD. In CONFIDENCE, initial combination therapy with finerenone plus empagliflozin led to a greater reduction in UACR than either

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therapy alone (347). Trial-level estimates integrating data from CREDENCE and FIDELIO suggest that combining an SGLT2 inhibitor with an MRA may substantially increase years free from kidney failure and mortality (348).

Emerging RCT and real-world evidence suggests that benefits are generally maintained when SGLT2 inhibitors, GLP-1–based therapies, or finerenone are combined (225,284,345,347,349).

Consensus Recommendations

- In people with CKD, an SGLT2 inhibitor with proven benefit should be initiated to improve kidney and heart failure outcomes and reduce MACE and should be continued until kidney replacement therapy is indicated, regardless of UACR or albuminuria.
- In people with CKD, GLP-1–based therapy with proven benefit should be initiated to improve kidney and heart failure outcomes and reduce MACE. Semaglutide is indicated to reduce the risk of CKD progression.
- In people with CKD and UACR >3.0 mg/mmol (>30 mg/g), a nonsteroidal MRA with proven benefit should be used to improve kidney and heart failure outcomes.
- SGLT2 inhibitors should form the foundation for heart failure/CKD protection; GLP-1–based therapies could be added for incremental MACE and kidney benefit plus weight/metabolic management and finerenone could be added, particularly in albuminuric CKD, to further reduce cardio-kidney events.
- Early combination therapy should be considered in people with concomitant CVD, CKD, and heart failure.
- Choice among individual SGLT2 inhibitors and GLP-1–based therapy should be based on country-specific indications and evidence on efficacy, safety, and outcome benefits, considering within-class heterogeneity.

Cardio-Kidney Benefits of GLP-1–Based Therapies and SGLT2 Inhibitors in Lower-Risk Populations

In lower-risk populations with type 2 diabetes (e.g., preserved kidney function, low levels of albuminuria, and no established heart failure/ASCVD), the cardio-kidney benefits of GLP-1–based therapies and SGLT2 inhibitors should be interpreted primarily through the distinction between relative and absolute treatment effects. While meta-analyses support consistent RR reductions for major outcomes, the absolute risk reduction over typical trial follow-up is often modest when baseline event rates are low. Conversely, as baseline cardio-kidney risk increases (e.g., albuminuric CKD, reduced eGFR, established ASCVD, or MLTCs), similar RR reductions translate into larger absolute risk reductions and more favorable numbers needed to treat, supporting earlier prioritization and layering of therapies. Evidence syntheses suggest that the absolute benefit of SGLT2 inhibitors on MACE reduction increases with baseline cardio-kidney risk (309). In high-risk CKD, dedicated outcome trials further illustrate clinically meaningful absolute benefits, such as FLOW, in which semaglutide reduced kidney outcomes and cardiovascular death (329). In a U.K. primary care study in type 2 diabetes (in individuals with eGFR $\geq$60 mL/min per 1.73 m^2, UACR <30 mg/mmol [<265 mg/g], without heart failure/ASCVD), a risk model combining baseline CKD with real-world–confirmed SGLT2 inhibitor effect (HR 0.58) estimated individual 3-year absolute kidney protection benefit and could prevent >10% more progression events by identifying a subgroup with greater absolute benefit (350).

Consensus Recommendation

- Treatment decisions should be individualized based on baseline absolute cardio-kidney risk and time horizon, as absolute benefit is substantially greater in people at higher cardio-kidney risk.

Additional Clinical Considerations

Age: Younger People With Diabetes

Incidence and prevalence of type 2 diabetes have increased significantly in concert with obesity among the adolescent and young adult population, with minority populations disproportionately affected (351,352). A younger age at type 2 diabetes diagnosis has consistently been associated with a higher body weight (353) and affected young people have a more rapid deterioration in blood glucose levels, an attenuated response to diabetes medication, more rapid development of diabetes complications, and greater loss of life-years (354,355). Early disease onset, higher levels of hyperglycemia, and the multiple cardiometabolic risk factors found in younger adults with impaired glucose tolerance all contribute to an increase in risk of adverse outcomes (356). Most adolescents who develop type 2 diabetes will have microvascular complications by young adulthood (357). In addition, the UKPDS has found that individuals with type 2 diabetes onset before age 40 years (often referred to as early-onset type 2 diabetes) have greater risks of complications, poorer glucose levels, and excess mortality (26).

Most of the evidence for health behavior interventions, glucose-lowering approaches, and the efficacy of medications to improve cardiovascular and kidney outcomes in younger people with diabetes is poorly understood due to limited enrolment of this group in trials (358). Meta-analyses and individual trials suggest that SGLT2 inhibitors and GLP-1 RAs can be used to lower HbA_{1c} in young people with type 2 diabetes, with safety similar to that seen in older adults (359–365). The dual GLP-1/GIP agonist tirzepatide has also been found to significantly improve both HbA_{1c} and BMI in youth with inadequately controlled type 2 diabetes (366). Early use of combination therapy may be considered, as the Vildagliptin Efficacy in Combination with Metformin for Early Treatment of T2D (VERIFY) trial and other analyses suggest that this approach provides superior and more durable effects on blood glucose levels than monotherapy in people with early-onset diabetes and those with later-onset diabetes (367,368). Both dulaglutide and empagliflozin have also been found to attenuate hyperfiltration and either proteinuria or albuminuria in youth with type 2 diabetes (369,370); however, the durability of drug effects and any impact on clinically important cardio-kidney and other outcomes with use of any glucose-lowering medication in children and young adults remain unknown (371). Interventions targeting weight reduction in those living with overweight and obesity are essential in this group, as they are likely to not only reverse the etiological processes of type 2 diabetes but also reduce the risk of obesity-associated complications.

Consensus Recommendations

- Interventions targeting weight reduction are essential in people living with early-onset type 2 diabetes to reduce the risk of future complications.

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- Early-onset type 2 diabetes is associated with faster glycemic deterioration and earlier onset of complications, thus early deployment of SGLT2 inhibitors and GLP-1–based therapies, either alone or in combination, should be prioritized.
- Earlier use of GLP-1–based therapy or SGLT2 inhibitors must be accompanied by explicit counseling in women of reproductive potential regarding contraception and avoidance of exposure to medications that are currently not approved for use during pregnancy and could adversely affect a fetus (see "Sex Differences," below).

Age: Older People With Diabetes

Informed decisions regarding treatment of older adults (aged >65 years) with diabetes are limited by the historical underrepresentation of this group in clinical trials. Underlying pathophysiology and functional status are generally more important considerations in prescribing than age. Meta-analyses of data from large outcomes trials have found that the reductions in mortality and overall burden of cardiovascular events conveyed by SGLT2 inhibitors and GLP-1 RAs are generally consistent across age groups (289,372), even though the glycemic and weight loss effects of treatment may be attenuated in older age (373–375). One systematic review and network meta-analysis has suggested some heterogeneity in the cardioprotective effects of SGLT2 inhibitors and GLP-1 RAs by age; however, such conclusions are limited by the absence of comparative trials (373). A pooled analysis of data from two large outcomes trials found that the safety and beneficial effects of finerenone on cardiovascular and kidney outcomes in people with type 2 diabetes and CKD were not modified by age (376). Older age should not be an obstacle to treatment of individuals with established, or at high risk for, ASCVD, heart failure, or CKD. Because older adults often are at higher risk for cardiovascular and kidney events, they may derive greater benefits from the protective effects of these therapies (377).

The side effect and safety profiles of SGLT2 inhibitors and GLP-1–based therapies appear generally consistent across age groups, with a lower risk of hypoglycemia compared with sulfonylurea treatment (377). However, some meta-analyses and analyses of real-world evidence have suggested that older adults may be at increased risk for AKI, DKA, and genital mycotic infections with SGLT2 inhibitor therapy and at higher risk for nausea and vomiting with GLP-1–based therapy (146,378). People with diabetes should understand and be able to appropriately modify use of their prescribed medications during times of illness.

Consensus Recommendations

- In general, the selection of medications to improve cardiovascular and kidney outcomes should not differ for older people with diabetes.
- Medication choices for people who are older or frail, or who have MLTCs, may require modification for safety and tolerability.

Frailty

Importantly, not all older adults with diabetes are frail, and frailty may occur at younger ages. Frailty is a clinical syndrome characterized by decreased physiological reserve and resistance to stressors across multiple organ systems. Type 2 diabetes represents a model of accelerated biological aging, associated with declines in physical capacity, underpinned by dysfunction within skeletal muscle. The ability of people with type 2 diabetes to undertake activities of daily living and physical functioning in middle age has been shown to be similar to the ability of those at least a decade older within the general population (379).

Individuals with frailty are at increased risk for adverse outcomes (e.g., trials such as Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE] suggested that more frail individuals have worse outcomes and benefit less from intensive control of blood glucose levels and BP [380]). Deprescribing medication to avoid unnecessary medication or medications associated with harm, such as hypoglycemia and hypotension, may be important. Analyses of more recent trials of SGLT2 inhibitors and GLP-1–based therapies confirm that greater frailty is associated with poorer outcomes, including higher rates of both medication side effects and cardiovascular and kidney outcome events. However, few such trial participants had severe frailty, and frailty status is often not well captured (381,382). Where available, though, the data are reassuring. Analyses of CANVAS and CREDENCE data found consistent reductions in total and cardiovascular mortality and MACE with canagliflozin therapy in both frail and nonfrail subgroups (383), and a meta-analysis of trials assessing outcomes in frail or older people (age ≥65 years) with type 2 diabetes and heart failure found significant reductions in the risk of all-cause and cardiovascular mortality and HHF with SGLT2 inhibitor treatment compared with placebo (297). The effects of finerenone on kidney and cardiovascular outcomes appear consistent across frailty categories (382).

Race and Ethnicity

Although trial participants from minority ethnicity groups may have higher rates of cardiovascular and other MLTCs than White cohorts, they traditionally comprise small proportions of overall enrolled trial populations (384). While some analyses are limited by small numbers of participants from ethnic minority groups, thus far the large outcomes trials of SGLT2 inhibitors, GLP-1–based therapies, and finerenone have demonstrated beneficial effects and similar safety profiles in enrolled participants, irrespective of ethnicity (385–389). The increased burden of complications in underrepresented populations with diabetes should be factored into personalized treatment plans, and beneficial medications should be used irrespective of race or ethnicity. Ongoing and future trials should recruit to be representative of the overall population of people with diabetes so that the effects of interventions in understudied subgroups may be better ascertained (390,391).

Consensus Recommendation

- Selection of medications to improve cardiovascular and kidney outcomes should not differ by race or ethnicity. However, race and ethnicity may intersect with genetic ancestry, SDOH, access to care, and differential burden of cardiovascular, kidney, and other MLTCs. These factors should be considered within individualized risk assessment and may support earlier initiation, intensification of therapy, use of more-advanced treatment strategies, or more ambitious treatment goals in populations or individuals at higher risk.

Sex Differences

In women with reproductive potential, the use of highly effective contraception

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should be ensured, such as long-acting reversible contraception (intrauterine device or progesterone implant), prior to prescribing medications that may adversely affect a fetus. Diabetes significantly increases the risk of cardiovascular complications in both sexes, and CVD causes most hospitalizations and deaths in women and men with diabetes (392,393). In the general population, premenopausal women are at lower risk for cardiovascular events than men of the same age; however, this vascular protection or advantage is reduced in women who develop type 2 diabetes (394,395). In fact, the increase in RR of CVD due to type 2 diabetes is greater in women than in men (396–398). Despite this, women have been underrepresented in recent outcomes trials in diabetes, generally comprising about one-third of participants (373). Women tend to have differing patterns of cardiovascular complications compared with men and consistently poorer management of cardiovascular risk factors (399,400). Within-trial analyses and meta-analyses suggest no significant heterogeneity by sex in the effects of SGLT2 inhibitors, GLP-1–based therapies, and finerenone on cardiovascular and kidney outcomes (289,373,400–402). Continued efforts should be made to enroll women in outcomes trials and to identify and address modifiable cardiovascular risk factors in women with diabetes.

Consensus Recommendation

- Selection of medications to improve cardiovascular and kidney outcomes should not differ by sex. However, it is important to counsel women of reproductive potential regarding contraception and avoidance of exposure to medications that are currently not approved for use during pregnancy and may adversely affect a fetus.

People With Obesity-Related Conditions

MASLD and MASH

MASLD is a disease spectrum defined by the presence of hepatic steatosis together with at least one cardiometabolic risk factor, after exclusion of significant alcohol intake and other secondary causes. It affects more than 70% of individuals with type 2 diabetes, among whom more than half develop MASH, the progressive inflammatory form characterized histologically by steatosis with lobular inflammation and hepatocellular injury, with or without fibrosis. Fibrosis, particularly stages $\geq$ F2, determines prognosis and is strongly associated with increased liver-related, cardiovascular, and all-cause mortality and CKD (403,404).

Management of MASLD and MASH in people with type 2 diabetes requires an integrated strategy addressing metabolic control, cardiovascular and kidney risk reduction, and liver-specific outcomes. Although MASLD can occur in lean individuals, overweight and obesity substantially exacerbate steatohepatitis and fibrosis risk. Weight reduction is therefore a primary therapeutic target: a loss of at least 5% of body weight improves hepatic steatosis, while reductions of $\geq$7–10% are associated with resolution of MASH and regression of fibrosis, albeit with marked interindividual variability (405). Dietary interventions should aim to create a sustained energy deficit and are broadly aligned with recommendations for diabetes and obesity (403). Among dietary patterns, the Mediterranean diet has strong evidence for combined hepatic and cardiometabolic benefit (406). Regular physical activity is an essential adjunct, improving liver fat, aminotransferases, and insulin sensitivity, partly independent of weight loss. Both aerobic and resistance exercise are effective, tailored to individual capacity and preferences (407–409).

In type 2 diabetes, pharmacological management of MASLD and MASH should be embedded within a comprehensive cardiometabolic strategy that prioritizes early intervention, given the high prevalence of at-risk disease and the absence of effective therapies once cirrhosis is established. Optimization of glucose-lowering and weight management therapies offers a dual opportunity to address diabetes and obesity while modifying the natural history of liver disease. Semaglutide has the most robust data and is currently the only glucose-lowering or obesity medication approved for noncirrhotic MASH with moderate or advanced fibrosis. In the 72-week phase 3 ESSENCE trial that included 320 people with biopsy-proven MASH and stage 2 or 3 fibrosis, 56% of whom had type 2 diabetes, semaglutide achieved both resolution of steatohepatitis without fibrosis worsening and improvement in fibrosis without worsening of MASH (152). Mediation analyses suggest that its histological benefits are only partly explained by weight loss (410). However, semaglutide has not demonstrated histological efficacy in compensated MASH-related cirrhosis (411), underscoring the importance of treatment before cirrhosis develops. Other GLP-1–based therapies have more limited histological data; liraglutide demonstrated resolution of steatohepatitis and reduced fibrosis progression in the LEAN study (412), while dulaglutide and exenatide have shown solely reductions in liver fat on MRI-based end points in small, short-term RCTs (413,414). In the SYNERGY-NASH trial, a phase 2, 52-week, paired-biopsy trial in people with biopsy-confirmed MASH with F2–F3 fibrosis, 58% of whom had type 2 diabetes, tirzepatide achieved high rates of MASH resolution without fibrosis worsening and greater fibrosis improvement compared with placebo (415). These data support preferential use of GLP-1–based therapies, particularly semaglutide or tirzepatide, for glycemic management in individuals with type 2 diabetes and biopsy-proven MASH or high fibrosis risk, especially given the established cardiovascular benefits of this therapy. Pioglitazone remains an important therapeutic option, with multiple randomized trials (196,416) and meta-analyses (417,418) demonstrating improvement in steatohepatitis and a possible, albeit modest, effect on fibrosis, its benefits being consistent across histological and noninvasive end points (419–421). Pioglitazone improves insulin sensitivity and lipid metabolism, which are key drivers of MASH pathophysiology. Nevertheless its clinical use is limited by dose-dependent weight gain, fluid retention, and fracture risk, and caution is warranted in individuals with heart failure. Importantly, weight gain can be mitigated or reversed when pioglitazone is combined with a GLP-1 RA or an SGLT2 inhibitor, making combination therapy an attractive strategy in selected individuals (422–424), although confirmatory phase 3 trials with histological end points are still lacking.

SGLT2 inhibitors consistently reduce hepatic steatosis and improve noninvasive fibrosis markers (425–427). Histological evidence remains limited, although a recent trial with dapagliflozin reported modest improvements in MASH resolution and fibrosis end points among people with

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biopsy-proven MASH (including people with type 2 diabetes) in China (428). Hence, SGLT2 inhibitors should therefore be continued for their glycemic, cardiovascular, and kidney benefits but not selected primarily for liver disease modification. Other glucose-lowering agents generally lack evidence for histological benefit (429).

Beyond glucose-lowering therapies, resmetirom represents a major advance as the first agent approved specifically for noncirrhotic MASH with moderate to advanced fibrosis. As a thyroid hormone receptor β-agonist, it improves hepatic fat metabolism and fibrosis without affecting body weight or glycemic management. Resmetirom was reported to significantly increase MASH resolution and fibrosis improvement compared with placebo, with effects independent of background GLP-1 RA or SGLT2 inhibitor therapy (430). Gastrointestinal adverse effects are common but generally manageable, while changes in thyroid hormone parameters warrant monitoring. Patient and selection complexity and monitoring requirements suggest that initiation of resmetirom should occur within specialist care.

Finally, for individuals with decompensated cirrhosis, insulin remains the preferred therapy for glycemic management, given the limited safety data for most oral and injectable agents, whereas GLP-1–based therapies appear safe in compensated cirrhosis but lack proven efficacy (411).

Consensus Recommendations

- For people with diabetes and MASLD, weight reduction should be a primary therapeutic target, and lifestyle modification is foundational. Physical activity should be encouraged.
- For people with obesity, type 2 diabetes, and MASLD, a GLP-1–based therapy with proven benefit should be used.
- For people with diabetes and biopsy-proven MASH, a GLP-1–based therapy with proven benefit should be preferred. Pioglitazone or tirzepatide could also be used.
- Combination regimens with pioglitazone and GLP-1–based therapy should be considered for enhanced effect, while treatment with other glucose-lowering agents can be continued as indicated.
- Specifically for people with decompensated cirrhosis, insulin is the preferred agent. For individuals with moderate (stage F2) or advanced (stage F3) liver fibrosis, referral to a hepatologist should be coordinated to consider treatment with a thyroid hormone receptor β-agonist.

Obstructive Sleep Apnea

OSA is highly prevalent in people with type 2 diabetes, particularly in the presence of obesity. Continuous positive airway pressure (CPAP) remains the standard of care. Weight loss is an effective means for improving or resolving OSA, whether by lifestyle efforts, surgery, or medications. Pharmacological therapy should be viewed as complementary to established OSA treatments. Weight-reducing glucose-lowering agents are of particular interest given the strong pathophysiological link between adiposity and OSA.

Among GLP-1–based therapies, tirzepatide has demonstrated the most pronounced effects on OSA severity. In the SURMOUNT-OSA trials in adults with obesity and moderate-to-severe OSA without diabetes, weekly tirzepatide reduced the apnea-hypopnea index (AHI) by approximately 20–24 events per hour and improved sleep-related person-reported outcomes over 52 weeks (163). GLP-1 RAs also reduce OSA severity, although with more modest effects. In individuals with obesity without diabetes (431) and people with type 2 diabetes and severe OSA treated with CPAP (432), liraglutide improved AHI, a finding also verified in a relevant meta-analysis, with larger reductions observed with tirzepatide than with a GLP-1 RA (433).

SGLT2 inhibitors may also confer benefit in selected populations. In a randomized trial in people with heart failure and OSA (including individuals with type 2 diabetes), dapagliflozin reduced AHI, oxygen desaturation index, and hypoxic time over 3 months (434). CVOT subgroup exploratory analyses further suggest reduced incident OSA with empagliflozin and ertugliflozin in people with type 2 diabetes (435,436).

Consensus Recommendations

- For people with obesity, type 2 diabetes, and OSA, tirzepatide or a GLP-1 RA with proven benefit could be prioritized.

Osteoarthritis

In people with diabetes complicated by obesity and symptomatic knee osteoarthritis, selection of glucose-lowering therapy could prioritize agents that promote weight reduction. A recent 6-month randomized trial in 107 adults with overweight or obesity without diabetes demonstrated that metformin 2,000 mg daily improved WOMAC pain, stiffness, and function (437), broadly consistent with the findings of a small network meta-analysis (438). In contrast, liraglutide 3.0 mg daily did not improve knee-specific outcomes over 52 weeks despite weight loss (439), whereas semaglutide 2.4 mg weekly significantly improved pain and physical function in the STEP 9 trial (440). Importantly, all these studies excluded individuals with diabetes.

Cognitive Decline

Diabetes is associated with an increased risk of dementia, yet data from comparative effectiveness trials have not demonstrated consistent differences in cognitive outcomes across glucose-lowering drug classes (441). Recent meta-analyses suggest a possible reduction in cognitive impairment with GLP-1–based therapy, whereas SGLT2 inhibitors and pioglitazone appear neutral (442), although effect sizes are modest and not uniformly replicated (443). Emerging signals from small RCTs in Alzheimer disease populations without diabetes, including studies of liraglutide and other incretin-based therapies, suggest potential neurobiological effects (444); however, larger phase III trials have not shown clinical benefit (445). Accordingly, current practice should align with current standards of care: simplify regimens, individualize glycemic targets, and minimize hypoglycemia, while encouraging exercise, which has demonstrated moderate cognitive benefit in people with diabetes (446,447).

Consensus Recommendation

- There is not yet evidence to support preferred use of any glucose-lowering agents on cognitive outcomes. Hence, selection of glucose-lowering therapy for individuals with cognitive impairment should prioritize safety and simplicity.

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PUTTING IT ALL TOGETHER: STRATEGIES FOR IMPLEMENTATION

General Approach to Person-Centered Care

The overall goal of the management of type 2 diabetes is to maintain or improve quality of life and avoid (acute and chronic) complications. Glucose management, weight and cardiovascular risk factor management, and early use of organ-protective therapies are integral aspects of the holistic approach to achieve these goals.

The individual living with type 2 diabetes should be at the center of integrated care, and the management approach should account for the life-long nature of type 2 diabetes (Fig. 1). The integrated care of people living with type 2 diabetes must consider the individual's specific preferences and values, SDOH, barriers to care, MLTCs, degree of hyperglycemia, risks of complications, and susceptibility to medication side effects. SDOH must be assessed and addressed (14) to help achieve health equity. Recognition of the presence of MLTCs in type 2 diabetes is paramount (13). For example, type 2 diabetes is associated with an increased risk of cognitive impairment and dementia; this relationship is complicated and includes the contribution of both long-term hyperglycemia and hypoglycemia (448). Clinicians should be aware of the coexistence of type 2 diabetes with conditions such as dementia and mental health issues and refer when appropriate. The prevalence of mental health issues such as depression, diabetes distress, stigma, and disordered eating is high in people living with type 2 diabetes, particularly in those with early-onset type 2 diabetes (449), which has a detrimental effect on diabetes self-management and outcomes (450). Early identification through routine screening and appropriate treatment through DSMES, behavioral interventions, and person-centered care are essential to alleviating the rising burden of mental health issues in people with type 2 diabetes.

Communication between people living with type 2 diabetes and health care team members is at the core of integrated care, and clinicians must recognize the importance of language in diabetes care: it should be neutral, free of stigma, and based on facts; it must be strength-based (focus on what is working), respectful, and inclusive; it must encourage collaboration; and it must be person centered (451,452).

Much of the management of type 2 diabetes (e.g., self-management, health behaviors, pharmacotherapy, etc.) is goal based, making it important to incorporate "SMART" (specific, measurable, achievable, realistic, time-limited) goals to achieve improvements in care (2,3). These goals need to be agreed in partnership with the person living with type 2 diabetes and revisited regularly.

Consensus Recommendations

- Type 2 diabetes care should be integrated, with the person living with type 2 diabetes at the center.
- Care teams should identify and address the MLTCs present in people living with type 2 diabetes as part of integrated diabetes care, including those relating to mental health.
- Effective communication between all team members and the person living with type 2 diabetes should be maintained throughout care delivery.
- Goals of treatment should be specific, measurable, attainable, relevant, time based, and identified collaboratively and be agreed upon and revisited regularly with the person living with type 2 diabetes.
- Developing weight targets (achieved by any means) are as essential in diabetes management as glycemic targets.

Health Behaviors

Facilitating healthy behaviors is central to the comprehensive management of type 2 diabetes and should begin at diagnosis and continue throughout the life course. Core health behaviors include weight loss, the 24-h physical behaviors (the five S's: standing, stepping, sweating, strengthening, and sleep) and smoking cessation (Figs. 2 and 3). These behaviors should be assessed routinely, particularly when glycemic targets are not met or when initiating new pharmacological therapies or interventions such as metabolic surgery. Addressing health behaviors is foundational, not adjunctive, to effective type 2 diabetes care.

The five S's underscore how to incorporate 24-h physical behaviors into type 2 diabetes care. Gradual increases in activity volume and intensity generally do not require medical clearance, although additional assessment may be warranted for individuals with advanced microvascular complications, unstable heart failure, insulin use, or a history of hypoglycemia. Activity plans should be individualized based on preferences, functional status, and motivation. Special attention needs to be paid to increasing/maintaining muscle mass and strength in those at risk for sarcopenia, particularly in those treated with weight loss interventions. Resistance exercise is important in this context.

All individuals with type 2 diabetes should be offered MNT (49) to develop a personalized eating plan, focused on diet quality, eating patterns, and energy restriction, that reflects individual preferences, cultural context, and clinical goals. There is no single dietary pattern appropriate for all people living with type 2 diabetes; multiple dietary approaches, particularly the Mediterranean diet and low-carbohydrate diet, and potentially ketogenic diet and intermittent fasting strategies, can be effective when they are structured, sustainable, and aligned with the individual's circumstances. The need for ongoing or additional dietary counseling should be reassessed over time as clinical status and treatment goals evolve. The rapid uptake of GLP-1–based therapies and their major impact on weight has highlighted the importance of inclusion of integrated dietitian-led care in the treatment paradigm to safeguard the quality of food intake (e.g., protein) and mitigate nutritional risk and loss of lean mass (453).

Behavioral targets should follow the SMART principle, as these goals are more effective for achieving behavior change than nonspecific recommendations (454). Goals and targets should be routinely reviewed in clinical encounters. An all-or-none approach related to behavioral goals should be avoided, as any improvement in healthy behaviors can have a positive impact (455,456). Self-monitoring of health behaviors and achievements (e.g., physical activity monitoring, step count, and weight measurement) is crucial to the achievement of health behavior goals as it reinforces engagement and accountability.

Consensus Recommendations

- All individuals with type 2 diabetes should be offered MNT and plans should be reassessed regularly, paying attention to individualization of interventions.

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- The five S's physical behavior principles should be considered an essential component of type 2 diabetes management.
- People with type 2 diabetes undergoing interventions associated with significant weight loss, such as metabolic surgery or GLP-1–based therapies, should receive guidance on adequate protein intake and resistance exercise to help prevent lean mass loss.
- Goals for health behavior interventions should be SMART, agreed upon collaboratively, and revisited at regular intervals.

DSMES

DSMES is as important to the management of type 2 diabetes as the selection of medication (2,3,457,458). DSMES is a structured, evidence-based intervention that covers the span of topics important for self-management of diabetes, including nutrition, self-monitoring, pharmacotherapy, and reduction of risk of complications. DSMES should be offered on an ongoing basis and should be provided by trained diabetes care and education specialists; DSMES can be delivered using multiple approaches and in a variety of settings (2,3). There are four critical times for DSMES: at diagnosis; annually to address changes in medications and support health behaviors; at onset of new complications; and upon transitions in care. Evidence has consistently shown that DSMES significantly improves knowledge, glucose levels, and clinical and psychological outcomes and is cost-effective (459–465). Unfortunately, DSMES is underutilized (466–468). The care team must be aware of the available local DSMES resources and how to access them. DSMES is not a replacement for referral to mental health services. Psychiatric disorders, including disordered eating behaviors, are common, are often unrecognized, and contribute to poor outcomes in diabetes (469). Emerging evidence demonstrates the benefits of telehealth or web-based DSMES programs (470,471). Standardized DSMES programs are not accessible to everyone and can fall short of meeting person-centered diabetes education and support needs. The critical issue is the importance of ongoing access to person-centered care addressing individual risks and barriers to care as well as empowering self-management. This should be provided by trained personnel or validated programs.

Consensus Recommendations

- DSMES should be offered to all those living with type 2 diabetes and revisited regularly.

Therapeutic Inertia

Therapeutic inertia describes a lack of treatment intensification when targets or goals are not met. It also includes failure to deintensify management when people are overtreated. Interventions targeting therapeutic inertia have facilitated improvements in glycemic management and timely insulin intensification. For example, authorization for nonphysicians to prescribe (e.g., pharmacists, specialist nurses) may reduce therapeutic inertia (472).

Treatment Behaviors and Persistence

Suboptimal medication-taking behavior and low rates of continued medication use, or what is termed "persistence to therapy plans," affects almost half of people with type 2 diabetes, leading to suboptimal management as well as increased risks of diabetes complications and mortality and increased health care costs (473,474). Multiple factors contribute to inconsistent medication use and treatment discontinuation among people with diabetes, including perceived lack of efficacy, fear of hypoglycemia, lack of access, and adverse effects of medication (475). Focusing on facilitators of optimal medication-taking behavior, such as social/family/provider support, motivation, education, access to medications/foods, and personal preference, can provide benefits (476,477).

Weight and Body Composition Management in the Treatment of Type 2 Diabetes

Weight management should be a central focus for people living with type 2 diabetes. For many, a weight loss target of $\geq$5% confers meaningful metabolic benefit but increasing evidence from programs offering intense MNT and physical activity as well as those using newer, glucose- and weight-lowering pharmacological agents (e.g., GLP-1–based therapy) demonstrates that more substantial weight loss (approaching or exceeding 15%) can be achieved. This weight loss, particularly early in the disease course, increases the likelihood of achieving normoglycemia and thus diabetes remission (71,478,479). Equally, metabolic surgery, particularly early in the disease course, is also associated with diabetes remission (240).

Health behaviors, facilitated by MNT and DSMES, contribute to weight management, but it is the availability of agents such as GLP-1–based therapy that allows high weight loss efficacy and offers the opportunity to reach more ambitious targets (>15% weight loss). These pharmacological agents should be prioritized in the choice of glucose-lowering agents when overweight or obesity is present. Metabolic surgery can be considered for people with a BMI $\geq$30 kg/m^2 and type 2 diabetes. The benefits of metabolic surgery need to be balanced against potential adverse effects, which vary by procedure and include surgical complications, late metabolic or nutritional complications, and impact on psychological health (188–191,233,238). People being considered for metabolic surgery should be evaluated for associated psychological conditions and social and situational circumstances that may interfere with surgery outcomes. People who undergo metabolic surgery should receive long-term medical and behavioral support. Metabolic surgery should be performed in high-volume centers with experienced multidisciplinary teams (233,251).

With the increasing use of GLP-1–based therapies, the maintenance of weight, once the weight loss goal is achieved, is an increasingly important consideration, as clinical trials demonstrate weight regain with cessation of GLP-1–based therapy (480). Furthermore, weight regain following initial weight loss is associated with an overall loss of lean mass and a return of fat mass to baseline levels (481), illustrating a potential detrimental effect of weight cycling on body composition. Optimal strategies for weight maintenance are emerging but the following strategies can be considered: an individualized, dose-tapering approach to a maintenance dose; a focus on health behaviors, including nutrition and physical activity; and use of other weight-lowering medications.

Consensus Recommendations

- DSMES and MNT should be offered to people with type 2 diabetes to

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identify and address barriers to health behavior change and support weight loss.
- Weight management goals should be individualized and agreed upon collaboratively, balancing clinical ambition with personal feasibility.
- In people with type 2 diabetes and overweight or obesity, use of agents with weight-lowering effects should be preferred as glucose-lowering therapy, and metabolic surgery should be considered.
- Focus on weight maintenance should be kept after goals are achieved.

Choice of Glucose-Lowering Medication

The choice of glucose-lowering agents should be directed by the individual profile of the person with type 2 diabetes, in particular the presence of overweight and MLTCs, risk of side effects, preferences, and context (Fig. 4). The selection of glucose-lowering therapy should be based on evidence originating from randomized clinical trials, supplemented by real-world evidence, as well as the impact of interventions on person-related outcomes. This is equally true for initial therapy and modifying therapy later based on disease progression or new insights. Pharmacological treatment of hyperglycemia must be integrated with DSMES and accompanied by a focus on healthy behaviors considering SDOH from diagnosis onwards. The holistic, multifactorial approach to type 2 diabetes must include evidence-based therapies for glycemic, weight, BP, and lipid management, as well as direct organ (heart/kidney/liver) protection (Fig. 5). For the last three decades, the standard approach was to add medications as needed. Today, we are recommending the use of best evidence and person preferences to craft an individualized program of behavioral approaches and medications to reach goals, which could involve both adding and subtracting medications.

An important reality is that type 2 diabetes is often accompanied by the presence of MLTCs from diagnosis, particularly in those with early-onset type 2 diabetes. Considering the growing evidence from clinical trials and observational studies, confirmed by real-world evidence, most people with type 2 diabetes should receive early on, potentially from diagnosis, a combination of cardiovascular risk factor management and DSMES, alongside health behavior interventions, an SGLT2 inhibitor, and/or a GLP-1–based therapy. This approach targets both glucose lowering (without a risk of hypoglycemia) and weight management and targets direct organ protection. Moreover, this approach helps to avoid clinical inertia and has the potential of achieving normoglycemia. This preferred, proactive approach is supported by the overwhelming evidence on glucose-lowering efficacy and direct organ protection of these pharmacological agents, together with the observation that they are now part of the essential medicines as defined by the World Health Organization, and affordability and access is improving as patents expire. In people with BMI >35 kg/m^2, in addition to DSMES, dietary interventions, and physical activity, early introduction of metabolic surgery is an option. In the presence of

USE OF GLUCOSE-LOWERING MEDICATIONS EARLY IN CARE

GOAL: PREVENT LONGITUDINAL COMPLICATIONS ASSOCIATED WITH T2D

Incorporate SGLT2i and/or GLP-1–based therapy§ early to modify disease and complication risk***

Phenotype	SGLT2i†	GLP-1–based therapy†§
Glucose-lowering efficacy	+	++
Weight-lowering efficacy	+	++
ASCVD/high-risk ASCVD	**	**
CKD	**	**
HF		
-HFrEF	**	
-HFpEF‡	**	**
MASH/MASLD¶	*	**

Figure 5—Use of glucose-lowering medications early in care. **Outcomes evidence. *Improvement in markers. ++Highest efficacy. +High efficacy. ***Use combination therapy based on target achievement and individual CVD and CKD risk. ¶Pioglitazone may be considered. †Where evidence and/or label indicate (Table 1). ‡Trials of GLP-1–based therapies only included participants with a BMI ≥30 kg/m^2. §Includes GLP-1 RA and the dual GLP-1/GIP agonist tirzepatide. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2D, type 2 diabetes.

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MASLD, alongside use of GLP-1–based therapy with proven benefits, SGLT2 inhibitors, pioglitazone, or metabolic surgery could be considered.

In people with lower risk, such as those with minimal hyperglycemia, lesser degrees of excess weight, and no organ damage, or limited life expectancy, a more stepwise approach may be considered. In the setting of resource constraints, prioritization of the highest-risk groups for access to more expensive pharmacological agents may be needed, with consideration of absolute risk reductions in addition to RR reductions.

In others, SGLT2 inhibitors and/or GLP-1–based therapy may not be tolerated or may even be contraindicated. Then, other glucose-lowering medications should be considered. The evidence on other glucose-lowering agents (i.e., metformin, DPP-4 inhibitors, TZDs, sulfonylureas) has not changed in recent years, but they, in particular metformin, still have value in many people living with type 2 diabetes, as they offer robust glucose lowering. The selection of these glucose-lowering agents should be determined by the balance between their glucose-lowering efficacy and the side effect profile of the individual agents (Table 1).

Although longer-term evidence on durability of glucose-lowering efficacy by newer pharmacological agents and metabolic surgery is growing, many people living with type 2 diabetes will see a deterioration of glucose levels, despite maximal dietary and physical activity measures, reflecting the inability of these interventions to arrest the deterioration of β-cell function. Thus, many require a combination of agents, and some will need introduction of insulin to maintain good glucose levels, essential to prevention of microvascular disease. As stated in previous consensus documents, the preferred way of initiating insulin in people living with type 2 diabetes remains basal insulin, as it is easy to manage and achieves the main goal of insulin therapy in type 2 diabetes, namely the suppression of hepatic glucose output and lowering fasting glucose levels (Supplementary Fig. 1). Basal insulin analogs are preferred over NPH insulin, based on their lower risk of (mostly nocturnal) hypoglycemia. When initiating insulin, health behaviors should be revisited and rereferral to DSMES is warranted, as well as a review of concomitant glucose-lowering therapies. As such, medications that promote hypoglycemia and weight gain (such as sulfonylureas) should be stopped, while agents that promote weight loss, reduce insulin needs, and limit hypoglycemia (such as metformin, SGLT2 inhibitors, or GLP-1–based therapy) should be maintained or introduced simultaneously. Use of fixed-dose combinations may help limit the number of medications and injections needed (482).

Since the last consensus report, once-weekly insulins have been introduced, offering a more convenient form of insulin therapy. These provide a safe and effective way of introducing basal insulin in people living with type 2 diabetes, with fewer injections, although careful dose titration and monitoring for hypoglycemia remain important (208,210) (Supplementary Fig. 1).

The use of prandial insulin, administered via multiple daily injections of insulin, inhaled insulin, premixed insulin formulations, combination of basal and prandial insulin, or continuous insulin delivery (insulin pumps and automated insulin delivery [AID] systems; see below), may be required when postprandial glucose levels remain suboptimal despite optimal lifestyle, pharmacological, or surgical interventions. Extra support is required as the introduction of prandial insulin can be associated with further weight increase and increased risk of hypoglycemia (483). In individuals on longstanding insulin therapy, introduction of a GLP-1–based therapy and/or an SGLT2 inhibitor is warranted to limit insulin doses and weight as well as exploit their organ-protecting effects (48). Upon addition of a highly effective medication on the background of insulin therapy, insulin dose reductions, increased monitoring, and more frequent dose adjustments are required, particularly in those whose glucose levels are near target (e.g., <8%) (484,485).

Therapeutic inertia in intensification of glucose-lowering therapy, including the introduction of insulin, should be avoided. When clinicians are not familiar with insulin therapy, referral to specialist care is warranted. A critical appraisal of diabetes subtype in people not reaching glycemic targets should be conducted to avoid misdiagnosis.

When introduction of insulin is required, or when agents such as sulfonylureas are used, special attention needs to be given to populations in which hypoglycemia is most dangerous, such as people with frailty or older people who live alone. Consideration of less-stringent targets in such settings is prudent, and deprescribing should be considered if asymptomatic or severe hypoglycemia ensues. In addition, in people with frailty, potential health gains achieved by using potent agents such as GLP-1–based therapies or SGLT2 inhibitors need to be evaluated carefully, considering potential undesirable losses of lean mass (43,101,257,260).

Finally, it needs to be stated that, although improving, the evidence on interventions generally in specific subpopulations (e.g., younger and older people, women, and various racial and ethnic groups) continues to be limited. This lack of evidence is, however, not a reason to withhold interventions, including pharmacotherapies, in these subpopulations, given their proven benefits in the general population.

Consensus Recommendations

- The choice of glucose-lowering agents should be individualized based on the clinical profile of the person living with type 2 diabetes, including the presence of overweight, obesity, or sarcopenia, as well as other MLTCs, adverse effect profile of agents, individual preferences, and personal circumstances.
- In addition to DSMES and interventions focused on health behaviors, most people living with type 2 diabetes would benefit from early introduction of an SGLT2 inhibitor and/or GLP-1–based therapy, potentially from diagnosis.
- When clinically indicated, insulin should be initiated as basal insulin only, usually after GLP-1–based therapy, while maintaining other glucose-lowering agents, particularly cardio-kidney–protective agents such as SGLT2 inhibitors. Further intensification of therapy should be individualized based on the person's clinical profile, risk, circumstances, and preferences.
- Deintensification of glucose-lowering therapy associated with hypoglycemia risk (particularly sulfonylurea) should be addressed in people with frailty and type 2 diabetes.
- Targeted screening for secondary causes of hyperglycemia (e.g., hypercortisolism) should be considered for adults with treatment-resistant type 2 diabetes despite guideline-directed therapy with multiple agents.

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Place of Technology

People with type 2 diabetes are increasingly using CGM for monitoring glucose levels, either continuously or periodically. A growing body of evidence supports the use of CGM in people with type 2 diabetes, including clinically meaningful improvements in glucose levels and self-management, particularly among people treated with insulin (27,28,486,487). A growing number of clinical trials report statistically significant improvements in HbA_{1c} and TIR, with reductions in time spent above and below range, but overall, the effect size is modest, and most trials are often of short duration and small (28,488). Most studies report an improvement in person-reported outcomes with CGM, independent of the type of CGM, thus supporting use, at least periodically, of CGM by those living with type 2 diabetes (488).

AID has been evaluated in people living with type 2 diabetes and suggests an improved TIR (3.9–10.0 mmol/L [70–180 mg/dL]), with decreased time spent above range (489–491). Time spent in hypoglycemia was not affected. Weight was slightly increased in those using AID, highlighting the importance of using AID alongside other interventions such as DSMES and other glucose-lowering agents that may prevent weight gain.

Novel technologies are also entering the hospital setting, where CGM is now widely used, independent of diabetes subtype. CGM use is accompanied by a modest improvement in overall glucose levels, with less time spent in hypoglycemia. However, incorporating CGM use in nonendocrine wards requires adaptation of the hospital organization and additional training of health care professionals. Trials with closed-loop insulin delivery systems in the hospital setting are ongoing. First reports suggest improvements in glucose levels with less time spent in hyperglycemia, compared with use of CGM only, with no effect on time spent in hypoglycemia. Again, trials have been small and short in duration (492).

SDOH must be addressed to ensure equitable access to diabetes technology for all those with type 2 diabetes who stand to benefit.

Consensus Recommendations

- Evidence-based diabetes technologies, with proven benefits in people with type 2 diabetes, should be considered as adjunctive tools within a comprehensive, integrated diabetes management plan and should be individualized based on clinical need, preference, and skill level.
- CGM should be considered in people living with type 2 diabetes, especially those on insulin.

Implementation of Evidence-Based Interventions for Type 2 Diabetes: Importance of Organization of Care

Real-world and modeling evidence on newer therapies shows that SGLT2 inhibitors and GLP-1–based therapies provide cardiovascular, kidney, metabolic, and health care utilization benefits (493–499), but their population impact is constrained by access, utilization, persistence, and cost (500,501). Cost and access barriers are being mitigated in many countries, related to patent expirations and market forces. Therapeutic inertia is recognized as a major factor in the underuse of evidence-based screening for complications and interventions for type 2 diabetes management (502).

An important strategy to overcome therapeutic inertia in the management of type 2 diabetes is the adaptation of health care systems. Ideally, this entails the adoption of community-based, multidisciplinary primary care that incorporates nonphysician health care providers (503). Individualization of care and consideration of preferences and SDOH are also key for implementation of clinical guidelines (Fig. 6).

Systems of care have a significant role in improving diabetes management and outcomes because they can facilitate the implementation of evidence-based interventions (Fig. 6). The structure and organization of the health care team will vary across systems but generally involve multiple disciplines (2,3). It is increasingly recognized that wider team-based care (e.g., including nurses, pharmacists, and dietitians as key members of the health care team [504–506]) has the potential to improve diabetes care. Technology is now an important tool to enhance communication, support, and monitoring, and digital health interventions demonstrate the potential to improve outcomes such as glucose levels (507). However, digital tools, such as telehealth and mHealth interventions that include apps, wearables, and digital coaching, have been shown to be most effective when they are multicomponent, interactive, personalized, sustained over 6–12 months, and clinician led, with modest but consistent HbA_{1c} reductions (507–509). Social media health information should be recognized as an important determinant of treatment implementation and diabetes self-management, as digital narratives can shape peoples' expectations, perceptions of benefits and harms, medication-taking behaviors, and decisions to continue or discontinue therapy; accordingly, it represents a relevant domain for communication between health care professionals and people with diabetes and a priority area for future research (11). Novel treatment support modalities (nurse-led coaching, clinician feedback, pharmacist-led telemonitoring) offer benefits beyond glucose lowering by improving access, engagement, satisfaction, and cost-effectiveness, outperforming passive apps or DSMES alone (470,504,510,511). Combining behavioral interventions with digital technology seems to be a particularly useful implementation strategy that enhances feasibility. Behavioral interventions such as transtheoretical model (TTM)-based motivational interviewing have been shown to produce additive glucose-lowering benefits by improving self-management and self-efficacy (512), and TTM-based, telemedicine lifestyle interventions can achieve improvements in self-management, self-efficacy, and glucose levels (513). Models to integrate care infrastructure and pathways (e.g., shared care, chronic care model) for such interventions can improve health outcomes in people living with type 2 diabetes (Fig. 6), but poor sustainability due to workforce, time, and cost constraints is a limiting factor (514). Another novel approach is pairing training of primary health care professionals with patient previsit prompting, which has proved to be a cost-effective and safe way of deprescribing glucose-lowering drugs with hypoglycemia risk in older adults with type 2 diabetes (515).

Finally, health systems must attend to equity in the delivery of all diabetes care, including access to DSMES and the more expensive, organ-protecting pharmacotherapies (SGLT2 inhibitors and GLP-1–based therapy) and technologies (e.g., CGM) (516–518). Improving the care of

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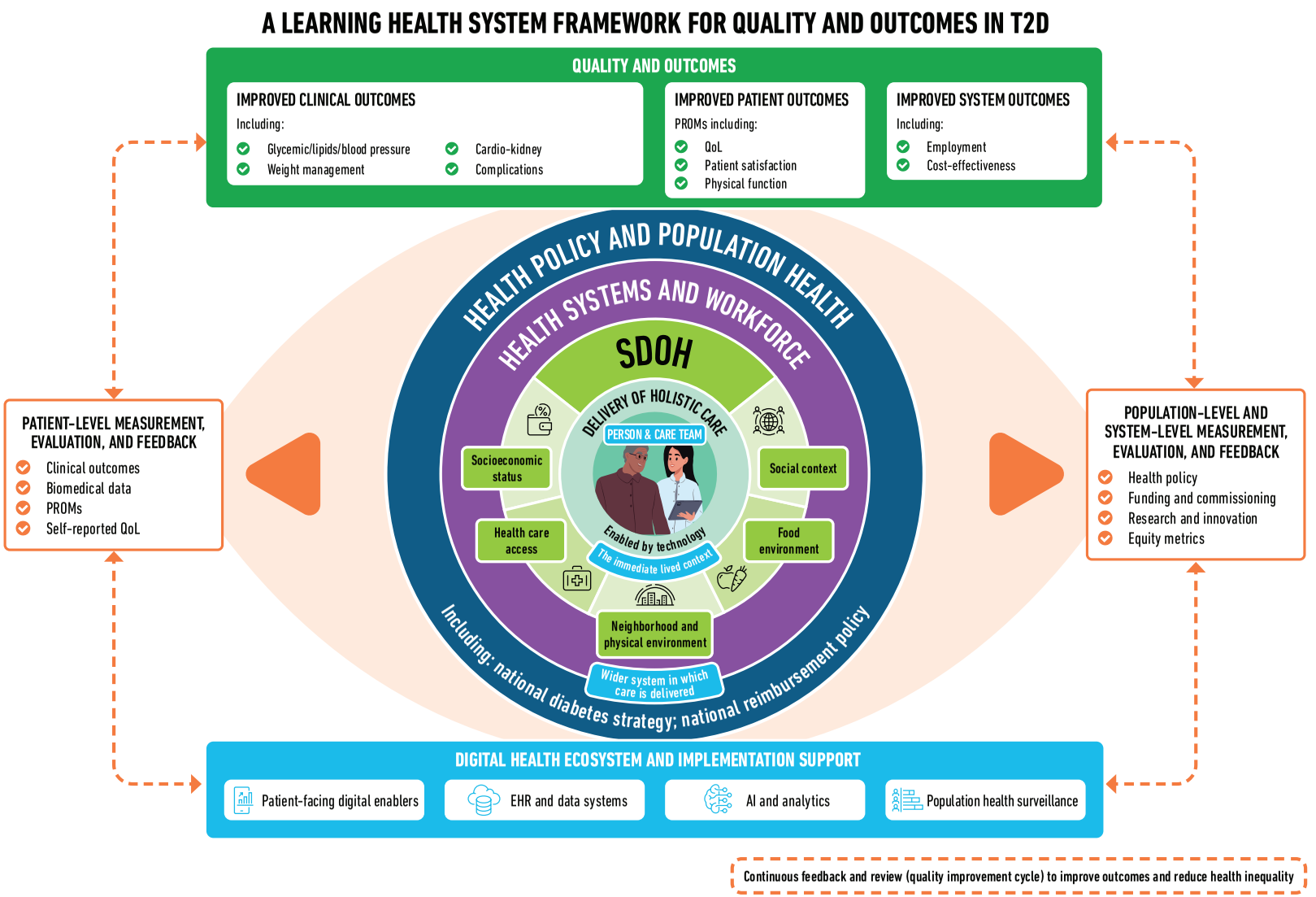


Figure 6—A learning health system framework for quality and outcomes in type 2 diabetes. AI, artificial intelligence; EHR, electronic health record; PROMs, patient-reported outcome measures; QoL, quality of life; T2D, type 2 diabetes.

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type 2 diabetes by integrating DSMES, promotion of health behaviors, and use of glucose-lowering pharmacotherapy tailored to the individual (including MLTCs) continues to require system-level change, which should empower primary care as the central hub of care in many settings. Innovative models of care that include remote e-health interventions and combinations of digital–human interventions are needed to support people living with type 2 diabetes (Fig. 6). Notably, equitable access to diabetes technology remains a major challenge in both low- and high-income countries. In addition to cost, the digital divide (including limited access to compatible smartphones, reliable high-speed internet, and cloud-based platforms) as well as poor health and digital literacy, particularly among older adults, can substantially hinder the adoption and effective use of diabetes technologies across nations and socioeconomic groups.

Consensus Recommendations

- Health care systems should be organized to deliver individualized diabetes care that is integrated into the daily lives of people with type 2 diabetes.
- Care for people with type 2 diabetes should be individualized, with explicit consideration of each person's clinical risks, personal preferences, lived context, and SDOH, including socioeconomic status, food security, housing stability, and access to care.
- The management plan for people with type 2 diabetes should incorporate all MLTCs, with treatment priorities, glycemic targets, and pharmacological choices informed by the overall disease burden.
- Care delivery for people with type 2 diabetes should leverage innovative models, including digital health tools and interprofessional team-based care, to expand access and support self-management.
- Health care systems should establish mechanisms to identify and address inequities in the delivery of evidence-based care for people with type 2 diabetes, ensuring that health care is affordable and accessible to all.

KEY KNOWLEDGE GAPS AND A CALL TO ACTION

This update has broadened the focus from prior statements on the management of hyperglycemia to the holistic management of type 2 diabetes and its associated MLTCs. While suggesting individualizing care for each person with diabetes, we recognize that for most people that should comprise lifestyle and behavioral coaching focusing on nutrition, physical activity, self-monitoring, DSMES, and, for most, medications with disease-modifying characteristics, such as GLP-1–based therapies and SGLT2 inhibitors, in order to meet weight, glycemic, and cardiovascular risk targets as well as address cardiometabolic disease. There is an increasing focus on achieving remission of type 2 diabetes; however, current definitions predominantly based on glycemic thresholds falling below the diagnostic range in the absence of glucose-lowering therapy are inherently simplistic. While useful operationally, such definitions do not fully capture the complex underpinning pathophysiology or the broader trajectories of cardiometabolic disease. Hyperglycemia represents one component of disease burden and may not reflect ongoing pathophysiological processes, including excess adiposity, insulin resistance, β-cell function, inflammation, and residual cardiovascular and kidney risk. Furthermore, individuals meeting current remission criteria still carry substantial long-term risk of relapse and complications. A broader conceptual framework built on type 2 diabetes modification may be more clinically meaningful, recognizing sustained improvements in metabolic health, organ protection, adiposity, functional health, and long-term outcomes rather than glucose alone. Such an approach aligns more closely with contemporary understanding of type 2 diabetes as a chronic, progressive multisystem disease. As we stated in 2022, the major opportunities to improve diabetes outcomes in the near term come from more effective and equitable implementation of best evidence through organization of care at all levels and from addressing SDOH. That said, many details of optimal management have not been established and require further study. Examples include the following:

- Consensus is emerging that early intensive therapy in type 2 diabetes is associated with sustained benefits, but trial evidence for glycemic targets of <53 mmol/mol (<7%) is poorly developed and for CGM targets is essentially nonexistent. We need trials to provide convincing evidence for new targets.
- The aim of achieving "remission" should perhaps be rethought as not just achieving euglycemia absent of glucose-lowering medications for 3 months but perhaps as a means to reduce the risk of developing associated complications/conditions. In that context, should the definition of remission be broadened to include modifications of associated long-term conditions, whether treatment with medications continues?
- We need to develop optimal strategies to maintain remission over time.
- We have burgeoning pharmacological and technological applications in type 2 diabetes management. How can we optimally sequence them and when is enough in fact enough?
- Most studies of GLP-1–based therapies recruit people with overweight or obesity. How should GLP-1–based therapies be used in people where weight loss is not desired? Currently, in people with type 2 diabetes where GLP-1–based therapy is desired for glycemic or cardiovascular benefit but weight loss is not desired, dulaglutide may be preferred.
- We need better trial evidence for early intensive therapy in early-onset type 2 diabetes, particularly in youth with type 2 diabetes in whom the lifetime risk of complications is highest. Similarly, there is inadequate understanding of how and when to deintensify therapy later in life.
- Women's health approaches in the context of diabetes management have been understudied. A new issue is how GLP-1–based treatments should be managed in the context of pregnancy. GLP-1–based therapies are not recommended for use during pregnancy and could adversely affect a fetus. However, discontinuing GLP-1–based therapies may result in excessive weight gain and loss of glycemic management during pregnancy with potential harms for both mother and baby. Further study is desperately needed.
- How should adiposity be measured to best reflect the metabolic impact of adiposopathy and what should be targets for medical and surgical weight loss programs?

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- What are optimal lifestyle programs to support GLP-1–based therapy, including MNT and the five S's, to reach weight targets and preserve fat-free mass (particularly skeletal muscle mass and bone) and function? Furthermore, what are the best ways of tackling accelerated aging, considering outcomes related to whole-body health and physical function?
- With the emergence of increasingly effective weight loss drugs, we need to understand whether high doses of moderately effective agents are equivalent to modest doses of highly effective agents for outcomes and also the optimum approaches for maintenance of weight loss.
- What should be the evaluation strategy for people with inadequate responses to generally effective therapies? Recent studies suggest screening for hypercortisolism identifies a treatable cause in ∼25%. There must be others.
- Developing a better understanding of the role of cortisol-directed therapy in type 2 diabetes is needed.
- We still do not have compelling evidence for whether GLP-1–based therapy and SGLT2 inhibitors should be routinely combined, or whether there is an optimal sequence by which they should be added.

Precision or personalized medicine has been a North Star for a decade but remains an evolving goal in type 2 diabetes (519). Advances in biomarker development and leveraging artificial intelligence are potentially transformational not only in targeting treatments based on individual characteristics but also in facilitating DSMES, medication management and titration, and care coordination, essentially every aspect of modern medicine. Artificial intelligence has the potential to deliver both substantial advances and disruptive changes in medicine and wider society. The emerging nature of threats such as disinformation, climate change, water quality, atmospheric particles and pollutants, microplastics, societal stressors, and lack of human engagement, among others, is recognized but not fully appreciated and their mitigation even less well understood.

We have made strong recommendations based on a high level of evidence for specific MLTCs. In approaching care holistically, it would be optimal to be able to make regulatory decisions and require equitable access in society based on broad benefits of highly effective therapies, whether behavioral or pharmacological. Regulatory and payment reform in most health care systems is needed.

Broad support for basic science remains foundational to the advances that will transform care in the next decade.

However, despite all the major advances in glucose-lowering and weight loss pharmacotherapies and digital technology, perhaps the greatest opportunity to improve outcomes for people living with type 2 diabetes remains getting the fundamentals of the core components right. Timely initiation and intensification of therapy, particularly the earlier and more comprehensive use of therapies with proven cardio-kidney benefit, such as SGLT2 inhibitors and GLP-1–based therapies, have the potential to substantially reduce long-term complications and premature mortality. Equally important is universal access to high-quality DSMES and well-organized systems of care. Structured surveillance for complications, combined with proactive risk management, remains essential. Collectively, with consistent delivery of these core components of care at scale, the ability to transform outcomes for people living with type 2 diabetes is within our grasp. This is not reliant on future innovations but is achievable now through consistent, equitable, and systematic implementation of strategies and therapies already available.

Acknowledgments. M. Bonar and C. Franklin (both Leicester Diabetes Centre, University of Leicester, and the University Hospitals of Leicester NHS Trust, Leicester, U.K.) assisted with the conception and execution of figures and tables; T. Yates and J. Henson (both Leicester Diabetes Centre, University of Leicester, and the University Hospitals of Leicester NHS Trust, Leicester, U.K.) and Z.I. Saeed and J.W. Ostrominski (both Brigham and Women's Hospital, Harvard Medical School, Boston, MA) supported the production and content of Fig. 3. We acknowledge the support of C. Stendall and M. Spencer (both Leicester Diabetes Centre, University of Leicester, and the University Hospitals of Leicester NHS Trust, Leicester, U.K.), R.R. Bannuru, A. Bennett, and J. Neumiller (all ADA, Arlington, VA), P. Niemann, M. Schönke, and L. Rother (all EASD, Dusseldorf, Germany), the Committee for Clinical Affairs of the EASD, and the Professional Practice Committee of the ADA.

V.R.A., J.G., A.T., and J.B.B. are editors of *Diabetes Care* but were not involved in any of the decisions regarding review of the manuscript or its acceptance.

Funding. This activity was funded by the ADA and the EASD.

Duality of Interest. M.J.D. has acted as a consultant/advisor and speaker for Eli Lilly, Novo Nordisk, and Sanofi, has acted as a consultant/advisor for Kailera, has attended advisory boards for AbbVie, Amgen, AstraZeneca, Biomea Fusion, Carmot/Roche, Daewoong Pharmaceutical, Sanofi, Zealand Pharma, Regeneron, GSK, Innovent Bio, and EktaH, and has acted as a speaker for AstraZeneca, Boehringer Ingelheim, Obesity Alliance, and Zuellig Pharma. She has received grants from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. V.R.A. has institutional contracts with Amgen, AstraZeneca, Applied Therapeutics, Biomea, Corcept, Eli Lilly, Fractyl, Kailera, Novo Nordisk, Pfizer, Recordati, Rhythm, and Servier and is a consultant for Baim, Mediflix, Roche, and Sanofi. M.B. is a member of the ADA Board of Directors and has received research funding (to institution) from the ADA. He is editor in chief of *BMJ Open Diabetes Research and Care*. N.A.E. has served on the advisory board for Novo Nordisk. F.G. has received research support from Eli Lilly and Roche Diabetes Care, has received consulting fees from Eli Lilly, Novo Nordisk, and Kayothera, and serves or has served on advisory boards for AstraZeneca, Biomea, Boehringer Ingelheim, Eli Lilly, Kayothera, Lifescan, Merck Sharp & Dohme, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi. He serves or has served on boards for EASD/European Foundation for the Study of Diabetes (EFSD) and European Diabetes Forum (EUDF). He has given lectures, presentations, or educational events for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Lifescan, Merck Sharp & Dohme, Medtronic, Novo Nordisk, Roche Diabetes Care, and Sanofi and has received support for medical writing and statistical analysis from Eli Lilly, Novo Nordisk, Roche Diabetes Care, and Sanofi. J.G. is or has acted as a consultant for Aqua, AstraZeneca, Bayer, Boehringer Ingelheim, Fractyl, vTv, Lilly, Novo Nordisk, Roche, Sparrow Pharmaceuticals, Vertex, and Zealand. She has received research support from Boehringer Ingelheim, Cour, GentiBio, Merck, and Metsera. R.R.K. currently serves as Chief Scientific and Medical Officer of the ADA. N.M.M. is an author of modules for UpToDate on MNT for type 2 diabetes and prevention of type 2 diabetes. She is entitled to royalties for this authorship. C.M. serves or has served on the advisory panel for Novo Nordisk, Sanofi, Eli Lilly and Company, Novartis, Dexcom, Boehringer Ingelheim, Bayer, Roche, Abbott, Medtronic, Insulet, Biomea Fusion, SAB Bio, vTv Therapeutics, and Vertex. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for C.M. from Dexcom, Novo Nordisk, and Sanofi. C.M. serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Eli Lilly and Company, Medtronic, Dexcom, Insulet, Abbott, Vertex, and Boehringer Ingelheim. Financial compensation for these activities has been received by KU Leuven. C.M. is president of EUDF. All external support of EUDF can be found on www.eudf.org. S.E.R. has received research funding (to institution) from Bayer and National Institute of Diabetes and Digestive and Kidney Diseases. She is on the steering committee for FineOne and has participated on

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the scientific advisory board for Bayer, Novo Nordisk, and Travere. P.R. has received grants or contracts (to institution) from AstraZeneca, Bayer, and Novo Nordisk and honoraria (to institution) from Astra Zeneca, Abbott, Bayer, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. He has received consulting fees from AstraZeneca, Abbott, Amgen, Bayer, Boehringer Ingelheim, Novo Nordisk, Lexicon, Roche, and Regeneron. He has received study medication from Astra Zeneca, Bayer, Novo Nordisk, and Lexicon. T.T. serves or has served on the advisory board for Novo Nordisk, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Sanofi, and Merck and on the speaker's bureau for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, AstraZeneca, Merck Sharp & Dohme, Servier, Merck, and Medtronic. P.T. serves or has served on the advisory board for Abbott, AstraZeneca, Boehringer Ingelheim, Danone, Eli Lilly, Novo Nordisk, and Lifescan. A.T. has received support for attending meetings from Bayer, Menarini, and Novo Nordisk outside the submitted work. He also serves as chair of the EASD Guidelines Oversight Committee. J.B.B. has received research support from Corcept, GentiBio, Novo Nordisk, and Sparrow Pharmaceuticals. He is or has acted as a paid consultant/on the advisory board for Aardvark Therapeutics, Altimmune, Alveus Therapeutics, Amgen, Antag, Aqua Medical, AstraZeneca, Corcept Therapeutics, Eli Lilly, General Medicines Inc., Kayothera, Metsera, Novo Nordisk, Pfizer, Recordati, Roche, Sparrow Pharmaceuticals, Vertex, vTv Therapeutics, and Zealand. He is an investor in Aardvark Therapeutics, Glyscend, Mellitus Health, Metsera, Pendulum Therapeutics, Praetego, and Stability Health. No other potential conflicts relevant to this article were reported.

Author Contributions. All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors approved the version to be published.

Data Availability. Details of the search strategy and list of identified articles can be found at https://doi.org/10.17605/osf.io/pu93h.

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