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CONSENSUS REPORT

Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Melanie J. Davies[1,2] · Vanita R. Aroda[3] · Billy S. Collins[4] · Robert A. Gabbay[5] · Jennifer Green[6] · Nisa M. Maruthur[7] · Sylvia E. Rosas[8] · Stefano Del Prato[9] · Chantal Mathieu[10] · Geltrude Mingrone[11,12,13] · Peter Rossing[14,15] · Tsvetalina Tankova[16] · Apostolos Tsapas[17,18] · John B. Buse[19]

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Abstract

The American Diabetes Association and the European Association for the Study of Diabetes convened a panel to update the previous consensus statements on the management of hyperglycaemia in type 2 diabetes in adults, published since 2006 and last updated in 2019. The target audience is the full spectrum of the professional healthcare team providing diabetes care in the USA and Europe. A systematic examination of publications since 2018 informed new recommendations. These include additional focus on social determinants of health, the healthcare system and physical activity behaviours including sleep. There is a greater emphasis on weight management as part of the holistic approach to diabetes management. The results of cardiovascular and kidney outcomes trials involving sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, including assessment of subgroups, inform broader recommendations for cardiorenal protection in people with diabetes at high risk of cardiorenal disease. After a summary listing of consensus recommendations, practical tips for implementation are provided.

Keywords Cardiovascular disease · Chronic kidney disease · Glucose-lowering therapy · Guidelines · Heart failure · Holistic care · Person-centred care · Social determinants of health · Type 2 diabetes mellitus · Weight management

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A consensus report of a particular topic contains a comprehensive examination and is authored by an expert panel and represents the panel's collective analysis, evaluation and opinion. MJD and JBB were co-chairs for the Consensus Report Writing Group. VRA, BSC, RAG, JG, NMM and SER were the writing group members for ADA. SDP, CM, GM, PR, TT and AT were the writing group members for EASD. The article was reviewed for EASD by its Committee on Clinical Affairs and approved by its Executive Board. The article was reviewed for ADA by its Professional Practice Committee.

Melanie J. Davies (for *Diabetologia*)
melanie.davies@uhl-tr.nhs.uk

John B. Buse (for *Diabetes Care*)
jbuse@med.unc.edu

Extended author information available on the last page of the article

Abbreviations

BGM	Blood glucose monitoring
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
CVOT	Cardiovascular outcomes trial
DKA	Diabetic ketoacidosis
DPP-4i	Dipeptidyl peptidase-4 inhibitors
DSMES	Diabetes self-management education and support
ETD	Estimated treatment difference
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1 RA	Glucagon-like peptide-1 receptor agonist(s)
HF	Heart failure
HHF	Hospitalisation for heart failure
MACE	Major adverse cardiovascular events
MNT	Medical nutrition therapy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
SGLT1i	Sodium–glucose cotransporter-1 inhibitor

SGLT2i	Sodium–glucose cotransporter-2 inhibitor(s)
TZD	Thiazolidinedione
UACR	Urinary albumin/creatinine ratio

Introduction

Type 2 diabetes is a chronic complex disease and management requires multifactorial behavioural and pharmacological treatments to prevent or delay complications and maintain quality of life (Fig. 1). This includes management of blood glucose levels, weight, cardiovascular risk factors, comorbidities and complications. This necessitates that care be delivered in an organised and structured way, such as described in the chronic care model, and includes a person-centred approach to enhance engagement in self-care activities [1]. Careful consideration of social determinants of health and the preferences of people living with diabetes must inform individualisation of treatment goals and strategies [2].

This consensus report addresses the approaches to management of blood glucose levels in non-pregnant adults with type 2 diabetes. The principles and approach for achieving this are summarised in Fig. 1. These recommendations are not generally applicable to individuals with diabetes due to other causes, for example monogenic diabetes, secondary diabetes and type 1 diabetes, or to children.

Data sources, searches and study selection

The writing group members were appointed by the ADA and EASD. The group largely worked virtually with regular teleconferences from September 2021, a 3 day workshop in January 2022 and a face-to-face 2 day meeting in April 2022. The writing group accepted the 2012 [3], 2015 [4], 2018 [5] and 2019 [6] editions of this consensus report as a starting point. To identify newer evidence, a search was conducted on PubMed for RCTs, systematic reviews and meta-analyses published in English between 28 January 2018 and 13 June 2022; eligible publications examined the effectiveness or safety of pharmacological or non-pharmacological interventions in adults with type 2 diabetes. Reference lists in eligible reports were scanned to identify additional relevant articles. Details of the keywords and the search strategy are available at https://data.mendeley.com/datasets/h5rcnxpk8w/2. Papers were grouped according to subject and the authors reviewed this new evidence. Up-to-date meta-analyses evaluating the effects of therapeutic interventions across clinically important subgroup populations were assessed in terms of their credibility using relevant guidance [7, 8]. Evidence appraisal was informed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines on the formulation of clinical practice recommendations [9, 10]. The draft consensus recommendations were evaluated by invited reviewers and presented for public comment. Suggestions were incorporated as deemed appropriate by the authors (see Acknowledgements). Nevertheless, although evidence based with stakeholder input, the recommendations presented herein reflect the values and preferences of the consensus group.

The rationale, importance and context of glucose-lowering treatment

Fundamental aspects of diabetes care include promoting healthy behaviours, through medical nutrition therapy (MNT), physical activity and psychological support, as well as weight management and tobacco/substance abuse counselling as needed. This is often delivered in the context of diabetes self-management education and support (DSMES). The expanding number of glucose-lowering interventions—from behavioural interventions to pharmacological interventions, devices and surgery—and growing information about their benefits and risks provide more options for people with diabetes and providers but complicate decision making. The demonstrated benefits for high-risk individuals with atherosclerotic CVD, heart failure (HF) or chronic kidney disease (CKD) afforded by the glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter-2 inhibitors (SGLT2i) provide important progress in treatment aimed at reducing the progression and burden of diabetes and its complications. These benefits are largely independent of their glucose-lowering effects. These treatments were initially introduced as glucose-lowering agents but are now also prescribed for organ protection. In this consensus report, we summarise a large body of recent evidence for practitioners in the USA and Europe with the aim of simplifying clinical decision making and focusing our efforts on providing holistic person-centred care.

Attaining recommended glycaemic targets yields substantial and enduring reductions in the onset and progression of microvascular complications [11, 12] and early intervention is essential [13]. The greatest absolute risk reduction comes from improving very elevated glycaemic levels, and a more modest reduction results from near normalisation of plasma glucose levels [2, 14]. The impact of glucose control on macrovascular complications is less certain but is supported by multiple meta-analyses and epidemiological studies. Because the benefits of intensive glucose control emerge slowly while the harms can be immediate, people with longer life expectancy have more to gain from early intensive glycaemic management. A reasonable HbA_{1c} target for most non-pregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) is around 53 mmol/mol (7%) or less [2]. Aiming for a lower HbA_{1c} level than this may have value if it can be achieved safely without significant hypoglycaemia or

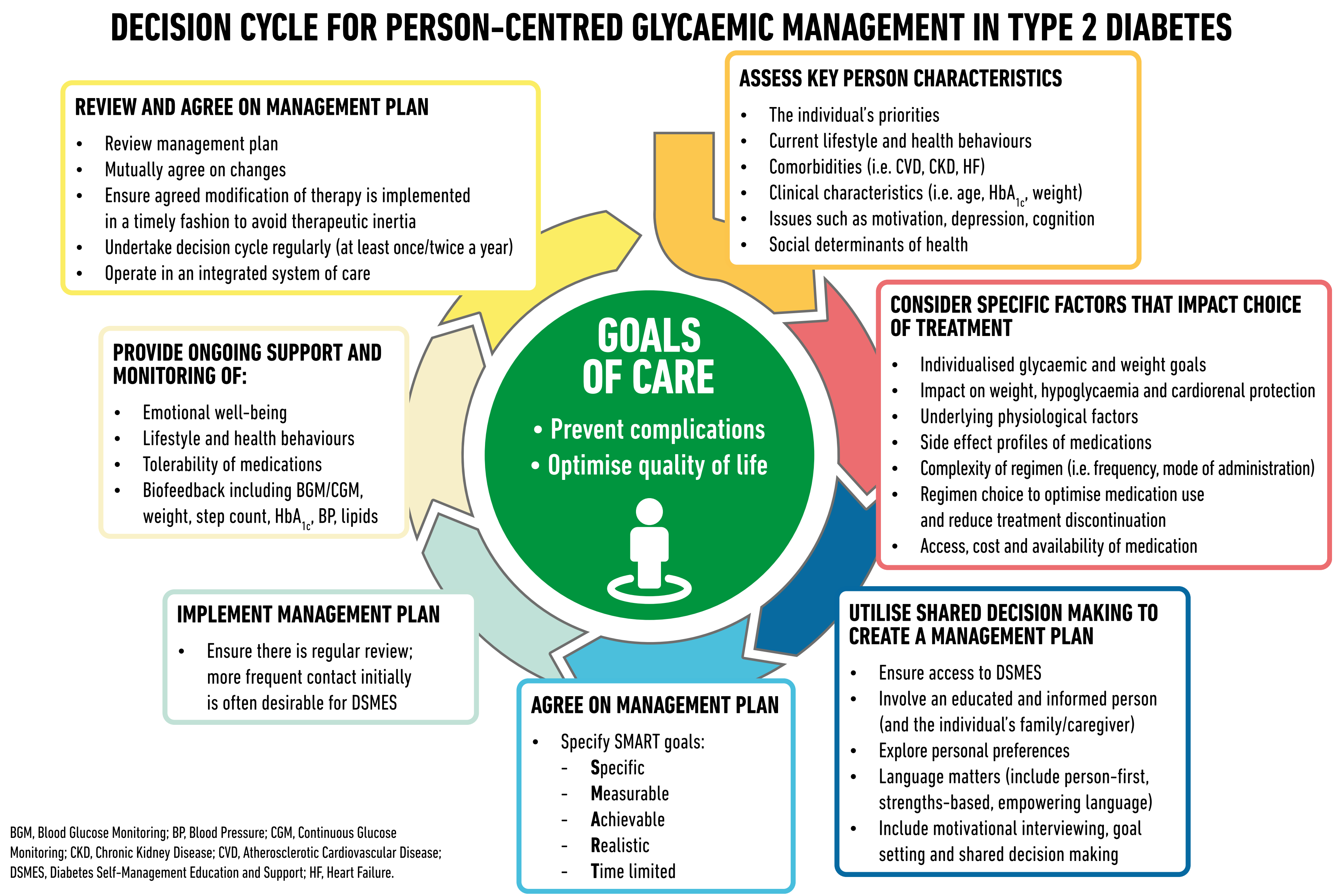


Fig. 1 Decision cycle for person-centred glycaemic management in type 2 diabetes. Adapted from [5] with permission from Springer Nature, © European Association for the Study of Diabetes and American Diabetes Association, 2018

other adverse treatment effects. A lower target may be reasonable, particularly when using pharmacological agents that are not associated with hypoglycaemic risk. Higher targets can be appropriate in cases of limited life expectancy, advanced complications or poor tolerability or if other factors such as frailty are present. Thus, glycaemic treatment targets should be tailored based on an individual's preferences and characteristics, including younger age (i.e. age <40 years), risk of complications, frailty and comorbid conditions [2, 15–17], and the impact of these features on the risk of adverse effects of therapy (e.g. hypoglycaemia and weight gain).

Principles of care

Language matters

Communication between people living with type 2 diabetes and healthcare team members is at the core of integrated care, and clinicians must recognise how language matters. Language in diabetes care should be neutral, free of stigma and based on facts; be strengths-based (focus on what is working), respectful and inclusive; encourage collaboration; and be person-centred [18]. People living with diabetes should not be referred to as 'diabetics' or described as 'non-compliant' or blamed for their health condition.

Diabetes self-management education and support

DSMES is a key intervention, as important to the treatment plan as the selection of pharmacotherapy [19–21]. DSMES is central to establishing and implementing the principles of care (Fig. 1). DSMES programmes usually involve face-to-face contact in group or individual sessions with trained educators, and key components of DSMES are shown in Supplementary Table 1 [19–24]. Given the ever-changing nature of type 2 diabetes, DSMES should be offered on an ongoing basis. Critical junctures when DSMES should be provided include at diagnosis, annually, when complications arise, and during transitions in life and care (Supplementary Table 1) [22].

High-quality evidence has consistently shown that DSMES significantly improves knowledge, glycaemic levels and clinical and psychological outcomes, reduces hospital admissions and all-cause mortality and is cost-effective [22, 25–30]. DSMES is delivered through structured educational programmes provided by trained diabetes care and education specialists (termed DCES in the USA; hereafter referred to as 'diabetes educators') that focus particularly on the following: lifestyle behaviours (healthy eating, physical activity and weight management), medication-taking behaviour, self-monitoring when needed, self-efficacy, coping and problem solving.

Importantly, DSMES is tailored to the individual's context, which includes their beliefs and preferences. DSMES can be provided using multiple approaches and in a variety of settings [20, 31] and it is important for the care team to know how to access local DSMES resources. DSMES supports the psychosocial care of people with diabetes but is not a replacement for referral for mental health services when they are warranted, for example when diabetes distress remains after DSMES. Psychiatric disorders, including disordered eating behaviours, are common, often unrecognised and contribute to poor outcomes in diabetes [32].

The best outcomes from DSMES are achieved through programmes with a theory-based and structured curriculum and with contact time of over 10 h [26]. While online programmes may reinforce learning, a comprehensive approach to education using multiple methods may be more effective [26]. Emerging evidence demonstrates the benefits of telehealth or web-based DSMES programmes [33] and these were used with success during the COVID-19 pandemic [34–36]. Technologies such as mobile apps, simulation tools, digital coaching and digital self-management interventions can be used to deliver DSMES and extend its reach to a broader segment of the population with diabetes and provide comparable or even better outcomes [37]. Greater HbA_{1c} reductions are demonstrated with increased engagement of people with diabetes [35, 38]. However, data from trials of digital strategies to support behaviour change are still preliminary in nature and quite heterogeneous [22, 37].

Individualised and personalised approach

Type 2 diabetes is a very heterogeneous disease with variable age at onset, related degree of obesity, insulin resistance and tendency to develop complications [39, 40]. Providing person-centred care that addresses multimorbidity and is respectful of and responsive to individual preferences and barriers, including the differential costs of therapies, is essential for effective diabetes management [41]. Shared decision making, facilitated by decision aids that show the absolute benefit and risk of alternative treatment options, is a useful strategy to determine the best treatment course for an individual [42–45]. With compelling indications for therapies such as SGLT2i and GLP-1 RA for high-risk individuals with CVD, HF or CKD, shared decision making is essential to contextualise the evidence on benefits, safety and risks. Providers should evaluate the impact of any suggested intervention in the context of cognitive impairment, limited literacy, distinct cultural beliefs and individual fears or health concerns. The healthcare system is an important factor in the implementation, evaluation and development of the personalised approach. Furthermore, social determinants of health—often out of direct control of the individual and potentially representing lifelong risk—contribute to medical and psychosocial outcomes and must be addressed to improve health outcomes. Five social determinants of health areas have been identified: socioeconomic status (education, income and occupation), living and working conditions, multisector domains (e.g. housing, education and criminal justice system), sociocultural context (e.g. shared cultural values, practices and experiences) and sociopolitical context (e.g. societal and political norms that are root cause ideologies and policies underlying health disparities) [46]. More granularity on social determinants of health as they pertain to diabetes is provided in a recent ADA review [47], with a particular focus on the issues faced in the African American population provided in a subsequent report [48]. Environmental, social, behavioural and emotional factors, known as psychosocial factors, also influence living with diabetes and achieving satisfactory medical outcomes and psychological well-being. Thus, these multifaceted domains (heterogeneity across individual characteristics, social determinants of health and psychosocial factors) challenge individuals with diabetes, their families and their providers when attempting to integrate diabetes care into daily life [49].

Current principles of, and approaches to, person-centred care in diabetes (Fig. 1) include assessing key characteristics and preferences to determine individualised treatment goals and strategies. Such characteristics include comorbidities, clinical characteristics and compelling indications for GLP-1 RA or SGLT2i for organ protection [6].

Weight reduction as a targeted intervention

Weight reduction has mostly been seen as a strategy to improve HbA_{1c} and reduce the risk for weight-related complications. However, it was recently suggested that weight loss of 5–15% should be a primary target of management for many people living with type 2 diabetes [50]. A higher magnitude of weight loss confers better outcomes. Weight loss of 5–10% confers metabolic improvement; weight loss of 10–15% or more can have a disease-modifying effect and lead to remission of diabetes [50], defined as normal blood glucose levels for 3 months or more in the absence of pharmacological therapy in a 2021 consensus report [51]. Weight loss may exert benefits that extend beyond glycaemic management to improve risk factors for cardiometabolic disease and quality of life [50].

Glucose management: monitoring

Glycaemic management is primarily assessed with the HbA_{1c} test, which was the measure used in trials demonstrating the benefits of glucose lowering [2, 52]. As with any laboratory test, HbA_{1c} measurement has limitations [2, 52]. There may be discrepancies between HbA_{1c} results and an individual's true mean blood glucose levels, particularly in certain racial and ethnic groups and in conditions that alter erythrocyte turnover, such as anaemia, end-stage kidney disease (especially with erythropoietin therapy) and pregnancy, or if an HbA_{1c} assay insensitive to haemoglobin variants is used in someone with a haemoglobinopathy. Discrepancies between measured HbA_{1c} levels and measured or reported glucose levels should prompt consideration that one of these may not be reliable [52, 53].

Regular blood glucose monitoring (BGM) may help with self-management and medication adjustment, particularly in individuals taking insulin. BGM plans should be individualised. People with type 2 diabetes and the healthcare team should use the monitoring data in an effective and timely manner. In people with type 2 diabetes not using insulin, routine glucose monitoring is of limited additional clinical benefit while adding burden and cost [54, 55]. However, for some individuals, glucose monitoring can provide insight into the impact of lifestyle and medication management on blood glucose and symptoms, particularly when combined with education and support [53]. Technologies such as intermittently scanned or real-time continuous glucose monitoring (CGM) provide more information and may be useful for people with type 2 diabetes, particularly in those treated with insulin [53, 56].

When using CGM, standardised, single-page glucose reports, such as the ambulatory glucose profile, can be uploaded from CGM devices. They should be considered as standard metrics for all CGM devices and provide visual cues for management opportunities. Time in range is defined as the percentage of time that CGM readings are in the range 3.9–10.0 mmol/l (70–180 mg/dl). Time in range is associated with the risk of microvascular complications and can be used for assessment of glycaemic management [57]. Additionally, time above and below range are useful variables for the evaluation of treatment regimens. Particular attention to minimising the time below range in those with hypoglycaemia unawareness may convey benefit. If using the ambulatory glucose profile to assess glycaemic management, a goal parallel to an HbA_{1c} level of <53 mmol/mol (<7%) for many is time in range of >70%, with additional recommendations to aim for time below range of <4% and time at <3.0 mmol/l (<54 mg/dl) of <1% [2].

Treatment behaviours, persistence and adherence

Suboptimal medication-taking behaviour 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 glycaemic and CVD risk factor control as well as increased risks of diabetes complications, mortality and hospital admissions and increased healthcare costs [58–62]. Although this consensus report focuses on medication-taking behaviour, the principles are pertinent to all aspects of diabetes care. Multiple factors contribute to inconsistent medication use and treatment discontinuation among people with diabetes, including perceived lack of medication efficacy, fear of hypoglycaemia, lack of access to medication and adverse effects of medication [63]. Focusing on facilitators of adherence, such as social/family/provider support, motivation, education and access to medications/foods, can provide benefits [64]. Observed rates of medication adherence and persistence vary across medication classes and between agents; careful consideration of these differences may help improve outcomes [61]. Ultimately, individual preferences are major factors driving the choice of medications. Even when clinical characteristics suggest the use of a particular medication based on the available evidence from clinical trials, preferences regarding route of administration, injection devices, side effects or cost may prevent use by some individuals [65].

Therapeutic inertia

Therapeutic (or clinical) inertia describes a lack of treatment intensification when targets or goals are not met. It also includes failure to de-intensify management when people are overtreated. The causes of therapeutic inertia are multifactorial, occurring at the levels of the practitioner, person with diabetes and/or healthcare system [66]. Interventions targeting therapeutic inertia have facilitated improvements in glycaemic management and timely insulin intensification [67, 68]. For example, the involvement of multidisciplinary teams that include non-physician providers with authorisation to prescribe (e.g. pharmacists, specialist nurses and advanced practice providers) may reduce therapeutic inertia [69, 70].

Therapeutic options: lifestyle and healthy behaviour, weight management and pharmacotherapy for the treatment of type 2 diabetes

This section summarises the lifestyle and behavioural therapy, weight management interventions and pharmacotherapy that support glycaemic management in people with type 2 diabetes. Specific pharmacological treatment options are summarised in Table 1. Additional details are available in the previous ADA/EASD consensus report and update [5, 6] and the ADA's 2022 Standards of medical care in diabetes [71].

Nutrition therapy

Nutrition therapy is integral to diabetes management, with goals of promoting and supporting healthy eating patterns, addressing individual nutrition needs, maintaining the pleasure of eating and providing the person with diabetes with the tools for developing healthy eating [22]. MNT provided by a registered dietitian/registered dietitian nutritionist complements DSMES, can significantly reduce HbA_{1c} and can help prevent, delay and treat comorbidities related to diabetes [19]. Two core dimensions of MNT that can improve glycaemic management include dietary quality and energy restriction.

Dietary quality and eating patterns

There is no single ratio of carbohydrate, proteins and fat intake that is optimal for every person with type 2 diabetes. Instead, individually selected eating patterns that emphasise foods with demonstrated health benefits, minimise foods shown to be harmful and accommodate individual preferences with the goal of identifying healthy dietary habits that are feasible and sustainable are recommended. A net energy deficit that can be maintained is important for weight loss [5, 6, 22, 72–74].

A network analysis comparing trials of nine dietary approaches of >12 weeks' duration demonstrated reductions in HbA_{1c} from −9 to −5.1 mmol/mol (−0.82% to −0.47%), with all approaches compared with a control diet. Greater glycaemic benefits were seen with the Mediterranean diet and low carbohydrate diet [75]. The greater glycaemic benefits of low carbohydrate diets (<26% of energy) at 3 and 6 months are not evident with longer follow-up [72]. In a systematic review of trials of >6 months' duration, compared with a low-fat diet, the Mediterranean diet demonstrated greater reductions in body weight and HbA_{1c} levels, delayed the requirement for diabetes medication and provided benefits for cardiovascular health [76, 77]. Similar benefits have been ascribed to vegan and vegetarian diets [78].

There has been increased interest in time-restricted eating and intermittent fasting to improve metabolic variables, although with mixed, and modest, results. In a meta-analysis there were no differences in the effect of intermittent fasting and continuous energy restriction on HbA_{1c}, with intermittent fasting having a modest effect on weight (−1.70 kg) [79]. In a 12 month RCT in adults with type 2 diabetes comparing intermittent energy restriction (2092–2510 kJ [500–600 kcal] diet for 2 non-consecutive days/week followed by the usual diet for 5 days/week) with continuous energy restriction (5021–6276 kJ [1200–1500 kcal] diet for 7 days/week), glycaemic improvements were comparable between the two groups. At 24 months' follow-up, HbA_{1c} increased in both groups to above baseline [80], while weight loss (−3.9 kg) was maintained in both groups [81]. Fasting may increase the rates of hypoglycaemia in those treated with insulin and sulfonylureas, highlighting the need for individualised

Table 1 Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects: Effect on MACE	CV effects: HF	Renal effects: Progression of DKD	Renal effects: Dosing/use considerations*	Oral/SQ	Cost	Clinical considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 ml/min per 1.73 m^2	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
SGLT2 Inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk, rare in T2DM: discontinue, evaluate and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycaemic DKA); discontinue before scheduled surgery (e.g. 3-4 days), during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotising fasciitis of the perineum (Fournier's gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumours in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients 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 patients 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 are suspected
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumours in rodents; human relevance not determined • Counsel patients 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 patients 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 are suspected
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	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
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low	• Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (oedema; heart failure) • Benefit in NASH • Risk of bone fractures • Weight gain: consider lower doses to mitigate weight gain and oedema
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycaemia	Oral	Low	• FDA Special Warning on increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide); glimepiride shown to be CV safe (see text) • Use with caution in persons at risk for hypoglycaemia
Insulin – **Human**	High to very high	Yes	Gain	Neutral	Neutral	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	SQ; inhaled	Low (SQ)	• Injection site reactions • Higher risk of hypoglycaemia with human insulin (NPH or premixed formulations) vs analogues
Insulin – **Analogues**								SQ	High	

CV, Cardiovascular; CVOT, Cardiovascular Outcomes Trial; DKA, Diabetic Ketoacidosis; DKD, Diabetic Kidney Disease; DPP-4, Dipeptidyl peptidase-4; eGFR, Estimated Glomerular Filtration Rate; GI, Gastrointestinal; GIP, Gastric Inhibitory Polypeptide; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; NASH, Non-Alcoholic Steatohepatitis; MACE, Major Adverse Cardiovascular Events; SGLT2, Sodium-glucose Cotransporter-2; SQ, Subcutaneous; T2DM, Type 2 Diabetes Mellitus

* For agent-specific dosing recommendations, please refer to manufacturers' prescribing information

1, Tsapas A, Avgerinos I, Karagiannis T et al. Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2020 Aug 18;173(4):278–86; 2, Tsapas A, Karagiannis T, Kakotrichi P et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes Obes Metab. 2021;23(9):2116–24.

education and proactive medication management during significant dietary changes [82].

Non-surgical energy restriction for weight loss

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 glycaemic and weight management goals in adults with type 2 diabetes [5, 22]. Structured nutrition and lifestyle programmes may be considered for glycaemic benefit and can be adapted for specific cultural indications [83–87].

The Diabetes Remission Clinical Trial (DiRECT) demonstrated greater remission of diabetes with a weight management programme than with usual best practice care in adults with type 2 diabetes within 6 years of diagnosis. The structured, primary care-led intensive weight management programme involved total diet replacement (3452–3569 kJ/day [825–853 kcal/day] for 3–5 months) followed by stepped food reintroduction and structured support for long-term weight loss maintenance. In the whole study population, remission directly varied with degree of weight loss [88]. At the 2 year follow-up, sustained remission correlated with extent of sustained weight loss. In the whole study population, of those maintaining at least 10 kg weight loss, 64% achieved diabetes remission. However, only 24% of the participants in the intervention group maintained at least 10 kg weight loss, highlighting both the potential and the challenges of long-term durability of weight loss [89].

The Look AHEAD: Action for Health in Diabetes (Look AHEAD) trial on the longer-term effects of an intensive lifestyle intervention in adults who were overweight/obese with type 2 diabetes showed improvements in diabetes control and complications, depression, physical function and health-related quality of life, sleep apnoea, incontinence, brain structure and healthcare use and costs, with positive impacts on composite indices of multimorbidity, geriatric syndromes and disability-free life-years. This should be balanced against potential negative effects on body composition, bone density and frailty fractures [90, 91]. Although there was no difference in the primary cardiovascular outcome or mortality rate between the intervention and the control groups, post hoc exploratory analyses suggested potential benefits in certain groups (e.g. in those who achieved at least 10% weight loss in the first year of the study). Progressive metabolic benefits were seen with greater degrees of weight loss from >5% to ≥15%, with an overall suggestion that ≥10% weight loss may be required to see benefits for CVD events and mortality rate and other complications such as non-alcoholic steatohepatitis [50, 90, 92–95].

Physical activity behaviours including sleep

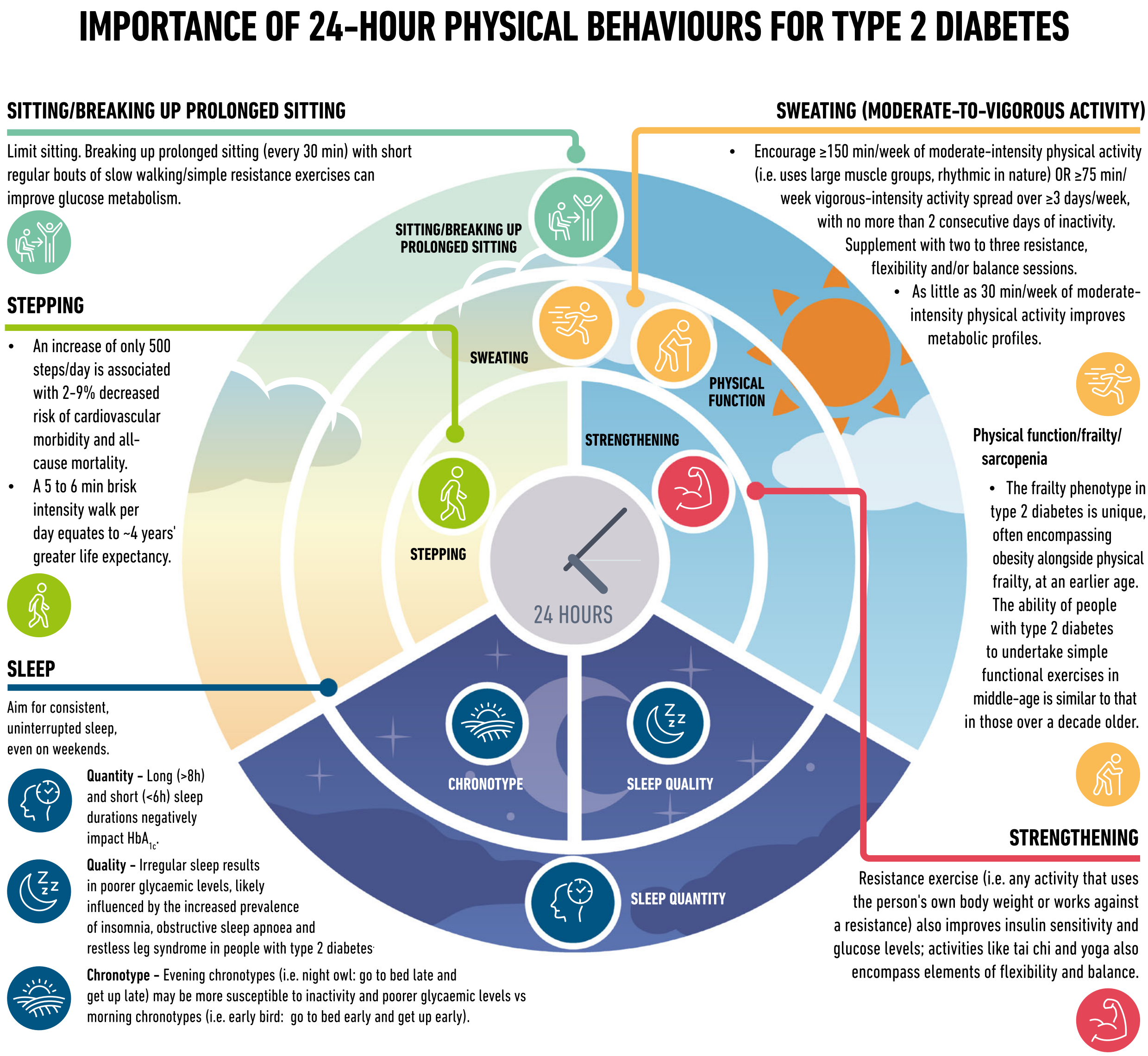
Physical activity behaviours significantly impact cardiometabolic health in type 2 diabetes (Fig. 2) [96–117]. Regular aerobic exercise (i.e. involving large muscle groups and rhythmic in nature) improves glycaemic management in adults with type 2 diabetes, resulting in less daily time in hyperglycaemia and reductions of ~7 mmol/mol (~0.6%) in HbA_{1c} [118], and induces clinically significant benefits in cardiorespiratory fitness [101, 110, 119]. These glycaemic effects can be maximised by undertaking activity during the postprandial period and engaging in activities for ≥45 min [101, 120]. Resistance exercise (i.e. using your own body weight or working against a resistance) also improves blood glucose levels, flexibility and balance [101, 110]. This is important given the increased risk of impaired physical function at an earlier age in type 2 diabetes [112].

A wide range of physical activities, including leisure time activities, can significantly reduce HbA_{1c} levels [5, 22, 121, 122]. Even small, regular changes can make a difference to long-term health, with an increase of only 500 steps/day associated with 2–9% decreased risk of cardiovascular morbidity and all-cause mortality rates [105–107]. Beneficial effects are evident across the continuum of human movement, from breaking prolonged sitting with light activity [103] to high-intensity interval training [123].

Sleep

Healthy sleep is considered a key lifestyle component in the management of type 2 diabetes [124], with clinical practice guidelines promoting the importance of sleep hygiene [113]. Sleep disorders are common in type 2 diabetes and cause disturbances in the quantity, quality and timing of sleep and are associated with an increased risk of obesity and impairments in daytime functioning and glucose metabolism [114, 115]. Additionally, obstructive sleep apnoea affects over half of people with type 2 diabetes and its severity is associated with blood glucose levels [115, 116].

The quantity of sleep is known to be associated (in a 'U' shaped manner) with health outcomes (e.g. obesity and HbA_{1c}), with both long (>8 h) and short (<6 h) sleep durations having negative impacts [97]. By extending the sleep duration of short sleepers, it is possible to improve insulin sensitivity and reduce energy intake [117, 125]. However, 'catch-up' weekend sleep alone is not enough to reverse the impact of insufficient sleep [126].



	Glucose/insulin	Blood pressure	HbA_{1c}	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓ (green)	↓ (yellow)	↓ (red)	↓ (red)	↑ (red)	↓ (red)	↑ (red)
STEPPING	↓ (green)	↓ (yellow)	↓ (yellow)	↓ (yellow)	↑ (red)	↓ (green)	↑ (green)
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓ (green)	↓ (green)	↓ (green)	↓ (green)	↑ (green)	↓ (green)	↑ (green)
STRENGTHENING	↓ (green)	↓ (yellow)	↓ (green)	↓ (yellow)	↑ (green)	↓ (red)	↑ (yellow)
ADEQUATE SLEEP DURATION	↓ (green)	↓ (red)	↓ (green)	↓ (red)	?	↓ (yellow)	↑ (yellow)
GOOD SLEEP QUALITY	↓ (green)	↓ (green)	↓ (green)	↓ (green)	?	↓ (yellow)	↑ (green)
CHRONOTYPE/CONSISTENT TIMING	↓ (yellow)	?	↓ (yellow)	?	?	↓ (yellow)	?

IMPACT OF PHYSICAL BEHAVIOURS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, HbA_{1c}, lipids, depression); ? no data available;
↑ Green arrows = strong evidence; ↑ Yellow arrows = medium strength evidence; ↑ Red arrows = limited evidence.

Fig. 2 Importance of 24-hour physical behaviours for type 2 diabetes

Weight management beyond lifestyle interventions

Medications for weight loss in type 2 diabetes

Weight loss medications are effective adjuncts to lifestyle interventions and healthy behaviours for management of weight and have also been found to improve glucose control in people with diabetes [127].

Newer therapies have demonstrated very high efficacy for weight management in people with type 2 diabetes. In the Semaglutide Treatment Effect in People with Obesity (STEP) 2 trial, subcutaneous semaglutide 2.4 mg once a week as an adjunct to a lifestyle intervention performed better than either semaglutide 1.0 mg or placebo, with weight loss of 9.6% (6.2% more than with placebo and 2.7% more than with semaglutide 1.0 mg). More than two thirds of participants in the semaglutide 2.4 mg arm achieved an HbA_{1c} level of ≤48 mmol/mol (≤6.5%) [128]. However, the weight loss was less pronounced than the 14.9% weight loss (vs 2.4% with placebo) seen in the STEP 1 trial in adults with overweight or obesity without diabetes [129]. Tirzepatide, a novel glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, at weekly doses of 5 mg, 10 mg and 15 mg reduced body weight by 15%, 19.5% and 20.9%, respectively, compared with 3.1% with placebo at 72 weeks in people with obesity but without diabetes; however, tirzepatide has not yet been approved for weight management by regulatory authorities [130]. Studies in adults with overweight or obesity suggest that withdrawing treatment with semaglutide leads to increases in body weight [131], highlighting the chronic nature of, and need for, obesity/weight management.

Metabolic surgery

Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates [127, 132]. Metabolic surgery also appears to be effective for diabetes remission in people with type 2 diabetes and a BMI ≥25 kg/m^2, although efficacy for both weight loss and diabetes remission appears to vary by surgical type [133–135]. One mixed-effects meta-analysis model has estimated a 43% diabetes remission rate (95% CI 34%, 53%) following metabolic surgery in people with type 2 diabetes and a BMI <30 kg/m^2 [136], significantly higher than that achieved with traditional medical management [137]. However, there is a strong association between duration of diabetes and the likelihood of postoperative diabetes remission. People with more recently diagnosed diabetes are more likely to experience remission after metabolic surgery, and the likelihood of remission decreases significantly with duration of diabetes longer than about 5–8 years [138]. Even in people with diabetes who do not achieve postoperative diabetes remission, or relapse after initial remission, metabolic surgery is associated with better metabolic control than medical management [137, 139]. In the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, metabolic surgery was also associated with improvements in patient-reported outcomes related to physical health; however, measures of social and psychological quality of life did not improve [140]. It is important to note that many of these estimates of benefit included data from non-randomised studies and compared outcomes with medical treatments for obesity that were less effective than those available today.

Medications for lowering glucose

Cardiorenal-protective glucose-lowering medications

Sodium–glucose cotransporter-2 inhibitors The SGLT2i are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose. They have intermediate-to-high glycaemic efficacy, with lower glycaemic efficacy at lower eGFR. However, their scope of use has significantly expanded based on cardiovascular and renal outcomes studies [5, 141]. Cardiorenal outcomes trials have demonstrated their efficacy in reducing the risk of composite major adverse cardiovascular events (MACE), cardiovascular death, myocardial infarction, hospitalisation for heart failure (HHF) and all-cause mortality and improving renal outcomes in individuals with type 2 diabetes with an established/high risk of CVD. This is discussed in the section on 'Personalised approach to treatment based on individual characteristics and comorbidities: recommended process for glucose-lowering medication selection'. Evidence supporting their use is summarised in Table 1 [141, 142].

Recent data have increased confidence in the safety of the SGLT2i drug class [141, 142]. Their use is associated with increased risk for mycotic genital infections, which are reported to be typically mild and treatable. While SGLT2i use can increase the risk of diabetic ketoacidosis (DKA), the incidence is low, with a modest incremental absolute risk [142]. The SGLT2i cardiovascular outcomes trials (CVOTs) have reported DKA rates of 0.1–0.6% compared with rates of <0.1–0.3% with placebo [143–147], with very low rates in the HF [148–151] and CKD [152, 153] outcomes studies. Risk can be mitigated with education and guidance, including education on signs and symptoms of DKA that should prompt medical attention, and temporary discontinuation of the medication in clinical situations that predispose to ketoacidosis (e.g. during prolonged fasting and acute illness, and perioperatively, i.e. 3 days prior to surgery) [154–158]. The Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) RCT demonstrated a low risk of DKA (0.3% vs 0% in dapagliflozin-treated vs placebo-treated participants) with structured monitoring of acid–base balance and kidney function during inpatient use in adults admitted with COVID-19 and at least one cardiometabolic risk factor without evidence of critical illness [159].

While early studies brought attention to several safety areas of interest (acute kidney injury, dehydration, orthostatic hypotension, amputation and fractures) [5, 6], longer-term studies that have prospectively assessed and monitored these events [160, 161] have not seen a significant imbalance in risks. Analyses of SGLT2i outcomes trial data also suggest that people with type 2 diabetes and peripheral arterial disease derive greater absolute outcomes benefits from SGLT2i therapy than those without peripheral arterial disease, and without an increase in risk of major adverse limb events [162]. In post hoc analyses, SGLT2i use has been associated with reduced incidence of serious and non-serious kidney-related adverse events in people with type 2 diabetes and CKD, and greater full recovery from acute kidney injury [163].

Glucagon-like peptide-1 receptor agonists GLP-1 RA augment glucose-dependent insulin secretion and glucagon suppression, decelerate gastric emptying, curb post-meal glycaemic increments and reduce appetite, energy intake and body weight [5, 6, 164]. Beyond improving HbA_{1c} in adults with type 2 diabetes, specific GLP-1 RA have also been approved for reducing risk of MACE in adults with type 2 diabetes with established CVD (dulaglutide, liraglutide and subcutaneous semaglutide) or multiple cardiovascular risk factors (dulaglutide) (Table 1) and for chronic weight management (subcutaneous liraglutide titrated to 3.0 mg once daily; subcutaneous semaglutide titrated to 2.4 mg once weekly). This is discussed in the sections on 'Medications for weight loss in type 2 diabetes' and 'Personalised approach to treatment based on individual characteristics and comorbidities: recommended process for glucose-lowering medication selection'. GLP-1 RA are primarily available as injectable therapies (subcutaneous administration), with one oral GLP-1 RA now available (oral semaglutide) [165].

The recent higher dose GLP-1 RA studies have indicated incremental benefits for glucose and weight at higher doses of GLP-1 RA, with greater proportions of people achieving glycaemic targets and the ability of stepwise dose escalation to improve gastrointestinal tolerability. The Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes (AWARD)-11 trial evaluated higher doses of dulaglutide (3.0 mg and 4.5 mg weekly) compared with 1.5 mg weekly, demonstrating superior HbA_{1c} reductions (−19.4 vs −16.8 mmol/mol [−1.77 vs −1.54%], estimated treatment difference [ETD] −2.6 mmol/mol [−0.24%]) and weight loss (−4.6 vs −3.0 kg, ETD −1.6 kg) with dulaglutide 4.5 mg compared with 1.5 mg at 36 weeks in people with type 2 diabetes inadequately controlled with metformin [166]. Likewise, the SUSTAIN FORTE trial studied higher doses of once-weekly subcutaneous semaglutide (2.0 mg) compared with the previously approved 1.0 mg dose, reporting a mean change in HbA_{1c} from baseline to week 40 of −23 vs −21 mmol/mol (−2.1 vs −1.9%; ETD −2 mmol/mol [−0.18%]) and weight change of −6.4 kg with semaglutide 2.0 mg and −5.6 kg with semaglutide 1.0 mg (ETD −0.77 kg [95% CI −1.55, 0.01]) [167].

The most common side effects of GLP-1 RA are gastrointestinal in nature (nausea, vomiting and diarrhoea) and tend to occur during initiation and dose escalation and diminish over time. Gradual up-titration is recommended to mitigate gastrointestinal effects [164, 168, 169]. Education should be provided when initiating GLP-1 RA therapy. GLP-1 RA promote a sense of satiety, facilitating reduction in food intake. It is important to help people distinguish between nausea, a negative sensation, and satiety, a positive sensation that supports weight loss. Mindful eating should be encouraged: eating slowly, stopping eating when full and not eating when not hungry. Smaller meals or snacks, decreasing intake of high-fat and spicy foods, moderating alcohol intake and increasing water intake are also recommended. Slower or flexible dose escalations can be considered in the setting of gastrointestinal intolerance [168, 169].

Data from CVOTs on other safety areas of interest (pancreatitis, pancreatic cancer and medullary thyroid cancer) indicate that there is no increase in these risks with GLP-1 RA. GLP-1 RA are contraindicated in people at risk of the rare medullary thyroid cancer [164], that is, those with a history or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2, due to thyroid C-cell tumours seen in rodents treated with GLP-1 RA in preclinical studies. Increased retinopathy complications seen in the SUSTAIN 6 CVOT appear attributable to the magnitude and rapidity of HbA_{1c} reductions in individuals with pre-existing diabetic retinopathy and high glycaemic levels, as has been seen in previous studies with insulin [170, 171]. GLP-1 RA are also associated with higher risks of gallbladder and biliary diseases [172].

Other glucose-lowering medications

Metformin Because of its high efficacy in lowering HbA_{1c}, minimal hypoglycaemia 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 ongoing acceptance that other approaches may be appropriate. Notably, the benefits of GLP-1 RA and SGLT2i for cardiovascular and renal outcomes have been found to be independent of metformin use and thus these agents should be considered in people with established or high risk of CVD, HF or CKD, independent of metformin use [173–175]. Early combination therapy based on the perceived need for additional glycaemic efficacy or cardiorenal protection can be considered at treatment initiation to extend the time to treatment failure [176]. 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 [177]. 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, particularly in those with anaemia or neuropathy [178, 179].

Dipeptidyl peptidase-4 inhibitors Dipeptidyl peptidase-4 inhibitors (DPP-4i) are oral medications that inhibit the enzymatic inactivation of endogenous incretin hormones, resulting in glucose-dependent insulin release and a decrease in glucagon secretion. They have a more modest glucose-lowering efficacy and a neutral effect on weight and are well tolerated with minimal risk of hypoglycaemia. CVOTs have demonstrated the cardiovascular safety without cardiovascular risk reduction of four DPP-4i (saxagliptin, alogliptin, sitagliptin and linagliptin) [141]. Reductions in risk of albuminuria progression were noted with linagliptin in the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial [180]. While generally well tolerated, an increased risk of HHF was found with saxagliptin, which is reflected in its label, and there have been rare reports of arthralgia and hypersensitivity reactions with the DPP-4i class [16].

The high tolerability and modest efficacy of DPP-4i may mean that they are suitable for specific populations and considerations. For example, in a 6 month open-label RCT comparing a DPP-4i (linagliptin) with basal insulin (glargine) in long-term care and skilled nursing facilities, mean daily blood glucose was similar, with fewer hypoglycaemic events with linagliptin compared with insulin [181]. Treatment of inpatient hyperglycaemia with basal insulin plus DPP-4i has been demonstrated to be effective and safe in older adults with type 2 diabetes, with similar mean daily blood glucose but lower glycaemic variability and fewer hypoglycaemic episodes compared with the basal–bolus insulin regimen [182].

Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist In May 2022, the FDA approved tirzepatide, a GIP and GLP-1 RA, for once-weekly subcutaneous administration to improve glucose control in adults with type 2 diabetes as an addition to healthy eating and exercise. In the Phase III clinical trial programme, tirzepatide demonstrated superior glycaemic efficacy to placebo [183, 184], subcutaneous semaglutide 1.0 mg weekly [185], insulin degludec [186] and insulin glargine [187]. For HbA_{1c}, placebo-adjusted reductions of 21 mmol/mol (1.91%), 21 mmol/mol (1.93%) and 23 mmol/mol (2.11%) were demonstrated with tirzepatide 5, 10 and 15 mg weekly, respectively, and mean weight reductions of 7–9.5 kg were seen [183]. Additional metabolic benefits included improvements in liver fat content and reduced visceral and subcutaneous abdominal adipose tissue volume [188]. Based on meta-analysis findings, tirzepatide was superior to its comparators, including other long-acting GLP-1 RA, in reducing glucose and body weight, but was associated with increased odds for gastrointestinal adverse events, in particular nausea [189]. Similar warnings and precautions are included in the prescribing information for tirzepatide as for agents in the GLP-1 RA class. Additionally, current short-term data from RCTs suggest that tirzepatide does not increase the risk of MACE vs comparators; however, robust data on its long-term cardiovascular profile will be available after completion of the SURPASS-CVOT trial [190]. Tirzepatide has received a positive opinion in the EU.

Sulfonylureas As per the previous consensus report and update, sulfonylureas are assessed as having high glucose-lowering efficacy, but with a lack of durable effect, and the advantages of being inexpensive and accessible [5, 6]. However, due to their glucose-independent stimulation of insulin secretion, they are associated with an increased risk for hypoglycaemia. Sulfonylureas are also associated with weight gain, which is relatively modest in large cohort studies [191]. Use of sulfonylureas or insulin for early intensive blood glucose control in the UK Prospective Diabetes Study (UKPDS) significantly decreased the risk of microvascular complications, underscoring the importance of early and continued glycaemic management [192]. Adverse cardiovascular outcomes with sulfonylureas in some observational studies have raised concerns, although findings from systematic reviews have found no increase in all-cause mortality rates compared with other active treatments [191]. The incidence of cardiovascular events was comparable in those treated with a sulfonylurea or pioglitazone in the Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT) [193], and no difference in the incidence of MACE was found in people at high cardiovascular risk treated with glimepiride or linagliptin [194], a medication whose cardiovascular safety was demonstrated in a population at high cardiovascular and renal risk [195].

Thiazolidinediones Thiazolidinediones (TZDs) are oral medications that increase insulin sensitivity and are of high glucose-lowering efficacy [5, 6]. TZDs have a high durability of glycaemic response, most likely through a potent effect on preserving beta cell function [196]. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) in adults with type 2 diabetes and macrovascular disease, a reduction in secondary cardiovascular endpoints was seen, although significance was not achieved for the primary outcome [197]. In the Insulin Resistance Intervention After Stroke (IRIS) study in adults without diabetes but with insulin resistance (HOMA-IR >3.0) and recent history of stroke or transient ischaemic attack, there was a lower risk of stroke or myocardial infarction with pioglitazone vs placebo [198, 199]. Beneficial effects on non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been seen with pioglitazone [200, 201]. However, these benefits must be balanced against possible side effects of fluid retention and congestive HF [196, 197, 202], weight gain [196–198, 202, 203] and bone fracture [204, 205]. Side effects can be mitigated by using lower doses and combining TZD therapy with other medications (SGLT2i and GLP-1 RA) that promote weight loss and sodium excretion [199, 206].

Insulin The previous consensus report and update provide detailed descriptions of the different insulins [5, 6]. 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 [5, 6]. Careful consideration should be given to the pharmacokinetic and pharmacodynamic profiles of the available insulins, and the matching of the dose and timing to an individual's physiological requirements. Numerous formulations of insulin are available, with advances in therapy geared toward better mimicking physiological insulin release patterns. Challenges of insulin therapy include weight gain, the need for education and titration for optimal efficacy, risk of hypoglycaemia, the need for regular glucose monitoring, and cost. The approval of biosimilar insulins may improve accessibility at lower treatment costs. Both insulin glargine U100 and insulin degludec have demonstrated cardiovascular safety in dedicated CVOTs [207, 208]. Comprehensive education on self-monitoring of blood glucose, diet, injection technique, self-titration of insulin and prevention and adequate treatment of hypoglycaemia are of utmost importance when initiating and intensifying insulin therapy [5, 6]. Novel formulations and devices including prefilled syringes, auto-injectors and intranasal insufflators are now available to administer glucagon in the setting of severe hypoglycaemia and should be considered for those at risk [209].

Starting doses of basal insulin (NPH or analogue) are estimated based on body weight (0.1–0.2 U/kg per day) and the degree of hyperglycaemia, with individualised titration as needed. A modest but significant reduction in HbA_{1c} and the risk of total and nocturnal hypoglycaemia has been observed for basal insulin analogues vs NPH insulin [210]. Longer-acting basal insulin analogues have a lower risk of hypoglycaemia than earlier generations of basal insulin, although may cost more. Concentrated insulins allow injection of a reduced volume [5]. Cost and access are important considerations and can contribute to treatment discontinuation. Short- and 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, retaining the pharmacokinetic properties of the individual components. Premixed insulin may offer convenience for some but reduces treatment flexibility. Rapid-acting insulin analogues are also formulated as premixes, combining mixtures of the insulin with protamine suspension and the rapid-acting insulin. Analogue-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 hypoglycaemia while using mixed insulin is important. Insulins with different routes of administration (inhaled, bolus-only insulin delivery patch pump) are also available [211–213].

Combination glucagon-like peptide-1/insulin therapy Two fixed-ratio combinations of GLP-1 RA with basal insulin analogues are available: insulin degludec plus liraglutide (IDegLira) and insulin glargine plus lixisenatide (iGlarLixi). The combination of basal insulin with GLP-1 RA results in greater glycaemic lowering efficacy than the mono-components, with less weight gain and lower rates of hypoglycaemia than with intensified insulin regimens, and better gastrointestinal tolerability than with GLP-1 RA alone [214, 215]. In studies of people with type 2 diabetes inadequately controlled on basal insulin or GLP-1 RA, switching to a fixed-ratio combination of basal insulin and GLP-1 RA demonstrated significant improvements in blood glucose levels and achievement of glycaemic goals with fewer hypoglycaemic events than with basal insulin alone [216–220].

Less commonly used glucose-lowering medications Alpha-glucosidase inhibitors improve glycaemic control by reducing postprandial glycaemic excursions and glycaemic variability and may provide specific benefits in cultures and settings with high carbohydrate consumption or reactive hypoglycaemia [221, 222]. Other glucose-lowering medications (i.e. meglitinides, colesevelam, quick-release bromocriptine and pramlintide) are not commonly used in the USA and most are not licensed in Europe. There was no new evidence that impacts clinical practice.

Comparative efficacy of glucose-lowering agents

In a network meta-analysis of 453 trials assessing glucose-lowering medications from nine drug classes, the greatest reductions in HbA_{1c} were seen with insulin regimens and GLP-1 RA [223]. A network meta-analysis comparing the effects of glucose-lowering therapy on body weight and blood pressure indicates that the greatest efficacy for reducing body weight is seen with subcutaneous semaglutide followed by the other GLP-1 RA and SGLT2i, and the greatest reduction in blood pressure is seen with the SGLT2i and GLP-1 RA classes [224]. As discussed above, the novel GIP and GLP-1 RA tirzepatide was associated with greater glycaemic and weight loss efficacy than semaglutide 1 mg weekly [185].

Combination therapy

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. While traditional recommendations have focused on the stepwise addition of therapy, allowing for clear delineation of positive and negative effects of new drugs, there are data to suggest benefits of combination approaches in diabetes care. Combination therapy has several potential advantages, including (1) increased durability of the glycaemic effect [225–227], addressing therapeutic inertia, (2) simultaneous targeting of the multiple pathophysiological processes characterised by type 2 diabetes, (3) impacts on medication burden, medication-taking behaviour and treatment persistence and (4) complementary clinical benefits (e.g. on glycaemic control, weight and cardiovascular risk profiles) [215, 228–244].

The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) was a multicentre open-label RCT designed to test four different diabetes medication classes in people with type 2 diabetes and compare their ability to achieve and maintain HbA_{1c} levels <53 mmol/mol (<7%). Eligible participants had their metformin therapy optimised and were randomly assigned to receive a sulfonylurea (glimepiride), a DPP-4 inhibitor (sitagliptin), a GLP-1 RA (liraglutide) or basal insulin (insulin glargine), with the primary outcome being the time to metabolic failure, defined as the time to an initial HbA_{1c} level ≥53 mmol/mol (≥7%), if it was confirmed at the next visit to remain above that threshold. Starting with a mean baseline HbA_{1c} level of 58 mmol/mol (7.5%) before the addition of one of the four medications, over 5 years of follow-up, 71% of the cohort reached the primary metabolic outcome. Insulin glargine and liraglutide were significantly, albeit modestly, more effective at achieving and maintaining HbA_{1c} targets. Liraglutide exhibited a lower risk than the pooled effect of the other three medications on a composite cardiovascular outcome comprising MACE, revascularisation, or HF or unstable angina requiring hospitalisation [245, 246].

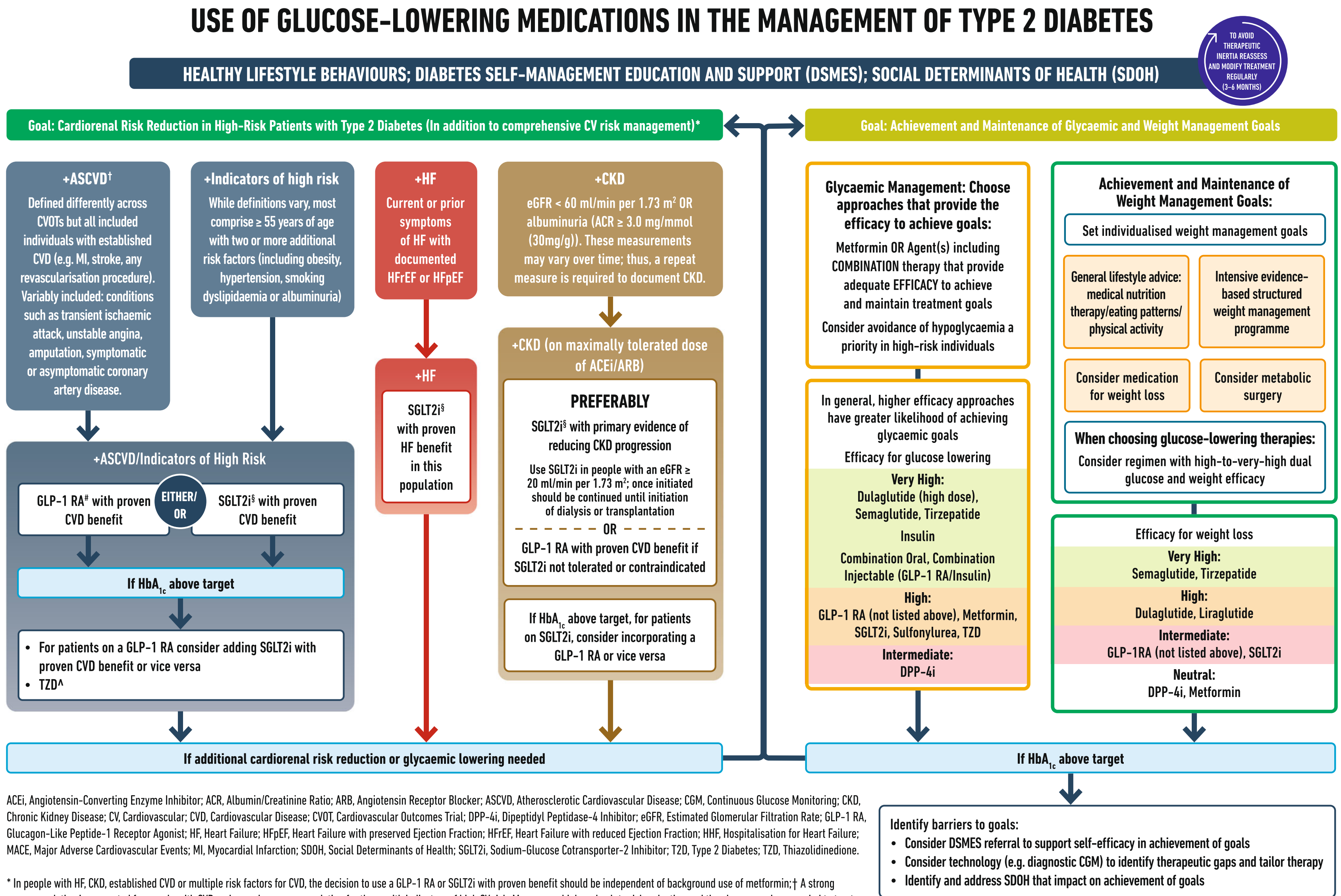
Personalised approach to treatment based on individual characteristics and comorbidities: recommended process for glucose-lowering medication selection

People with cardiorenal comorbidities

The 2018 ADA/EASD consensus report and 2019 update focused on the consideration of clinically important factors when choosing glucose-lowering therapy. In people with established CVD or with a high risk for CVD, GLP-1 RA were prioritised over SGLT2i. Given their favourable drug class effect in reducing HHF and progression of CKD, SGLT2i were prioritised in people with HF, particularly those with a reduced ejection fraction, or CKD. Since 2019, additional cardiovascular, kidney and HF outcomes trials have been completed, particularly with SGLT2i. In addition, updated meta-analyses have been published that compare subgroup populations based on clinically relevant characteristics, such as presence of CVD, use of background therapy with metformin, stage of CKD, history of HF and age. Collectively, this new evidence was systematically retrieved and appraised to be incorporated into these clinical practice recommendations (Fig. 3).

New evidence from cardiorenal outcomes studies since the last consensus report

In the Evaluation of Ertugliflozin Efficacy and Safety CVOT (VERTIS CV), which recruited exclusively people with established CVD and type 2 diabetes, ertugliflozin was similar to placebo with respect to the primary MACE outcome and all key secondary outcomes (including a composite kidney outcome) except for HHF [146]. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study included adults with type 2 diabetes with an eGFR from 30 to <90 ml/min per 1.73 m^2 and albuminuria (30–500 mg/mmol [300–5000 mg/g] creatinine) [152]. In CREDENCE, canagliflozin treatment significantly reduced the risk of a composite primary outcome of progression to renal replacement therapy, eGFR of <15 ml/min per 1.73 m^2, a doubling



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin;† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

Fig. 3 Use of glucose-lowering medications in the management of type 2 diabetes of serum creatinine level or death from cardiovascular or kidney causes. The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) trial recruited participants with and without type 2 diabetes with an eGFR of 25–75 ml/min per 1.73 m^2 and a urinary albumin/creatinine ratio (UACR) of 20–500 mg/mmol [200–5000 mg/g] [153]. Results of the trial demonstrated a clear benefit of dapagliflozin on a composite kidney outcome, on individual kidney-specific outcomes and on cardiovascular death or HHF, both in the overall population and in the subgroup of people with diabetes (68% of participants). In CREDENCE, the SGTL2i was continued until initiation of dialysis or transplantation.

The Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial assessed sotagliflozin (a dual SGLT1i/SGLT2i, currently not approved for type 2 diabetes in the USA or the EU) in people with type 2 diabetes who had CKD and additional cardiovascular risk factors [147]. Sotagliflozin reduced the composite endpoint of cardiovascular mortality, HHF or urgent visits for HF compared with placebo, but had no effect on the composite kidney endpoint.

SGLT2i have been recently assessed in people with HF in dedicated HF outcome trials. In the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced), empagliflozin reduced the primary composite endpoint of cardiovascular mortality or HHF in people with HF and a reduced ejection fraction, irrespective of the presence of type 2 diabetes (50% of participants) [149]. Notably, this beneficial effect of empagliflozin regardless of diabetes status was consistently evident in those with a preserved ejection fraction (>40%), as demonstrated in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure and a Preserved Ejection Fraction (EMPEROR-Preserved) [151]. Additionally, the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial showed that, in people with type 2 diabetes and worsening HF, sotagliflozin reduced the total number of cardiovascular deaths or hospitalisations or urgent visits for HF compared with placebo regardless of ejection fraction [150]. All these data corroborate the salutary drug class effects of SGLT2i on HF-related outcomes in the setting of HF, irrespective of ejection fraction or diabetes status.

Finally, among GLP-1 RA, the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial demonstrated a beneficial effect of weekly efpeglenatide on MACE and on a composite kidney outcome (decrease in kidney function or severe albuminuria) [247]. Of note, an exploratory analysis suggested a possible dose–response effect of efpeglenatide on MACE. In a CVOT of an osmotic mini-pump delivering exenatide subcutaneously (ITCA 650) over 3–6 months, ITCA 650 had a neutral effect on MACE compared with placebo over 16 months [248]. Both trials recruited individuals with type 2 diabetes with an established, or high, risk for CVD. Neither efpeglenatide nor ITCA 650 have received marketing authorisation by the FDA or EMA. As mentioned previously, the cardiovascular effects of tirzepatide are being assessed in the ongoing SURPASS-CVOT trial, with dulaglutide as an active comparator.

Evidence is emerging regarding the potential benefits of combined treatment with both an SGLT2i and a GLP-1 RA on outcomes. A post hoc analysis of data from the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) has suggested that the combination of exenatide once-weekly (EQW) plus open-label SGLT2i reduces all-cause mortality rates and attenuates the decline in eGFR compared with treatment with EQW alone [244]. Importantly, a prespecified exploratory analysis of the AMPLITUDE-O trial found comparable benefits of GLP-1 RA treatment in participants who were receiving an SGLT2i as background therapy (15% of the total trial population) and those who were not [241].

Results from evidence syntheses

Recent cardiovascular, kidney and HF outcomes trials have been incorporated in updated meta-analyses assessing SGLT2i or GLP-1 RA, both in the overall trial populations and in clinically relevant subgroups. Pairwise meta-analyses of SGLT2i CVOTs verified that SGLT2i reduced MACE, HHF and a composite kidney outcome in the overall population vs placebo [142, 249]. Regarding GLP-1 RA, a meta-analysis of relevant CVOTs demonstrated the favourable effect of GLP-1 RA vs placebo on MACE and its individual components including stroke, HHF and a composite kidney outcome including severe albuminuria [250, 251]. It should be noted, however, that the overall effect estimate for HHF seems to have been driven by CVOTs of albiglutide and efpeglenatide, which are not available for clinical use. Similarly, the overall effect estimate for the composite kidney outcome was most likely driven by the effect of GLP-1 RA on severe albuminuria only and not on hard kidney endpoints. Of note, the beneficial kidney effects of canagliflozin, dapagliflozin and empagliflozin were also evident for hard kidney outcomes including chronic dialysis and kidney transplantation [252]. When individual components of MACE were analysed separately, GLP-1 RA reduced all three outcomes, with a more pronounced effect on stroke followed by cardiovascular death and myocardial infarction [253, 254]. Conversely, SGLT2i, albeit reducing cardiovascular death, had a neutral effect on stroke [142, 255].

The applicability of data to support selection of subgroups has been questioned because of a lack of RCTs focusing on specific populations, such as those using vs those not using metformin. This has been examined in subgroup analyses of recent meta-analyses [6]. It should be noted that findings of subgroup analyses should not be regarded as conclusive, their credibility should always be formally assessed and, ideally, they should be complemented by findings from relevant RCTs [7, 8]. Recently published subgroup analyses have explored the role of background use of metformin as a potential effect modifier of cardiovascular benefit. For SGLT2i, no differences were observed in MACE, cardiovascular death or HHF, major kidney outcomes and mortality rates in those using vs those not using metformin [174]. Further, for GLP-1 RA, no differences were shown in MACE and mortality outcomes [256–258] in metformin users compared with non-users. The similarity of the direction and magnitude of the effect estimates between individual trials, the number of trials that contributed data, mostly to within-trial comparisons, and the statistical analyses implemented support the credibility of the conclusions favouring use of SGLT2i or GLP-1 RA in individuals with compelling indications independent of the use of metformin.

Similarly, other subgroup analyses have explored the role of baseline cardiovascular risk as a potential effect modifier regarding the effect of treatment on MACE, HHF or kidney outcomes. Consistency of findings from between-trial and within-trial comparisons, formal statistical testing verifying the absence of a subgroup effect and the similarity of baseline cardiovascular risk across different cardiovascular risk categories between individual CVOTs despite the use of seemingly different enrolment criteria suggest the benefits of the use of SGLT2i or GLP-1 RA in people with type 2 diabetes and established CVD and in those at high cardiovascular and/or kidney risk [142, 253]. Of note, the level of certainty in this recommendation is higher for the former subgroup, because some CVOTs recruited exclusively people with established CVD, while fewer events were recorded for participants with cardiovascular risk factors only in CVOTs that recruited both subgroup populations. In addition, the definition used for risk factors was not identical among CVOTs. However, in general it comprised age ≥55 years plus two or more additional risk factors (including obesity, hypertension, smoking, dyslipidaemia or albuminuria). Furthermore, in terms of absolute effects, the cardiovascular benefits of GLP-1 RA and SGLT2i were less pronounced in people with three or more cardiovascular risk factors than in those with established CVD. This was shown in a network meta-analysis that estimated the absolute effects of treatment with GLP-1 RA or SGLT2i on cardiovascular and kidney outcomes for different categories of baseline cardiovascular risk by combining relative effect estimates with baseline risk estimates [259].

Subgroup meta-analyses based on participants' kidney function indicated that the salutary effects of SGLT2i on MACE, cardiovascular death or HHF, and a composite kidney outcome (substantial loss of kidney function, end-stage kidney disease or death due to kidney disease) do not significantly differ among subgroups based on eGFR [142, 252]. Moreover, the overall effect on MACE and the kidney outcome seemed to be consistent across the three subgroups (normal urine albumin excretion rate [UACR <3.0 mg/mmol (<30 mg/g)], moderate albuminuria [UACR 3.0–30 mg/mmol (30–300 mg/g)] and severe albuminuria [UACR ≥30 mg/mmol (≥300 mg/g)]) [252]. In addition, no modification of the effect estimates for MACE, cardiovascular death or HHF, and the composite kidney outcome was observed for SGLT2i in subgroup meta-analyses based on history of HF [142]. Regarding GLP-1 RA, a subgroup meta-analysis found that their effect on MACE did not significantly differ between people with an eGFR <60 ml/min per 1.73m^2 and those with an eGFR ≥60 ml/min per 1.73 m^2 [253]. Moreover, the effect on MACE did not appear to differ between people with lower and higher HbA_{1c} at baseline, both for SGLT2i and for GLP-1 RA [142, 253]. Nevertheless, the conclusions of all subgroup analyses should be regarded with increased caution because of the small number of trials contributing data to within-trial comparisons, heterogeneity between individual trials or lack of formal statistical testing.

Comparative effectiveness data

While CVOTs and pairwise meta-analyses allow inferences about the overall efficacy and safety of novel glucose-lowering therapies, none of them directly compared SGLT2i with GLP-1 RA. However, the comparative effectiveness of the two drug classes has been assessed in three recent network meta-analyses, which found that, in people with type 2 diabetes, SGLT2i were superior to GLP-1 RA in reducing HHF and a composite kidney outcome, while GLP-1 RA seemed more efficacious in reducing the risk of stroke [223, 259, 260]. No important differences between the two drug classes were evident in terms of mortality rates and other cardiovascular outcomes. These conclusions are further supported by observational data from a large population-based cohort study in the USA, which showed that SGLT2i reduced HHF compared with GLP-1 RA in people both with CVD (HR 0.71; 95% CI 0.64, 0.79) and without CVD (HR 0.69; 95% CI 0.56, 0.81). Differences between the two drug classes with regard to mortality rates and other cardiovascular outcomes were not clinically important [261].

In terms of differences among individual SGLT2i and GLP-1 RA, choice should be based on country-specific label indications and data on efficacy, safety and outcome benefits considering within-class heterogeneity. No CVOT is available focusing on people with type 2 diabetes who are at low cardiovascular risk. Some inferences about the effect of glucose-lowering medications as primary cardiovascular prevention in populations with low cardiovascular risk can be made from network meta-analyses, suggesting that no agent or drug class has a notable beneficial effect on cardiovascular events in low-risk individuals with diabetes [223, 259].

Additional clinical considerations

Age: older people with diabetes

Type 2 diabetes represents a model of accelerated biological ageing. As such, type 2 diabetes is associated with declines in physical capacity, underpinned by dysfunction within skeletal muscle. The ability of people with type 2 diabetes to undertake simple functional exercises in middle-age has been shown to be like those at least a decade older within the general population. Importantly, this places people living with type 2 diabetes at a high risk of impaired physical function and frailty, which in turn reduces quality of life and increases healthcare use. As such, frailty is increasingly recognised as a major complication of type 2 diabetes and an important target for treatment [112, 262].

Informed decisions regarding treatment of older (>65 years) adults with diabetes are limited by the under-representation of such participants in clinical trials. When older individuals have been studied, analyses from 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 blood pressure [263]. However, our confidence in selecting medications to improve outcomes has improved, in part because of regulatory requirements to include older people in trials to determine the efficacy and safety of new drugs for diabetes [264, 265]. For example, a recent meta-analysis of 11 large outcomes trials found that, in those aged 65 years or older, the cardiovascular and/or kidney outcomes benefits of GLP-1 RA or SGLT2i therapy were consistent with the effects seen in the overall trial population [266]. Therefore, recommendations for the selection of medications to improve cardiovascular and kidney outcomes do not differ for older people. Older age should not be an obstacle to treatment of individuals with established or high risk for CVD. However, medication choices for people who are frail or who have multiple comorbidities may require modification for safety and tolerability. People with diabetes should also understand and be able to appropriately modify use of their prescribed medications during times of illness. Frailty is associated with poorer prognosis, and some attenuation of benefit from intensive glucose-lowering and blood pressure-lowering treatments has been demonstrated in frail individuals [263]. Consideration of de-prescribing medication to avoid unnecessary medication or medication associated with harm, such as hypoglycaemia and hypotension, is important in such populations.

Age: younger people with diabetes

Rates of impaired glucose tolerance and/or impaired fasting glucose and type 2 diabetes have increased significantly in the adolescent and young adult population, in concert with increases in obesity [267]. It is estimated that one in five adolescents and one in four young adults now have impaired glucose tolerance and/or impaired fasting glucose in the USA, which in turn increases the risks of progression to type 2 diabetes, CKD and cardiovascular complications [267]. Minority populations are particularly affected, with half or more of newly diagnosed cases of type 2 diabetes in childhood and adolescence occurring in Hispanic, non-Hispanic Black, Asian/Pacific Islander and American Indian populations [268]. Affected young people have a more rapid deterioration in blood glucose levels, an attenuated response to diabetes medication and more rapid development of diabetes complications [269–273]. Early disease onset, higher levels of hyperglycaemia, and the multiple cardiometabolic risk factors found in adolescents and young adults with impaired glucose tolerance and/or impaired fasting glucose and diabetes all contribute to an increase in risk of adverse outcomes [267]. Most children and adolescents who develop type 2 diabetes will have microvascular complications by young adulthood [274]; in addition, a recently identified 25% increase in the risks of hyperglycaemic crises, acute myocardial infarction, stroke and lower extremity amputation over a 5 year period was most notable in people with diabetes aged 18–44 years [275]. Younger people with type 2 diabetes should be considered at very high risk for complications and treated correspondingly. Early use of combination therapy may be considered, as the Vildagliptin Efficacy in combination with metfoRmIn for earlY treatment of type 2 diabetes (VERIFY) trial findings suggest that this approach provides superior and more durable effects on blood glucose levels than metformin monotherapy in people with both early-onset (age <40 years) and later-onset diabetes [276]. Most of the evidence for health behaviour interventions, glucose-lowering approaches and the effectiveness of medications to improve cardiovascular and kidney outcomes in younger people with diabetes is poorly understood because of the very limited enrolment of this group in completed trials [15]. Beyond the scope of this statement, there are data emerging on the use of GLP-1 RA and SGLT2i in children that suggest glycaemic benefit; however, the durability of this effect and any impact on cardiorenal outcomes in children and young adults remain unknown.

Race and ethnicity

Although specific populations are disproportionately affected by diabetes, they are consistently under-represented in outcomes and other trials. A meta-analysis of six large cardiovascular and kidney outcomes trials found that non-White participants had higher rates of cardiovascular and other comorbidities than the White cohort but comprised only about 21% of the overall enrolled trial populations. Importantly, both non-White and White subgroups had significant reductions in the risk of cardiovascular death or HHF with SGLT2i therapy compared with placebo (OR 0.66 and 0.82, respectively) [277]. The increased burden of complications in under-represented populations with diabetes should be factored into personalised 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 [278, 279].

Sex differences

In women with reproductive potential, the use of highly effective contraception 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 hospitalisations and deaths in women and men with diabetes [280, 281]. In the general population, 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 [282, 283]. In fact, the increase in relative risk of CVD due to type 2 diabetes is greater in women than in men [284–286]. Despite this, women have been under-represented in recent CVOTs in diabetes, comprising between 28.5% and 35.8% of participants [287]. This analysis also described differing patterns of cardiovascular complications in women compared with men, and poorer management of cardiovascular risk factors in women [287]. Within-trial analyses and meta-analyses suggest that there are likely no between-sex differences in outcomes achieved with SGLT2i and GLP-1 RA therapy [288, 289]. Continued efforts should be made to enrol women in outcomes trials and to identify and address modifiable cardiovascular risk factors in women with diabetes.

Obesity and weight-related comorbidities, particularly NAFLD and NASH

The care of people with diabetes who have weight-related comorbidities such as NAFLD, HF with preserved ejection fraction or obstructive sleep apnoea should include strategies intended to result in weight loss. People with type 2 diabetes frequently have NAFLD and are at increased risk for progression to more severe stages of liver disease, including NASH, hepatic fibrosis and cirrhosis [290]. The management of type 2 diabetes in people with NASH should include lifestyle modification with a goal of weight loss, including strong consideration of medical and/or surgical approaches to weight loss in those at higher risk of hepatic fibrosis [291]. Pioglitazone, GLP-1 RA therapy and metabolic surgery have all been shown to reduce NASH activity; pioglitazone therapy and metabolic surgery may also improve hepatic fibrosis [188, 292–298].

Although not licensed for this purpose, it has therefore been suggested that people with type 2 diabetes at intermediate to high risk of fibrosis should be considered for treatment with pioglitazone and/or a GLP-1 RA with evidence of benefit [291, 299]. Although SGLT2i therapy has also been shown to reduce elevated levels of liver enzymes and hepatic fat content in people with NAFLD, at this time there is less evidence to support use of this class of drug as treatment for NASH [300–302]. NAFLD, and in particular NASH, is also associated with an increased risk of cardiovascular complications; therefore, people with NAFLD should have their cardiovascular risk factors assessed and managed to minimise this risk [303].

SGLT2i have been shown to reduce incident obstructive sleep apnoea in two SGLT2i CVOTs based on adverse event reporting [304, 305]. However, it is not clear that the data collected on incident obstructive sleep apnoea in these trials were complete, or that the benefit is mediated through changes in weight.

Consensus recommendations

- All people with type 2 diabetes should be offered access to ongoing DSMES programmes.
- Providers and healthcare systems should prioritise the delivery of person-centred care.
- Optimising medication adherence should be specifically considered when selecting glucose-lowering medications.
- MNT focused on identifying healthy dietary habits that are feasible and sustainable is recommended in support of reaching metabolic and weight goals.
- Physical activity improves glycaemic control and should be an essential component of type 2 diabetes management.
  - Adults with type 2 diabetes should engage in physical activity regularly (>150 min/week of moderate- to vigorous-intensity aerobic activity) and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks.
  - Aerobic activity should be supplemented with two to three resistance, flexibility and/or balance training sessions/week. Balance training sessions are particularly encouraged for older individuals or those with limited mobility/poor physical function.
- Metabolic surgery should be considered as a treatment option in adults with type 2 diabetes who are appropriate surgical candidates with a BMI ≥40.0 kg/m^2 (BMI ≥37.5 kg/m^2 in people of Asian ancestry) or a BMI of 35.0–39.9 kg/m^2 (32.5–37.4 kg/m^2 in people of Asian ancestry) who do not achieve durable weight loss and improvement in

comorbidities (including hyperglycaemia) with non-surgical methods.

- In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.
- In people with CKD and an eGFR ≥20 ml/min per 1.73 m^2 and a UACR >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes. Indications and eGFR thresholds may vary by region. If such treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcomes benefit could be considered to reduce MACE and should be continued until kidney replacement therapy is indicated.
- In people with HF, SGLT2i should be used because they improve HF and kidney outcomes.
- In individuals without established CVD but with multiple cardiovascular risk factors (such as age ≥55 years, obesity, hypertension, smoking, dyslipidaemia or albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes.
- In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.
- SGLT2i and GLP-1 RA reduce MACE, which is likely to be independent of baseline HbA_{1c}. In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.
- In general, selection of medications to improve cardiovascular and kidney outcomes should not differ for older people.
- In younger people with diabetes (<40 years), consider early combination therapy.
- In women with reproductive potential, counselling regarding contraception and taking care to avoid exposure to medications that may adversely affect a fetus are important.

Putting it all together: strategies for implementation

Importance of integrated care

The overall goal of the management of type 2 diabetes is to maintain quality of life and avoid complications. The management approach must be holistic and multifactorial and account for the lifelong nature of type 2 diabetes (Figs 1, 3, 4). The person living with type 2 diabetes should be at the centre of care. The structure and organisation of the healthcare team will vary across systems but generally involves multiple disciplines, including the primary care provider, diabetologist, diabetes care and education specialist, registered dietitian/nutritionist, pharmacists, nurses and other specialists as needed (e.g. dentist, eye care professional, podiatrist, mental health provider, cardiologist, nephrologist, neurologist, hepatologist, sleep medicine specialist and pain management specialist) [306]. Technology is now an important tool to enhance communication, support and monitoring. Communication between people living with type 2 diabetes and healthcare team members is at the core of integrated care, and clinicians must recognise the importance of language in this communication.

Practical tips for clinicians (Supplementary Fig. 1)

- Acknowledge the lifelong and evolving nature of type 2 diabetes.
- Identify and coordinate with the team.
- Know your local resources.
- Language matters in diabetes care.

Individualisation of care

The integrated care of type 2 diabetes must consider the person with diabetes as an individual (Figs 1, 3, 4) with respect to specific preferences and values, social determinants of health, barriers to care, comorbid conditions, degree of hyperglycaemia, risks of complications and susceptibility to medication side effects. Attention should be given to how the balance of risks and benefits of each intervention is communicated to each person living with diabetes. 'Risk estimator' tools, especially for CVD risk, may also be helpful, but when using these tools one must be aware that they work best when they are derived from and/or are validated in a population similar to the population in which they are applied [307]. These risk estimator tools are often developed in populations that exclude younger and older people and under-represent women and various minority populations. Finally, shared decision making is essential to incorporating an individual's preferences and values when formulating a management plan.

Social determinants of health must be assessed and addressed [47] to achieve health equity in diabetes. Health systems must ensure equity in the delivery of all diabetes care, including access to the more expensive, organ-protecting pharmacotherapies (SGLT2i and GLP-1 RAs) and technologies (e.g. CGM).

Many people living with type 2 diabetes have multiple comorbidities, some related to diabetes, such as obesity, hypertension, dyslipidaemia, cardiorenal disease, NASH/NAFLD and mental health problems. Other important conditions whose relationship to diabetes is not as well established, such as chronic obstructive pulmonary disease and cancer, are prevalent.

Attention to these comorbidities should be paid throughout the lifespan of the person living with diabetes, as such comorbidities may impact the tailoring and implementation of the holistic plan for diabetes management, including choice of glucose-lowering medication.

Importantly, diabetes is associated with cognitive decrements, which can substantially impact management [308, 309]. Further, long-term hyperglycaemia is associated with worsening cognitive decline. Screening for cognitive impairment should be performed when risk factors are identified such as frequent hypoglycaemia, difficulty with diabetes self-management or unexplained falls. People with cognitive impairment should be referred for additional support. Other conditions such as serious mental illness and substance use disorders must also be identified and managed appropriately in the holistic approach to diabetes. Mental illness, including depression, is associated with an increased risk of diabetes and with poorer prognosis but may also complicate diabetes management and be a barrier to self-management.

Practical tips for clinicians (Supplementary Fig. 1)

- Consider each person living with diabetes as an individual with specific context, risks and preferences.
- Healthcare systems should monitor and address inequity in the delivery of evidence-based interventions for type 2 diabetes.
- Assess and address social determinants of health for each individual living with diabetes, particularly in those not achieving goals.
- Incorporate comorbidities when developing and implementing the management plan.

Diabetes self-management education and support

DSMES is critical to integrated, holistic, person-centred care in type 2 diabetes [19–21, 23] and is as important to the management plan as the selection of medication. DSMES should be offered on an ongoing basis, should be provided by trained diabetes care and education specialists and can be delivered using multiple approaches and in a variety of settings (Supplementary Table 1) [20, 31]. The care team must be aware of the available local DSMES resources and how to access them. Importantly, DSMES is complementary to but does not replace MNT (see below) [310] or referral for mental health services when they are warranted [49].

Practical tips for clinicians (Supplementary Fig. 1)

- Embrace DSMES as being as important as other aspects of diabetes care such as pharmacotherapy.
- Identify and know how to access your local DSMES resources.
- Impress on the person and the healthcare team the importance of DSMES in the ongoing holistic approach to the management of type 2 diabetes.
- Initiate or refer for DSMES at diagnosis, annually, with changes in social or health status and with transitions of care or life situation.

Facilitating healthy behaviours and weight management

Promotion of healthy behaviours is central to the holistic management of type 2 diabetes and should be addressed at the time of diagnosis and throughout the course of diabetes. Healthy behaviours include healthy nutrition, regular physical activity, adequate sleep and smoking cessation. Health behaviours should always be assessed and addressed when glycaemic targets are not met and when new pharmacotherapy or interventions (e.g. metabolic surgery) are initiated.

All individuals with type 2 diabetes should be offered MNT to develop a personal food plan in the context of diabetes. The need for additional dietary advice should be re-evaluated over time [310]. There is no single dietary pattern recommended for all individuals with type 2 diabetes; many dietary patterns can be effective for achieving treatment goals and a structured food plan should be based on an individual person's preferences and context.

Explicit physical activity and minimisation of sedentary time should be the focus of the physical activity regimen for people living with type 2 diabetes (Fig. 2). Individual preferences and circumstances should inform the specific activity regimen. A reasonable target for physical activity is at least 150 min/week. In addition to these activity minutes, breaking up sedentary time with activity breaks (e.g. 5 min activity break every hour) can be beneficial [101]. A gradual increase in overall volume and intensity of activity does not require medical clearance [101]. Additional clinical assessment may be warranted in those with moderate-to-severe diabetic retinopathy, diabetic kidney disease, peripheral neuropathy and unstable HF and for those prescribed insulin or with a history of hypoglycaemia [101]. Individual preferences, motivations and circumstances should inform choice.

Weight management should be a central focus for individuals with type 2 diabetes with overweight or obesity, with individualised weight loss goals. For most people, a target of at least 5% weight loss is reasonable and can be expected to have clinical benefits. Substantial (>10%) weight loss and weight loss early in the course of type 2 diabetes increase the chance of remission of disease [50]. The use of glucose-lowering agents that provide significant weight loss, particularly GLP-1 RA with high weight loss efficacy, should be

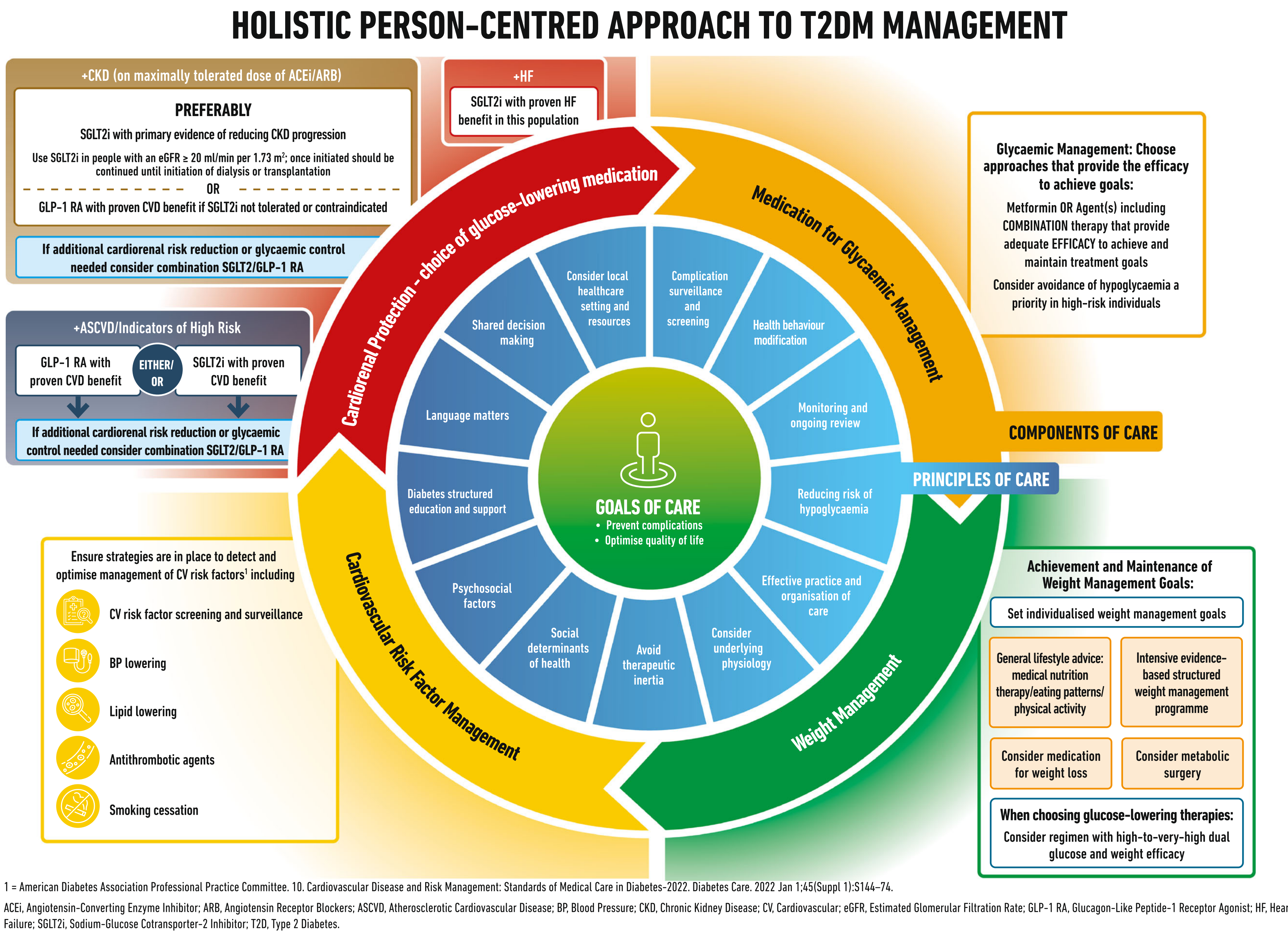


Fig. 4 Holistic person-centred approach to T2DM management

considered as they can often provide 10–15% weight loss or more. Metabolic surgery, which is most effective when performed early during diabetes, can be considered in those without a sufficient response to non-surgical weight loss interventions based on the specific context and preferences and should be accompanied by health behaviour interventions. The benefits of metabolic surgery need to be balanced against its potential adverse effects, which vary by procedure and include surgical complications, late metabolic or nutritional complications and impact on psychological health [5, 6, 127]. People being considered for metabolic surgery should be evaluated for comorbid psychological conditions and social and situational circumstances that may interfere with surgery outcomes. People who undergo metabolic surgery should receive long-term medical and behavioural support. Metabolic surgery should be performed in high-volume centres with experienced multidisciplinary teams [127].

SMART (specific, measurable, attainable, relevant, time-based) goals are more effective for achieving behaviour change than non-specific recommendations [311]. An 'all or none' approach related to behavioural goals should be avoided as any improvement in healthy behaviours can have a positive impact in diabetes [93, 312]. Self-monitoring of achievements (e.g. physical activity monitoring and weight measurement) is crucial to the achievement of health behaviour goals (Fig. 1). Behavioural health specialists or psychologists with specific training in behaviour change interventions can be of particular value as members of the team to help the person with type 2 diabetes achieve goals.

Practical tips for clinicians (Supplementary Fig. 2)

- Specific health behaviour and weight management goals should be agreed on between the person with type 2 diabetes and the care team; shared decision making is an important component of this discussion.
- Emphasise self-monitoring behaviours and review data collected (e.g. glucose monitoring, weight, tracking physical activity) in clinical visits to convey their importance in achieving the desired health behaviour goals.
- People taking insulin or a sulfonylurea should be educated about the risk, symptoms and treatment of hypoglycaemia when undertaking physical activity or adopting a specific nutritional plan; prescribe glucagon in people at risk for severe hypoglycaemia.
- DSMES and MNT can help the person living with diabetes to identify and address barriers to implementing healthier behaviours.

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 comorbidities, risk of side effects, preferences and context (Figs 3, 4). Pharmacological treatment of hyperglycaemia must be integrated in DSMES and accompanied by a focus on healthy behaviours from diagnosis onwards. This should be integrated as part of a holistic, multifactorial approach to type 2 diabetes that includes weight, blood pressure and lipid management (Fig. 4).

Whereas the pursuit of glycaemic control and the pursuit of organ-specific (e.g. heart and kidney) protection are complementary and not mutually exclusive, clinicians should not confuse the discussion of choice of agents for their glucose-lowering effect with the discussion of choice of specific agents for their direct organ-protecting effect. Some agents, in particular SGLT2i, have been shown to protect organs (heart, kidney) partly independently of their glucose-lowering effect, as this organ protection also occurs in those not affected by type 2 diabetes.

Based on these principles, regardless of HbA_{1c} level or the presence of other glucose-lowering agents, all individuals with diabetes and established or subclinical CVD should be prescribed an agent with proven cardiovascular benefit from the GLP-1 RA class or SGLT2i class [5, 6]. The evidence for cardiovascular benefits of GLP-1 RA and SGLT2i in those with only risk factors for CVD, based on MACE (myocardial infarction, stroke or cardiovascular death), is less robust, as fewer people with lower event rates are included in studies [313–315]. Furthermore, it is important to recognise that the predicted absolute benefit of an intervention is dependent on the absolute risk and thus those with prior CVD events are more likely to experience a benefit over intermediate time frames than those with cardiovascular risk factors only. Through shared decision making, considering an individual's lifelong CVD risk, introduction of a GLP-1 RA or SGLT2i with proven cardiovascular benefit into the regimen for a person with CVD risk factors can be considered in the context of increased treatment burden and potential side effects with lower absolute risk reduction.

All individuals with diabetes and CKD (eGFR <60 ml/min per 1.73 m^2 or UACR >3.0 mg/mmol [>30 mg/g]) should receive an agent with proven kidney benefit from the SGLT2i class (or GLP-1 RA class if SGLT2i are contraindicated or not preferred or their use is not permitted under license). Likewise, those with HF (HF with reduced ejection fraction or HF with preserved ejection fraction) should receive an agent from the SGLT2i class with proven benefit for HF. In both instances, the goal of organ protection with SGLT2i or GLP-1 RA should be independent of background glucose-lowering therapies, current HbA_{1c} level or target HbA_{1c} level (Figs 3, 4).

While there is compelling evidence to support a place for SGLT2i and the GLP-1 RA class in the treatment of many people with type 2 diabetes based on their direct organ-protecting effects, it is acknowledged that to date these agents are expensive. In the setting of resource constraints, prioritisation of the highest risk groups for access to these agents may be needed, with consideration of absolute risk reduction in addition to relative risk reductions.

Evidence on specific agents and their effects on other comorbidities, such as NAFLD, is emerging. For those with NAFLD/NASH at high risk of fibrosis, pioglitazone could be considered. There is emerging evidence for benefits of metabolic surgery and three classes of glucose-lowering therapy (GLP-1 RA, SGLT2i, and GIP and GLP-1 RA) [188, 292–298, 316].

Overall, for treatment of hyperglycaemia, metformin remains the agent of choice in most people with diabetes, based on its glucose-lowering efficacy, minimal risk of hypoglycaemia, lack of weight increase and affordability. Often, monotherapy with metformin will not suffice to maintain glucose levels at target. As proposed in the previous consensus report and update [5, 6], other classes of agents are useful in combination with metformin or when metformin is contraindicated or not tolerated. Selection of other glucose-lowering agents will be determined by the balance between the glucose-lowering efficacy and the side effect profile of the individual agents (see Table 1).

Special attention needs to be given to populations in which hypoglycaemia is most dangerous, for example people with frailty, in whom agents without risk of hypoglycaemia need to be prioritised. If sulfonylureas or insulin are used, consideration of less stringent targets in such settings is prudent and deprescribing if asymptomatic or severe hypoglycaemia ensues.

Finally, it needs to be stated that the evidence on organ-protecting or glucose-lowering effects of specific pharmacotherapies in specific subpopulations (e.g. younger and older people, women and various racial/ethnic groups) continues to be limited. This lack of evidence is, however, not a reason to withhold these medications in these subpopulations, given their proven benefits in large general populations.

Practical tips for clinicians (Supplementary Fig. 2)

- Providers should continually update their knowledge on the efficacy and side effects of diabetes pharmacotherapy (see Table 1).
- Identify relevant comorbidities (e.g. obesity, CVD, HF, CKD, NAFLD).
- Assess the profile of the person with diabetes (e.g. younger age, frailty, limited life expectancy, cognitive impairment, social determinants of health).
- Consider risk factors for medication adverse events (e.g. hypoglycaemia, volume depletion, genital infections, history of pancreatitis).
- Prioritise the use of organ-protective medications (GLP-1 RA, SGLT2i, TZD) in those with cardiorenal disease or NASH or at high risk.

Proactive care: avoiding inertia

Reassessment of individual glycaemic targets and their achievement at regular intervals is key (Figs 1, 3, 4). When targets are not met, in addition to addressing health behaviours and referral to DSMES, the intensification of glucose-lowering medication by combining agents with complementary mechanisms of action should be pursued. Traditionally, a stepwise approach was advocated, in which a new agent is added to the existing regimen, but evidence is growing to support a more proactive approach in many, by combining glucose-lowering agents from initial diagnosis [6].

Early use of combinations of agents allows tighter glucose control than monotherapy with the individual agents, and thus combinations of agents are indicated in those who have HbA_{1c} levels >16.3 mmol/mol (>1.5%) above their target at diagnosis (e.g. ≥70 mmol/mol [8.5%] in most) [6]. In particular, among young adults with type 2 diabetes, immediate and sustained glycaemic management should be pursued, aiming for HbA_{1c} <53 mmol/mol (7%) (or even lower). This presents the best opportunity to avoid complications of diabetes across the lifespan. Moreover, the pathophysiology of micro- and macrovascular damage shares more commonality than usually thought, suggesting that the prevention of microvascular disease may, in the long term, contribute to a reduction in macrovascular complications as well [317].

The knowledge base guiding clinicians beyond dual therapy in type 2 diabetes is still limited. In general, intensification of treatment beyond two medications follows the same general principles as the addition of a second medication, with the assumption that the effectiveness of third and fourth medications will be generally less than when they are used alone. Whereas solid evidence exists for combining SGLT2i and GLP-1 RA for weight and glucose lowering, emerging data suggest promise for combined effects on cardiorenal outcomes [228].

As more medications are added, there is an increased treatment burden and risk of adverse effects. It is important to consider medication interactions and whether regimen complexity may become an obstacle to adherence. Fixed-dose combination preparations can improve medication-taking behaviours. Finally, with each additional medication comes increased costs, which can affect medication-taking behaviour and medication effectiveness [318–326].

Response to all therapies should be reviewed at regular intervals, including the impact on efficacy (HbA_{1c}, weight), safety and organ protection. While most people with diabetes require intensification of glucose-lowering medications, some require medication reduction or discontinuation, particularly if the therapy is ineffective or associated with side effects such as hypoglycaemia or when glycaemic goals have changed because of a change in clinical circumstances (e.g. development of comorbidities or even healthy ageing). Medication should be stopped, or the dose reduced, if there are minimal benefits or if harm outweighs any benefit. Ceasing or reducing the dose of medications that have an increased risk of hypoglycaemia is suggested when any new glucose-lowering treatment (behavioural or medication) is started and the individual's glycaemic levels are close to target [66]. HbA_{1c} levels below 48 mmol/mol (6.5%) or substantially below the individualised glycaemic target as well as any increased risk of hypoglycaemia should prompt stopping or reducing the dose of medications associated with an increased risk of hypoglycaemia.

Practical tips for clinicians (Supplementary Fig. 2)

- Consider initial combination therapy with glucose-lowering agents, especially in those with high HbA_{1c} at diagnosis (i.e. >70 mmol/mol [>8.5%]), in younger people with type 2 diabetes (regardless of HbA_{1c}) and in those in whom a stepwise approach would delay access to agents that provide cardiorenal protection beyond their glucose-lowering effects.
- Avoid therapeutic inertia and re-evaluate health behaviours, individuals' medication-taking behaviours and side effects of agents at every clinic visit.
- When additional glycaemic control is needed, incorporate, rather than substitute, glucose-lowering therapies with complementary mechanisms of action.
- Consider fixed-dose combinations to reduce prescription burden.
- Consider de-intensification of therapy, e.g. in frail older adults and in the setting of hypoglycaemia-causing medications, in those with glycaemic metrics substantially better than target.

Place of insulin in type 2 diabetes

Insulin is a useful and effective glucose-lowering agent (Fig. 5). When glycaemic measurements do not reach targets, and insulin is the best choice for the individual, its introduction should not be delayed. When clinicians are not familiar with insulin use, referral to specialist care is indicated. However, with the growing evidence supporting use of particular agents in people with type 2 diabetes with specific profiles (comorbidities, overweight/obesity) and with the availability of multiple glucose-lowering agents with good efficacy and acceptable side effect profiles, the initiation of insulin can be postponed in many to later stages of the disease. GLP-1 RA should be considered in all when no contraindications are present before initiation of insulin therapy, as they allow lower glycaemic targets to be reached with a lower injection burden and lower risk of hypoglycaemia and weight gain than with insulin alone.

The preferred way of initiating insulin in people with type 2 diabetes is to add basal insulin to the existing pharmacological therapy, in conjunction with revisiting health behaviours and re-referral to DSMES. However, agents that cause hypoglycaemia in themselves, such as sulfonylureas, should be discontinued once insulin is started. Technologies allowing continuous monitoring of glucose levels without finger sticking have clear advantages in those on insulin. Other support tools and systems such as apps guiding insulin dose adaptation or phone-based guidance can also be helpful.

In specific circumstances, insulin may be the preferred agent for glucose lowering, specifically in the setting of severe hyperglycaemia (HbA_{1c} >86 mmol/mol [>10%]), particularly when associated with weight loss or ketonuria/ketosis and with acute glycaemic dysregulation (e.g. during hospitalisation, surgery or acute illness), in underweight people or when the diagnosis of type 1 diabetes is suspected.

If affordable, basal insulin analogue formulations are preferred to NPH insulin because of their reduced risk of hypoglycaemia, particularly nocturnal hypoglycaemia, when titrated to the same fasting glucose target [327]. Basal insulins are typically administered before bedtime but, with newer analogues, more flexibility in the timing of insulin injection is possible (i.e. any time of the day).

In some, as the disease progresses, despite titration of the basal insulin to correct fasting hyperglycaemia (typically more than 0.5 U/kg), mealtime insulin may have to be added to meet glycaemic targets, particularly postprandial glucose [328]. Mealtime insulin may be required to enhance postprandial blood glucose levels and achieve HbA_{1c} targets. Therapeutic inertia in intensification of insulin therapy should be avoided and, when clinicians are not familiar with multiple daily injection therapy, referral to specialist care and/or DSMES is warranted. A straightforward way to introduce mealtime insulin is to start with a short- or rapid-acting insulin injection before the meal associated with the largest glucose excursion. Adding mealtime rapid-acting insulin requires increased DSMES and self-monitoring of glucose levels and adds complexity and cost to the therapy. In contrast to basal insulin analogues, the evidence supporting the choice of mealtime rapid-acting insulin analogues is less clear [329]. Another simpler and still popular way of combining mealtime and basal insulin components is using premixed insulins. Insulin

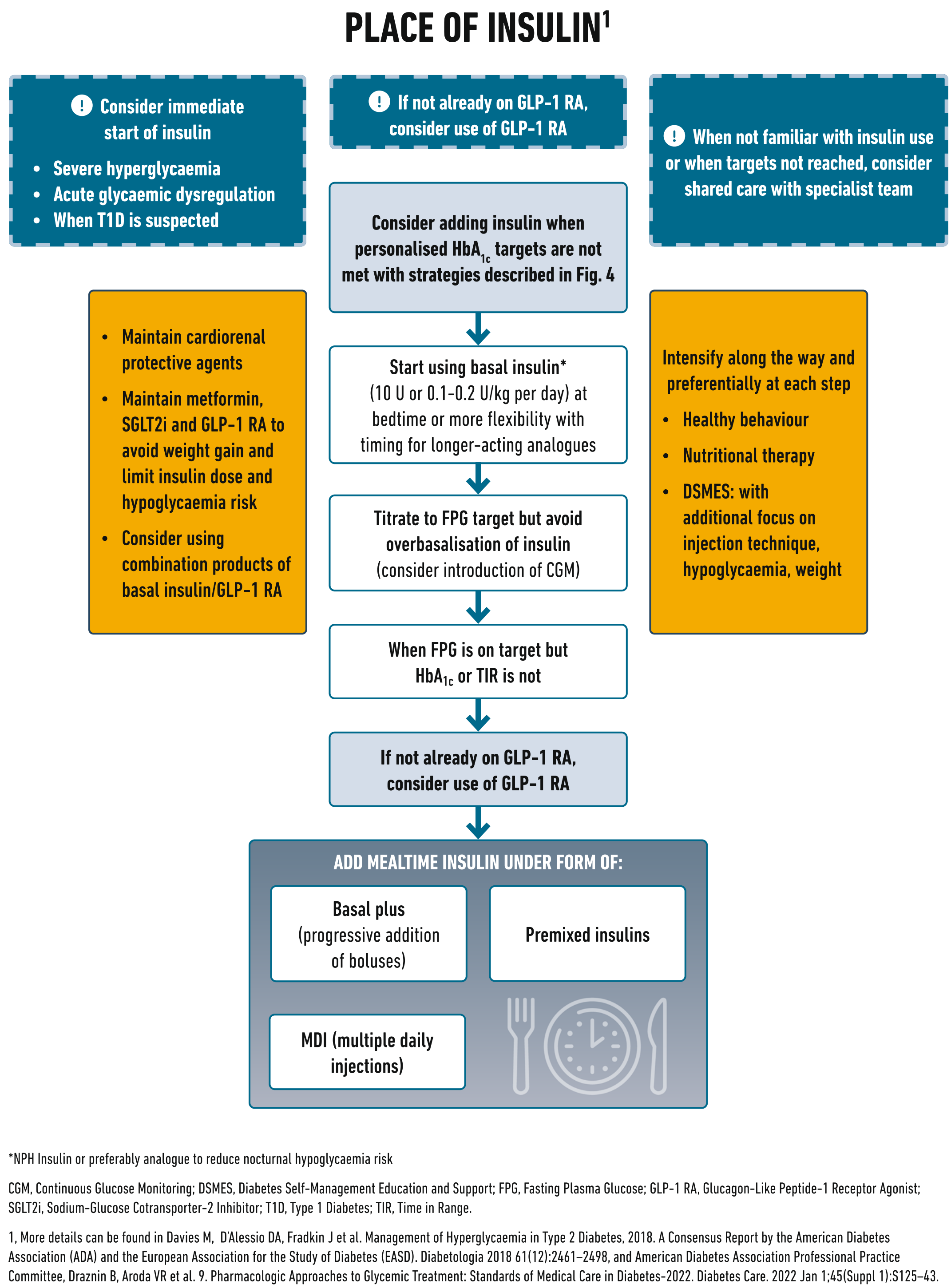


Fig. 5 Place of insulin[1]

analogue-based combinations have the advantage of resulting in fewer hypoglycaemic events and weight gain than are typically observed with human premixed insulin [330].

Finally, it needs to be re-emphasised that, in all insulin-treated people with type 2 diabetes, agents associated with cardiorenal protection or weight reduction should be kept in the treatment regimen whenever possible [331]. The combination of a basal insulin analogue and GLP-1 RA in one injection may be a simple way to reduce the burden and complexity of treatment [332].

Practical tips for clinicians (Supplementary Fig. 3)

- The use of a GLP-1 RA should be considered prior to initiation of insulin.
- When initiating insulin, start with a basal insulin and intensify the dose in a timely fashion, titrating to achieve an individualised fasting glycaemic target set for every person.
- When insulin is initiated, continue organ-protective glucose-lowering medications and metformin.
- Refer for DSMES when initiating insulin or advancing to basal–bolus therapy.

Place of technology

The use of technology in the therapy of people with type 2 diabetes is increasing through a broad range of approaches, for example telehealth, remote monitoring systems, CGM and behavioural aids to support physical activity, meal planning and monitoring, medication-taking behaviour, mindfulness and stress management. Evidence on the impact of these systems is variable and highly dependent on the embedding of the technology in a more comprehensive approach. Evidence for a beneficial impact of telehealth on achieving treatment goals in those living with type 2 diabetes is growing [333, 334]. During the COVID-19 pandemic, telehealth has proven to be an efficient way of overseeing the treatment of people with type 2 diabetes. In particular, interventions using apps as tools to support DSMES have been shown to have an impact on outcomes [34].

For those needing insulin as part of their treatment, smart insulin pens and insulin pumps (continuous subcutaneous insulin infusion [CSII]) are available. Specific evidence on the benefit of smart pens in people with type 2 diabetes is still scarce. CSII use is associated with small improvements in HbA_{1c} and fewer hypoglycaemic events, suggesting that CSII can be considered in people living with type 2 diabetes treated with multiple daily insulin injections and able to manage the device [71]. Again, for optimal effect, this technology should be embedded in an integrated approach to type 2 diabetes therapy, specifically to avoid weight gain [335].

In individuals with type 2 diabetes treated with insulin, CGM, both intermittently scanned CGM and real-time CGM, has gained traction, with evidence that CGM results in better overall glucose control as defined by HbA_{1c} and time in range (3.9–10.0 mmol/l [70–180 mg/dl]), fewer hyperglycaemic and hypoglycaemic episodes and improvements in diabetes distress [336, 337].

As with other wearables, for example those collecting steps walked or monitoring dietary intake, medication dose administered or sleep quality, use of CGM has also been proposed as a motivational tool for those with type 2 diabetes not on insulin therapy, but the evidence on this is modest [337].

Finally, to date, no convincing evidence is available on the use of hybrid closed loop systems specifically in people with type 2 diabetes.

Practical tips for clinicians (Supplementary Fig. 3)

- Technology can be useful in people with type 2 diabetes but needs to be part of an holistic plan of care and supported by DSMES.
- Consider CGM in people with type 2 diabetes on insulin.
- Adapt the clinic/system to optimise effective use of technology among people with type 2 diabetes, particularly to support behaviour change through self-monitoring.

Working within the system to deliver improved care

We are fortunate to have evidence on numerous effective interventions in type 2 diabetes, but translating this evidence into practice cannot rest only with front-line clinicians during individual clinic visits. The systems of care that support front-line clinicians have a significant role in improving diabetes clinical management, outcomes and experience for people living with diabetes. Front-line clinicians must inform and drive the design of care, but the systems of care should be held accountable for implementation. Supplementary Table 2, informed by the Effective Practice and Organisation of Care (EPOC) taxonomy [338], outlines key domains and questions that must be answered to achieve the goal of better care and outcomes for people living with type 2 diabetes. All levels of the care delivery system have a role and responsibility in improving diabetes management. Clinic leaders have a responsibility to improve workflows to make it easy to provide evidence-based care and provide data to inform quality improvement efforts. Continuing education is necessary to ensure evolving evidence reaches people living with type 2 diabetes. Policy makers have a responsibility to ensure that evidence-based interventions are available and affordable to all. Interventions to improve diabetes must also include the health system (including the microsystems within a system) and governmental agencies. Policy makers, together with all stakeholders, should reflect on care delivery: How, where and by whom is care delivered? Who coordinates care and the management of care processes? Practices and systems must establish enhanced communication technology to improve engagement. Governance arrangements must be implemented specifically around accountability for health professionals, with a focus on training and evaluation of quality of practice. Finally, reflection is needed around implementation strategies at the level of the system, facility and individual healthcare workers. These principles are aligned with recommendations outlined in the recent *Lancet* Commission on diabetes [339].

Practical tips for clinicians (Supplementary Fig. 3)

- Identify and incorporate continuing education activities on the management of type 2 diabetes for all members of the healthcare team.
- Team-based care is required for integrated care of diabetes; this includes coordination between multiple disciplines (diabetes care and education specialist, dietitians, psychologists, etc.) and often other medical specialties (primary care, endocrinology, ophthalmology, nephrology, etc.).
- Management of type 2 diabetes requires continuous quality improvement interventions tailored to the local setting.

Key knowledge gaps and a call to action

In this 100th year since the discovery and partial purification of insulin, we should remember the remarkable speed at which this first glucose-lowering medication was developed and distributed as life-saving therapy for people with diabetes. Through our experience in the last few years with the COVID-19 pandemic, we have demonstrated how quickly many governments, industry, healthcare systems and academic institutions can respond to global healthcare crises. Within a year of identification of the SARS-CoV-2 virus, preventive and therapeutic products were not only developed and tested but also administered on a massive scale. The annual global mortality rate directly attributable to diabetes is approximately 1.5 million people, with 540 million people affected [340, 341]. Although not as spectacular as the impact of COVID-19 on the health of society, diabetes is sure and steady in its burden, increasing in prevalence and with an increase in mortality and morbidity over time.

Two centuries of investigation into the pathophysiology of diabetes have led to the extraordinary advances in treatment of the last two decades. As reviewed in this consensus report, encouraging healthy behaviours, DSMES, medications, devices, technologies and organisation of care all represent effective tools for the management of diabetes to reduce its morbidity and mortality. However, despite the generous approach of Banting and Best in licensing the patent for insulin for one Canadian dollar, it is not yet readily available to all people with diabetes [342, 343]. Recent events have focused attention on the contribution of social determinants of health and a lack of equity in the delivery of care to disparate and unfavourable outcomes. Today, the major opportunities to improve diabetes outcomes in the near term come from more effective implementation of best evidence through organisation of care at all levels (national to individual practices) and from addressing social determinants of health. Every reader of this consensus report has a role to play in better implementation with a focus on equity. For providers, that could involve a focus on shared decision making to improve adherence to behavioural and medication interventions as well as organising practice to minimise therapeutic inertia and enhance engagement and support for all people with diabetes. For policy makers, healthcare systems, payors and companies with marketed products or services, ensuring equitable access to minimise health disparities should be a priority.

Broad support for basic science is necessary to bring about the next generation of interventions. Implementation science is an essential area for future work, particularly in the context of ‘learning healthcare systems’, in which internal data are systematically integrated with published evidence to drive quality improvement [344–346]. Precision medicine initiatives, whether ‘omics’-based or focused on social determinants of health, aim to optimally target interventions based on the wide heterogeneity of the population affected by diabetes. Precision medicine has tremendous but largely unrealised promise. When these efforts are driven by real-world data, causal inference study design and analysis create greater confidence in the implementation and evaluation of insights. Studies should be conducted to support the better understanding of precision medicine approaches to the full spectrum of diabetes interventions, from medications to behavioural treatments and diabetes support.

Several key areas where further research could better inform future consensus reports were of particular interest to the writing group. For each area, one could add the need for more precision medicine insights and a better understanding of the full spectrum of investigations that are supporting efforts to advance the field from basic to implementation science. With upwards of 10% of the population affected by diabetes and the enormous attendant costs, a focus on individualising care to make sure that the right person is getting the right therapy at the right time while working to overcome barriers dependent on social determinants of health is essential. Regulatory reform, more efficient study conduct and analysis, coordinated global efforts in defining outcomes and data collection instruments, data sharing, exploration of new forms of healthcare delivery (e.g. telehealth) and increased efforts to reach underserved populations, as were made to address COVID-19, would accelerate progress in defining and implementing optimal approaches for diabetes care.

- Study conduct. Across the spectrum from highly controlled trials to observational studies, paying greater attention to subgroups, in particular vulnerable populations, is essential. Dedicated studies in young adults with type 2 diabetes, or including much larger numbers of younger adults in broader studies, are essential to better understand how to mitigate their high risk of early disability. As more younger adults are being treated with therapies that have been inadequately studied in pregnancy, it is essential to describe the reproductive safety of recommended approaches. Similarly, there have been inadequate studies of frail older people and those aged >75 years with regard to understanding both appropriate targets and interventions, to minimise harms and maximise quality of life. Sex balance is another dimension where our present studies fail to be representative. Better recruitment, retention and analysis to ensure safety and effectiveness in populations historically underrepresented in studies and generally suffering from health inequities is a minimal first step to enhance health justice by sex, race/ethnicity and nationality, etc.

- Weight management. With the emergence of more effective behavioural and medical therapies and novel surgical approaches for the treatment of people who are overweight with diabetes, more direct comparisons are required to better target interventions based on impact and cost-effectiveness.
- Targets. Studies designed to explicitly examine glucose-centric vs weight-centric approaches to diabetes management are needed. The impact of prioritising early aggressive therapy to induce remission is unclear.
- Cardiorenal protection. Data are required to better inform when to select a GLP-1 RA and/or an SGLT2i in the setting of CVD but without HF or CKD, and to fully validate the recommendation for combination therapy in those at high risk who do not meet glycaemic targets. As discussed, there is considerable uncertainty about the absolute benefits of GLP-1 RA and SGLT2i for CVD outcomes in those with risk factors only. As a result, there is variability in the recommendations on how to define high-risk people with diabetes, to whom these disease-modifying agents should be prescribed to have the greatest benefit/impact. As all people with diabetes are at high risk of CVD, HF and CKD over time, real-world evidence and cost-effectiveness studies of GLP-1 RA and SGLT2i in broad populations would help to better target interventions to have the greatest impact on outcomes.
- Glucose monitoring. Further studies to understand the role and optimal implementation of CGM and/or episodic CGM in type 2 diabetes are needed.
- Comorbidities. There are numerous studies under way to understand the role of interventions in the setting of NAFLD and cognitive impairment. NAFLD is highly prevalent and thus understanding the impact of interventions on person-centred outcomes and costs is essential. Cognitive impairment is a major burden to people with diabetes, their families and society; better understanding of the pathophysiology and the impact of interventions is a challenging but high reward area for investigation. There are virtually no data to inform best practice in the care of people with diabetes and advanced CKD, particularly in dialysis-dependent kidney disease. Additional studies, particularly of GLP-1 RA, GIP and GLP-1 RA, and SGLT2i, will hopefully provide new avenues to reduce mortality in this population, in which there are enormous health disparities.
- Screening and prevention. Screening for diabetes and its complications and comorbidities remains inadequate. Early intervention to prevent progression is also generally suboptimal. National healthcare systems should comprehensively assess the implementation of recommendations and create incentives for effective programmes. To optimally target resources, additional studies may be required on natural history and subpopulations, as much of the rationale for screening is based on studies conducted decades ago.
- Technology. Remote care, wearables, apps and decision support aids have exploded in availability and clear rationale exists as to why they may be of benefit. However, their optimal application is poorly understood.
- Sleep and chronotype. Poor sleep is common and clearly associated with poor outcomes. Further studies are needed to understand behavioural sleep therapy and its benefits more fully, as well as the benefits of medication and device aids. As chronotype is potentially modifiable, future research should focus on social and lifestyle factors to optimise interventional responses.

Until science and medicine bring us further insights, we recommend empathic, person-centred decision making and support informed by an understanding of local resources and individual social determinants of health. Combined with consistent efforts to improve health behaviours (nutrition, activity, sleep and self-monitoring) and to provide DSMES, these form the foundation of diabetes management. In this context, acceptance of, adherence to and persistence with medical and behavioural interventions to support cardiorenal health, cardiovascular risk reduction and attainment of glycaemic and weight goals will prevent complications and optimise quality of life. We must establish and refine quality improvement efforts in diabetes care at the local level to equitably implement evidence-based interventions for the benefit of all people with type 2 diabetes.

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Affiliations

Melanie J. Davies[1,2] · Vanita R. Aroda[3] · Billy S. Collins[4] · Robert A. Gabbay[5] · Jennifer Green[6] · Nisa M. Maruthur[7] · Sylvia E. Rosas[8] · Stefano Del Prato[9] · Chantal Mathieu[10] · Geltrude Mingrone[11,12,13] · Peter Rossing[14,15] · Tsvetalina Tankova[16] · Apostolos Tsapas[17,18] · John B. Buse[19]

[1] Leicester Diabetes Research Centre, University of Leicester, Leicester, UK

[2] Leicester National Institute for Health Research (NIHR) Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Leicester, UK

[3] Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[4] National Heart, Lung, and Blood Institute, Bethesda, MD, USA

[5] ADA, Arlington, VA, USA

[6] Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA

[7] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[8] Kidney and Hypertension Unit, Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

[9] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[10] Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium

[11] Università Cattolica del Sacro Cuore, Rome, Italy

[12] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[13] Division of Diabetes and Nutritional Sciences, School of Cardiovascular and Metabolic Medicine and Sciences, King's College London, London, UK

[14] Steno Diabetes Center Copenhagen, Herlev, Denmark

[15] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[16] Department of Endocrinology, Medical University – Sofia, Sofia, Bulgaria

[17] Diabetes Centre, Clinical Research and Evidence-based Medicine Unit, Aristotle University Thessaloniki, Thessaloniki, Greece

[18] Harris Manchester College, University of Oxford, Oxford, UK

[19] University of North Carolina School of Medicine, Chapel Hill, NC, USA