diabetesresearchandclinicalpractice234(2026)113173

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Review

Glycaemic control remains central in type 2 diabetes mellitus management: key learnings from the latest International Diabetes Federation guidelines

Juliana C.N. Chan [a], Chaicharn Deerochanawong [b], Kamlesh Khunti [c], Mohamed Hassanein [d], Viswanathan Mohan [e,*]

[a] Department of Medicine and Therapeutics, Hong Kong Institute of Diabetes and Obesity (IDF Centre of Excellence in Diabetes Care) and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China
[b] Department of Medicine, Rangsit University, Pathum Thani, Thailand
[c] Diabetes Research Centre, University of Leicester, Leicester, United Kingdom
[d] Mohamed Bin Rashid University and Dubai Hospital, Dubai Health, Dubai, United Arab Emirates
[e] Madras Diabetes Research Foundation (ICMR Collaborating Centre of Excellence) and Dr. Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care), Chennai, Tamil Nadu, India

ARTICLE INFO

Keywords:
Cardiovascular-kidney outcomes
Clinical practice guidelines
Glycaemic control
Multifactorial management
Organ protection
Type 2 diabetes mellitus

ABSTRACT

The 2025 International Diabetes Federation (IDF) guidelines recognise global disparities in healthcare access, with ~ 80% of people with type 2 diabetes mellitus (T2D) living in low-to-middle–income countries (LMICs). A panel of international experts discussed the evidence underlying these updated guidelines. Randomised trials demonstrate cardiovascular-kidney protection with sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in high-risk people with T2D, although their role among those with low-risk disease remains less clear. Whilst advocating for the need to improve access to newer glucose-lowering drugs (GLDs) in LMICs, the IDF guidelines propose two standards-of-care ('optimal' or 'basic'), with the following key messages: (i) early glycaemic control using conventional GLDs prevents complications and preserves quality of life; (ii) multifactorial management using effective GLDs and organ-protective drugs (e.g. statins and renin–angiotensin–aldosterone system inhibitors) improve outcomes; (iii) individualised regimens with shared decision-making and treatment persistence maximises benefits and minimises harm; (iv) metformin is a foundation therapy, with no evidence supporting first-line SGLT2i or GLP-1 RA monotherapy in low-risk individuals; (v) sulphonylureas are highly effective and affordable GLDs, making them important options (particularly in low-resource settings); and (vi) initial combination therapy achieves early glycaemic control with increased durability versus stepwise GLD addition.

1. Introduction

Type 2 diabetes mellitus (T2D) is a progressive disease associated with high rates of microvascular and macrovascular complications (e.g. cardiovascular disease [CVD], chronic kidney disease [CKD]), comorbidities and premature mortality [1]. According to the International Diabetes Federation (IDF), the estimated global prevalence of diabetes in 2024 was 11.1%, corresponding to approximately 589 million adults (aged 20–79 years). By 2050, this figure is expected to rise to 13% (about 853 million) due to increased urbanisation and ageing populations [2]. Of note, 95% of this increase is expected to occur in low-to-middle–income countries (LMICs), where population growth is predicted to be greater than high-income countries [2]. For example, between 2024 and 2050, the age-standardised prevalence of T2D in the Middle East/North Africa region and South East Asia region is predicted to rise from 19.9% to 22.8% and 10.8% to 13.0%, respectively [2]. In some LMICs, the prevalence of macrovascular and microvascular complications also continues to increase, with poor glycaemic control being a key determinant [3].

All international guidelines for T2D management support the importance of tight glycaemic control for cardiovascular protection and microvascular benefits [4–6]. In recent years, there has been an increased emphasis on organ protection [5,7,8], which may have inadvertently de-emphasised the importance of effective glycaemic control

* Corresponding author at: Madras Diabetes Research Foundation (ICMR Collaborating Centre of Excellence) and Dr. Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care), No 6, Conran Smith Road, Gopalapuram, Chennai, Tamil Nadu 600086, India.
E-mail address: drmohans@diabetes.ind.in (V. Mohan).

https://doi.org/10.1016/j.diabres.2026.113173
Received 4 November 2025; Received in revised form 17 February 2026; Accepted 18 February 2026
Available online 19 February 2026

in providing cardiovascular-kidney protection [9]. Large-scale, long-term randomised controlled trials (RCTs), including the United Kingdom Prospective Diabetes Study (UKPDS) [10,11], the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [12,13], the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study [14,15] and the Veterans Affairs Diabetes Trial (VADT) [16,17], highlight the long-term benefits of early intensive glucose-lowering therapy in reducing microvascular complications and improving cardiovascular-kidney outcomes. In UKPDS, which enrolled newly diagnosed individuals with T2D, reducing glycated haemoglobin (HbA1c) by 0.9% (10 mmol/mol) resulted in long-term improvements in all-diabetes related outcomes, including cardiovascular-kidney disease [10]. These legacy effects were sustained up to 24 years after study completion [18]. A *meta*-analysis of 11 RCTs emphasised the importance of glycaemic control for prevention of microvascular and macrovascular complications [19]. A 2025 consensus statement highlighted the importance of early glycaemic control, in addition to targeting existing cardiovascular and kidney disease, as the central therapeutic goal in most people with T2D, while emphasising the importance of multifactorial management to account for the interindividual variability of disease [9].

Real-world data have demonstrated that many endocrinologists and about 50% of primary care physicians prescribed newer glucose-lowering drugs (GLDs; i.e. sodium–glucose cotransporter 2 inhibitors [SGLT2is] and glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) when managing individuals with T2D and CVD [20]. SGLT2is and GLP-1 RAs provide important cardiovascular-kidney benefits in individuals with prior complications or multiple risk factors [21]. Indeed, an international panel of clinicians, patients and methodologists have issued risk-stratified guidelines that strongly recommend the use of SGLT2is or GLP-1 RAs in individuals with higher risk (established CVD and/or CKD at higher risk of complications or established heart failure [HF]) [22,23]. In contrast to other international guidelines [4–6], these clinical practice guidelines focus on CVD and CKD risk factors and shared decision-making when considering SGLT2i or GLP-1 RA treatment, rather than achievement of HbA1c targets [22,23]. However, there are limited data on the benefits of these agents among people with T2D who do not have complications or few risk factors. The importance of phenotypic differences between Asian and European populations, particularly the low body mass index (BMI) and reduced insulin secretion in Asians, further calls for individualised therapies rather than a 'one-size-fits-all' approach to T2D management [24,25]. To address this evidence gap, the ongoing registry-based SGLT2i inhibitor or metformin as standard treatment of early-stage T2D (SMARTEST) RCT is comparing metformin versus dapagliflozin in people with recently diagnosed T2D (<4 months) and few risk factors [26,27].

The 2025 IDF guidelines adopt a global perspective to T2D management, recognising that new organ-protective GLDs, particularly GLP-1 RAs, are either not available or not affordable in many countries [6]. To harmonise glycaemic control and cardiovascular-kidney protection goals, the IDF guidelines provide two standard-of-care strategies for T2D management: 'optimal care' and 'basic care'. The guidelines emphasise the dual importance of using highly efficacious conventional GLDs (e.g. metformin, sulphonylureas [SUs]) and newer organ-protective GLDs (i.e. SGLT2is, GLP-1 RAs). These two strategies should be considered complementary rather than mutually exclusive [6].

This expert opinion article discusses the key messages of the latest IDF guidelines and their practical implications for achieving early glycaemic control and associated long-term cardiovascular-kidney protection, particularly in LMICs.

2. Methods

Five international diabetes experts (the authors) met at the IDF World Diabetes Congress in Bangkok, Thailand in April 2025 to discuss the 2025 IDF guidelines and their practical implications. Where appropriate, they referred to other guidelines for their relevance to LMICs and under-represented individuals in high-income areas. Each author conducted focused literature searches, identified key learning points and provided comments on practice priorities. The present article summarises key points from this meeting.

3. Key learnings from the latest guidelines

3.1. 2025 IDF guidelines

The 2025 IDF guidelines provide global recommendations for T2D management, recognising that around 80% of adults with T2D live in LMICs and do not have access to all GLDs and organ-protective therapies (Table 1) [6]. Indeed, only 4.6% of individuals with T2D in LMICs have access to all recommended treatments (i.e. all pharmacological and nonpharmacological treatments) [28]. Recognising ongoing efforts to address global disparities in healthcare access, these updated guidelines provide two concurrent standard-of-care options: 'optimal care' or 'basic care' (Fig. 1) [6]. In either option, treatment must be optimised to safely and effectively control blood glucose levels and reduce the risks of microvascular and macrovascular complications.

Metformin is recommended as the foundation therapy in both 'optimal' or 'basic' care (Table 2). This is applicable to newly diagnosed and treatment-experienced individuals with suboptimal glycaemic control, irrespective of their cardiovascular-kidney disease risk [6]. People with T2D require lifestyle modification and metformin-based combination therapy to achieve early glycaemic control with addition of GLP-1 RAs or SGLT2is, depending on the presence of complications. In newly diagnosed people with T2D and obesity, GLP-1 RAs plus metformin can be considered part of optimal care (when available/affordable) or SGLT2is plus metformin as part of basic care. People with

Table 1
Key points of the 2025 IDF global clinical practice recommendations [6].

Key point	Description
• Good glycaemic control is crucial	Reduces microvascular and macrovascular complications
• Early and intensive glycaemic control has lasting benefits	Induces remission, delays treatment escalation and reduces life-time risk of complications
• Glycaemic control and organ protection must be balanced	The organ-protective effects of new GLDs over conventional GLDs have not been proven in individuals with low cardiovascular-kidney risk
• Multifactorial treatment is key for reducing cardiovascular-kidney risk	A structured multi-pillar approach is recommended that integrates both conventional and newer GLDs to improve cardiovascular-kidney outcomes
• Treatment must be individualised	Consider each individual's complications, disease duration, body weight, access to healthcare, hypoglycaemia risk, cognitive-psychosocial behavioural status, life expectancy and support
• Metformin recommended as first-line monotherapy and cornerstone of combination therapy	Recommended as part of 'optimal' and 'basic' standard of care
• SGLT2is and GLP-1 RAs should not be used as first-line monotherapy	Recommended as part of combination therapy in individuals with cardiovascular-kidney risk factors
• SUs remain an important treatment option	Gliclazide and glimepiride have high efficacy in glucose lowering, with better safety profiles and neutral or superior cardiorenal effects than other SUs
• Initial intensive combination therapy may be beneficial	Can increase the durability of glycaemic control vs stepwise treatment intensification

GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDF, International Diabetes Federation; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SU, sulphonylurea.

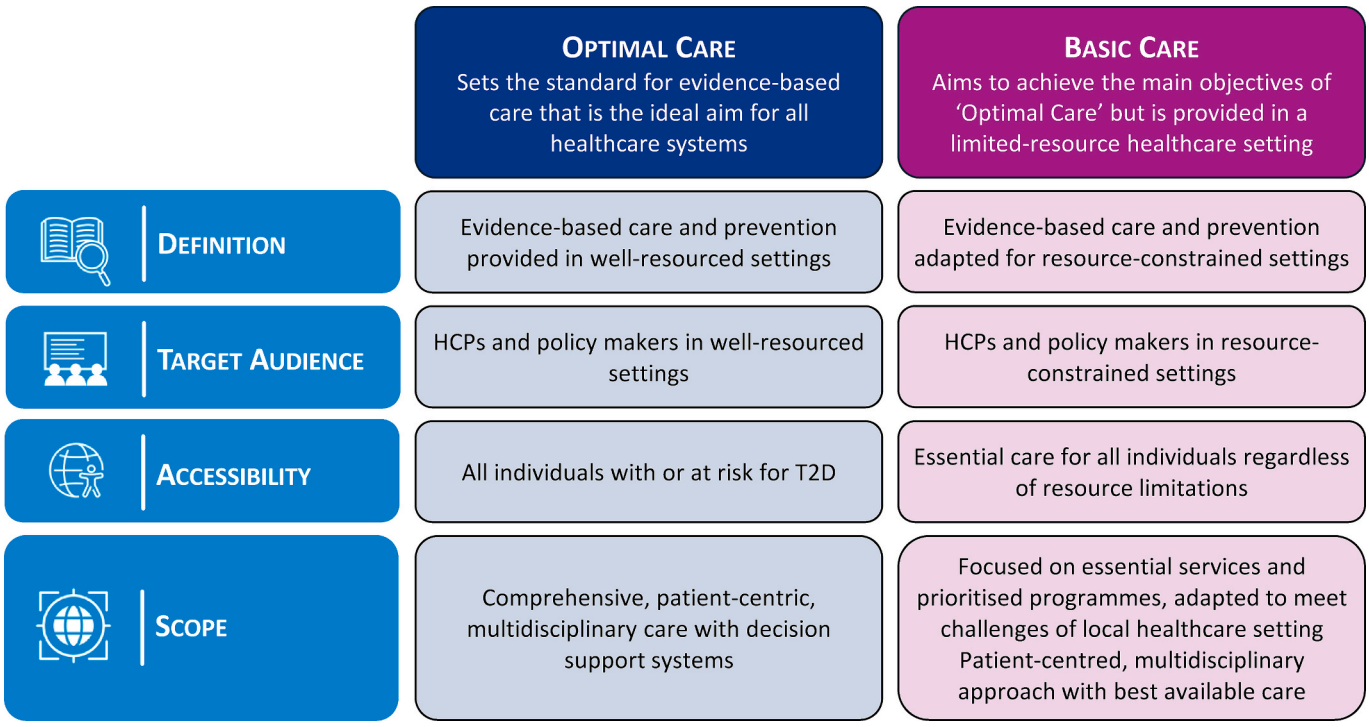

Fig. 1. Standard-of-care options in the 2025 IDF global clinical practice recommendations [6]. HCPs, healthcare providers; IDF, International Diabetes Federation; T2D, type 2 diabetes mellitus.

cardiovascular-kidney complications at diagnosis should receive GLP-1 RAs or SGLT2is in addition to metformin as part of optimal care, with SGLT2is being the preferred GLD in individuals with HF. In individuals without complications, metformin plus a second GLD (e.g. SU, SGLT2i or dipeptidyl peptidase 4 inhibitor [DPP4i]), can be used as part of basic care to achieve early glycaemic control and delay treatment escalation [6].

In treatment-experienced people with obesity and poorly controlled T2D, addition of GLP-1 RA to metformin is recommend as part of optimal care [6]. For basic care, the guidelines suggest adding an SGLT2i or *any* other available GLD to metformin. A preferred GLD is not specified, although metformin plus SGLT2i is prioritised. If SGLT2is are unavailable, ineffective or not well tolerated, any GLD can be added. In people receiving multiple GLDs with suboptimally controlled T2D, addition of SGLT2i or any available GLD (including insulin) is recommended. For optimal care in individuals with cardiovascular-kidney complications, SGLT2i or GLP-1 RA may be considered. It is important to emphasise that many individuals with complications have long-standing T2D accompanied by β-cell failure, and are receiving multiple GLDs and other organ-protective drugs. For example, the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) cardiovascular outcome trial (CVOT) demonstrated a lower risk of cardiovascular death or HF hospitalization with dapagliflozin versus placebo in 17,160 individuals with T2D and established atherosclerotic CVD (ASCVD; 40.6%) or multiple risk factors for ASCVD (59.4%) [29]. In DECLARE–TIMI 58, baseline GLDs included metformin in 82% of participants, SUs in 43% and insulin in 41%, while cardiovascular therapy included renin–angiotensin–aldosterone system inhibitors (RAASis) in 81% and lipid-lowering therapy (statins or ezetimibe) in 75% [29]. Thus, SGLT2i are favoured in people with T2D with established HF or CKD or at high risk of cardiovascular-kidney disease [6]. In individuals receiving basic care, addition of SGLT2i or any available GLD (including insulin) should be used to improve glycaemic control [6].

The guidelines recognise that 43% of the global T2D population have obesity and that a 1-kg body weight reduction can improve HbA1c by 0.1% (1 mmol/mol) [6]. Further, they emphasise the use of ethnicity-relevant BMI and waist circumference to define obesity. When selecting treatment for weight management, the guidelines recognise the benefits of metabolic surgery or incretin-based therapy (e.g. GLP-1 RA) for optimal care, while noting the poor accessibility, affordability and sustainability of these agents in LMICs [6].

In contrast with the ADA guidelines, which state that all SUs carry a risk of weight gain [30], the IDF guidelines recognise that not all SUs carry this adverse effect [6]. Data from the ADVANCE and Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes (CAROLINA) studies showed that gliclazide and glimepiride, respectively, were not associated with weight gain [31,32]. Weight gain associated with SU was mainly due to older SUs (e.g. glibenclamide [glyburide]) [11].

The latest IDF guidelines emphasise that newer SUs (e.g. glimepiride and gliclazide) also have improved cardiovascular safety and a lower hypoglycaemia risk than older SUs [6]. This is supported by a wealth of evidence. In CAROLINA, glimepiride was associated with a similar major adverse cardiovascular events (MACE) risk compared with the DPP4i linagliptin [32]. In a real-world Scottish Diabetes Research Network cohort, there was no increased risk of MACE or all-cause mortality with second-line SU therapy (gliclazide, glimepiride, glipizide or glibenclamide) versus DPP4i or thiazolidinedione (TZD) therapy [33]. In a *meta*-analysis of 18 studies of individuals with T2D treated with SU, those treated with gliclazide and glimepiride had the lowest mortality risk [34].

The World Health Organization's (WHO's) list of essential medicines only recommend gliclazide as the preferred SU agent and that glibenclamide should be avoided in individuals aged > 60 years [35]. Sulphonylureas with high-affinity for cardiac mitochondrial adenosine triphosphate-sensitive potassium channels (glibenclamide and glipizide) carry a greater MACE risk than low-affinity agents (gliclazide and glimepiride) [36]. In a nationwide study in Denmark, when compared with metformin, gliclazide was associated with similar risks of cardiovascular mortality, all-cause mortality or MACE, while other SUs (glimepiride, glibenclamide, glipizide and tolbutamide) had increased risk

Table 2
Summary of pharmacological treatment recommendations for T2D management from the IDF [6], ADA [30] and ADA/EASD [5].

	2025 IDF Global Clinical Practice Recommendations [6]	ADA Standard of Care in Diabetes 2025 [30]	2022 ADA/EASD Consensus Report [5]
No CV-kidney complications or at low risk	**Newly diagnosed individuals** Metformin (optimal or basic care); combination therapy with two GLDs is an option to overcome therapeutic inertia and improve glycaemic durability (optimal care) *With obesity:* Consider adding GLP-1 RA (optimal care) or SGLT2i (basic care)	Choice of GLD should be informed by weight management considerations, mitigation of MASLD or MASH risk, and achievement and maintenance of glycaemic goals Metformin is commonly used in newly diagnosed individuals and those needing treatment intensification to achieve and/or maintain treatment goals	Metformin or GLDs (including combination therapy) that provide adequate efficacy to achieve and maintain treatment goals GLDs with very high (dulaglutide, semaglutide, tirzepatide, insulin, combination oral therapy, combination injectable therapy) or high (other GLP-1 RAs, metformin, SGLT2i, SU, TZD) glucose-lowering efficacy are recommended *With obesity:* Consider regimen with very high (semaglutide, tirzepatide) or high (dulaglutide, liraglutide) dual glucose-lowering and weight-loss efficacy
	Treatment-experienced individuals *On metformin monotherapy:* Add SGLT2i (optimal care); Add SGLT2i or any available GLD (basic care) *With obesity:* Add GLP-1 RA (optimal care) *On combination therapy:* Add SGLT2i or GLP-1 RA, or another GLD, (including insulin as needed) if already taking SGLT2i or GLP-1 RA (optimal care) Add SGLT2i or any available GLD, including insulin as needed (basic care)	Individuals at low ASCVD risk may benefit from GLP-1 RA to reduce future risk of CV events	
With CV-kidney complications or at high risk	**Newly diagnosed individuals** Metformin plus SGLT2i (individuals with HF) or GLP-1 RA (optimal care) Metformin plus SGLT2i (basic care)	*With ASCVD:* Treatment should include GLDs with demonstrated CV benefits (GLP-1 RA and/or SGLT2i)	*With ASCVD:* GLP-1 RA with proven CVD benefit or SGLT2i with proven CVD benefit
	Treatment-experienced individuals *On metformin monotherapy:* Add SGLT2i or GLP-1 RA (optimal care) Add SGLT2i or any available GLD, including insulin as needed (basic care)	*With HFpEF or HFrEF:* SGLT2i *With symptomatic HFpEF and obesity:* GLP-1 RA *With CKD:* SGLT2i (if eGFR is >20 mL/min/1.73 m^2) or GLP-1 RA	*With HF:* SGLT2i with proven HF benefit *With CKD:* SGLT2i with proven CKD benefit (preferred) or GLP-1 RA with CVD benefit (if SGLT2i not tolerated or contraindicated)
	With obesity: Add GLP-1 RA (optimal care)		
	Individuals on combination therapy: Add SGLT2i or GLP-1 RA, or another GLD (including insulin as needed) if already taking SGLT2i or GLP-1 RA (optimal care) Add SGLT2i or any available GLD, including insulin as needed (basic care)	Individuals achieving glycaemic goals with other GLDs may benefit from switching to these preferred GLDs to reduce risk of ASCVD, HF and/or CKD	

ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drug; 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; IDF, International Diabetes Foundation; MASH, metabolic function-associated steatohepatitis; MASLD, metabolic function-associated steatotic liver disease; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulphonylurea; T2D, type 2 diabetes mellitus; TZD, thiazolidinedione.

[37]. A systematic review and *meta*-analysis of nine RCTs reported similar risks of all-cause mortality amongst individuals with T2D treated with metformin plus SUs versus their counterparts treated with metformin plus SGLT2is [38].

3.2. ADA standards of care in diabetes

Similar to the IDF guidelines, the 2025 ADA guidelines recommend first-line metformin treatment in individuals with T2D (Table 2). In contrast to the IDF guidelines, this ADA recommendation applies mainly to individuals with ASCVD, HF or CKD [30]. In individuals with established ASCVD, HF and/or CKD or high cardiovascular risk, SGLT2is or GLP-1 RAs are prioritised for their organ-protective effects, while recognising that GLP-1 RAs may also reduce the risk of future cardiovascular events in individuals at lower risk for ASCVD [30]. However, it should be noted that the majority of individuals with T2D do not have cardiovascular-kidney complications and, therefore, do not meet the ADA criteria for first-line SGLT2i or GLP-1 RA therapy [39].

The 2025 ADA treatment algorithm advocates for regular assessment of risk factors and a multidisciplinary approach to improve care standards aimed at preventing complications and improving quality of life [40]. In addition to lifestyle modification and self-management, optimal control of blood glucose, blood pressure (BP), lipids and body weight forms the four pillars of T2D management with an emphasis on individualised treatment [30]. In individuals who have not achieved their individualised body weight goals, affordable treatments to promote weight loss should be made available to avoid high out-of-pocket expenses.

The guidelines provide an overview of the efficacy, safety, potential benefits and costs of each GLD class [30]. Metformin and SUs have high glucose-lowering efficacy (reducing HbA1c by 1.0–2.0% [11–22 mmol/mol]), with insulin providing greater HbA1c reductions [41]. These three GLDs, which have been used for decades, are the fundamental tools for achieving glycaemic control. In all CVOTs of SGLT2is and GLP-

1 RAs, the majority of participants were treated with these background GLDs and other organ-protective drugs (i.e. statins and RAASis), with the newer GLDs conferring additional organ-protective effects [29,42–48]. Although rare, SGLT2is may be associated with an increased risk of stress hyperglycaemia and diabetic ketoacidosis (DKA) in people with T2D who have insulin deficiency [30]. Therefore, the guidelines recommend discontinuing SGLT2i therapy prior to scheduled surgery and during prolonged fasting or acute critical illness to mitigate the risk of SGLT2i-related DKA [30]. In these clinical scenarios, short-term glycaemic control should take priority over long-term organ protection.

The guidelines recognise that SUs have high glucose-lowering efficacy and neutral cardiovascular-kidney effects, albeit with increased risks of hypoglycaemia and weight gain [30]. For hypoglycaemia risk, the guidelines differentiate newer generation SUs with low-to-moderate risk (e.g. glimepiride, glipizide) from older generation SUs with moderate-to-high risk (e.g. glibenclamide) [49]. These recommendations were partly based on real-world evidence from the DIA-RAMADAN study [50], where individuals treated with gliclazide modified release had a lower risk of hypoglycaemia during Ramadan than those treated with glibenclamide [50]. Gliclazide is widely used in many countries [51,52], except in the US, where only glipizide, glimepiride and glibenclamide are available [53]; thus, gliclazide is not mentioned in the ADA guidelines. The cardiovascular safety and high glucose-lowering efficacy of SUs (particularly gliclazide) [32–34] support their continued use alongside metformin as the most affordable and available GLDs, especially in LMICs.

3.3. ADA/EASD consensus report

In contrast to the IDF guidelines, the 2022 ADA and European Association for the Study of Diabetes (EASD) consensus report states that GLDs other than metformin may be appropriate as first-line treatment in some individuals with T2D (Table 2) [5]. The ADA/EASD consensus states that SGLT2is and GLP-1 RAs should be considered independent of metformin in individuals with high cardiovascular risk or established CVD, HF or CKD. Metformin is not recommended in individuals with reduced kidney function (estimated glomerular filtration rate [eGFR] $<$ 30 mL/min/1.73 m^2) and the dose should be reduced in those with an eGFR of $<$ 45 mL/min/1.73 m^2 [5].

The consensus report concludes that SUs have high glucose-lowering efficacy, albeit with a less durable effect on glycaemic control and increased risk of hypoglycaemia and weight gain compared with other GLDs [5]. The report also recognises that SUs are not associated with an increased risk of CVD or all-cause mortality, and emphasises weight management as part of a holistic approach to T2D management. It highlights that the CVOTs have informed broader recommendations in individuals with established complications or at high risk of cardiovascular-renal complications [5]. The report also acknowledges that many individuals do not achieve HbA1c, BP and lipid targets, partially because of therapeutic inertia (i.e. failure of healthcare providers to initiate or intensify treatment when indicated [54]). Taking therapeutic inertia and treatment non-adherence into account, the importance of GLD combination therapy is highlighted, including fixed-ratio combinations (FRCs) of GLP-1 RA with basal insulin and fixed-dose combinations (FDCs) of SGLT2i plus SU, which can reduce regimen complexity and treatment burden [5]. The lower dose of each drug in the FRC or FDC also reduces risk of hypoglycaemia and other adverse effects compared with higher doses of separate GLDs [5].

4. Early and intensive glycaemic control

Intensive and early glycaemic control is associated with a reduced risk of non-fatal myocardial infarction (MI), microvascular outcomes (e.g. nephropathy, retinopathy) and MACE, as demonstrated by a systematic review and *meta*-analysis of 11 RCTs [19]. In a regression analysis of GLP-1 RA CVOT data, there was a near-linear relationship between HbA1c reductions and MACE incidence [55]. In the US Diabetes and Aging Study, mean HbA1c during the first year of treatment predicted the 10-year risk of macrovascular and microvascular complications, with prolonged exposure to high HbA1c being associated with an increased risk of complications in a stepwise manner [56]. Elevated HbA1c was also associated with worse microvascular and macrovascular outcomes in the UKPDS and the Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) trial [57,58].

In the UKPDS, intensive glycaemic control with insulin plus SU versus usual care reduced microvascular complications in individuals with newly diagnosed T2D (Fig. 2) [11]. In the 10-year post-trial follow-up analysis, the legacy effect of intensive glycaemic control translated into a reduced risk of macrovascular complications, mainly attributed to a reduction in MI events [10]. At 24 years after completion of UKPDS, these legacy effects were consistent and sustained, with significant reductions in all diabetes-related complications, MI, microvascular disease and all-cause mortality [18]. In a retrospective database analysis, individuals with HbA1c $\geq$ 7.0% ($\geq$53 mmol/mol) who did not receive treatment intensification within 1 year of diagnosis (26% of cohort) had increased risk of cardiovascular events, including MI, stroke and HF, after 5.3 years compared with their counterparts who received treatment intensification within the first year [59].

In ACCORD, ADVANCE and VADT, which enrolled individuals with longer duration of T2D (about 10 years), intensive glycaemic control was associated with a reduced risk of microvascular complications but not cardiovascular events [12–17]. These differences in individuals with longer disease duration emphasise the benefits of early and intensive glycaemic control for long-term organ protection. In a subgroup analysis of ADVANCE, intensive glycaemic control with gliclazide reduced the risk of vascular events and all-cause mortality regardless of age at diagnosis ($\leq$50, $>$50 to $\leq$ 60 or $>$ 60 years) or disease duration ($\leq$5, $>$5 to $\leq$ 10 or $>$ 10 years) [31].

5. Benefits of early multifactorial treatment

The complementary mechanism of actions of different GLD classes contribute to their beneficial effects as part of combination therapy on clinical outcomes [9,60]. CVOTs using SGLT2is [29,42,43] and GLP-1 RAs [44–48] confirmed the organ-protective effects of these agents in individuals with established ASCVD, CKD or multiple risk factors. However, earlier RCTs demonstrated the benefits of intensive glucose-lowering therapy (mainly with metformin, SU, TZD and insulin) versus standard care in individuals with a shorter disease duration and fewer diabetes-related complications [12–17]. These earlier RCTs had considerably longer durations than the CVOTs of SGLT2is or GLP-1 RAs and had outcomes that encompassed macrovascular and microvascular complications. In the more recent CVOTs, which did not comprehensively assess microvascular complications, participants had long-standing T2D with cardiovascular-kidney complications and were receiving multiple GLDs at recruitment, including metformin, SUs, DPP4is and insulin, with fair HbA1c control, along with drugs for control of BP and lipids, notably statins and RAASis (Fig. 3) [29,42–48,61,62]. Given the organ-protective effects of HbA1c reduction [55], the improved cardiovascular outcomes in the CVOT setting were likely due to the combined effects of both background conventional GLDs and newer organ-protective GLDs, emphasising the importance of GLD combination therapy.

In the Steno-2 RCT, intensive multifactorial management of individuals with T2D and microalbuminuria for 8 years provided long-term benefits after 21 years' follow-up, with reduced risks of ASCVD and end-stage kidney disease and increased survival (Fig. 2) [63–66]. The benefits of multifactorial risk factor control in reducing the risk of cardiovascular, end-stage kidney disease and mortality among individuals with newly diagnosed T2D have also been reported in routine clinical practice [67].

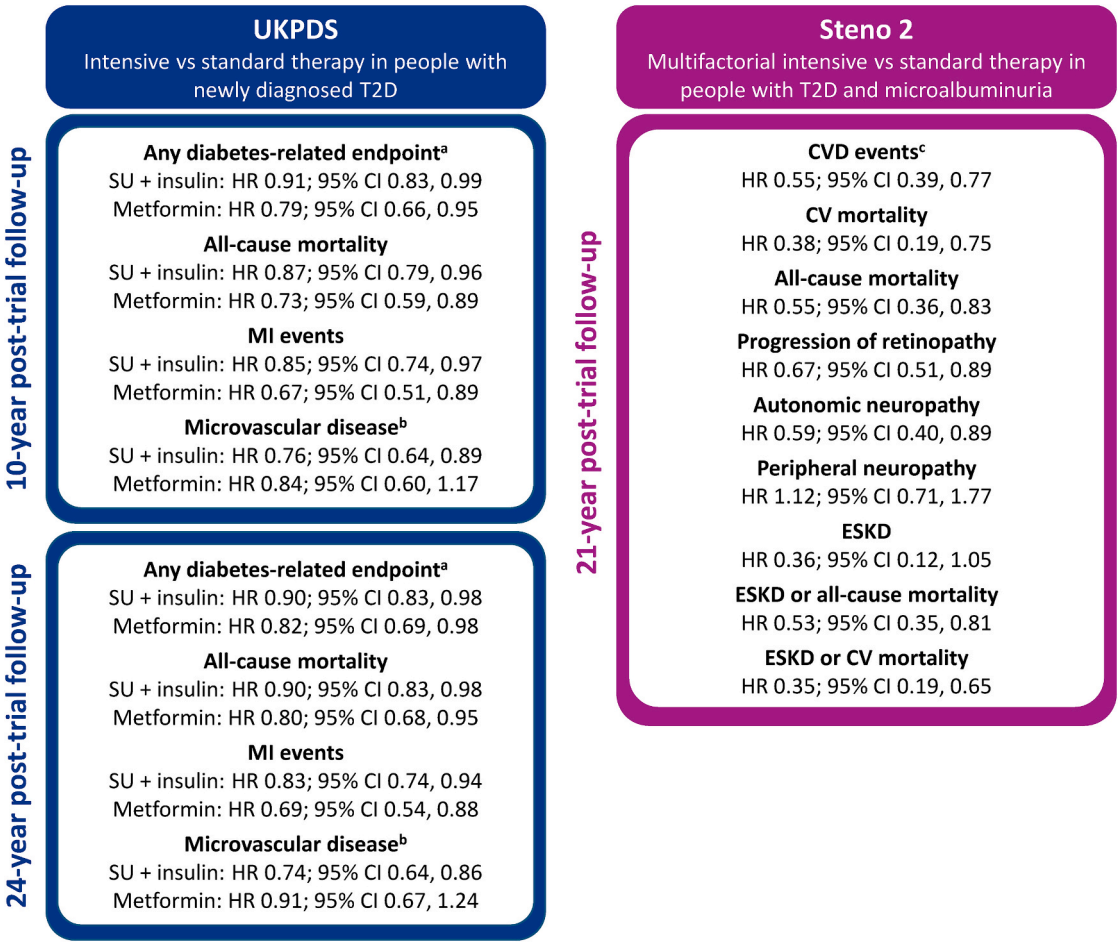

Fig. 2. Key studies showing the legacy effects of intensive versus standard glycaemic control in people with newly diagnosed T2D in the UKPDS [10,18] and the long-term benefits of multifactorial management of people with T2D and microalbuminuria in the Steno 2 study [65,66]. [a]Composite outcome of sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal MI, angina, HF, fatal or non-fatal stroke, renal death, renal failure, death from peripheral vascular disease, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction. [b]Composite outcome of vitreous haemorrhage, retinal photocoagulation, renal death or renal failure. [c]Composite outcome of death from CV causes, MI, stroke, amputation due to ischaemia and cardiac or peripheral vascularisation. CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; SU, sulphonylurea; T2D, type 2 diabetes mellitus; UKPDS, United Kingdom Prospective Diabetes Study.

Despite the confirmed benefits of multifactorial management, low proportions of individuals with T2D in the Indian Council of Medical Research (ICMR)-India Diabetes (INDIAB) study achieved target HbA1c, BP and low-density lipoprotein-cholesterol (LDL-C) – often known as the ABC goals – thereby contributing to their high cardiovascular risk [68]. In this national multi-centre survey, in which ABC goals were defined as HbA1c < 7.0% (<53 mmol/mol), BP < 140/90 mmHg and LDL-C < 2.6 mmol/L, 36.3%, 48.8% and 41.5% of individuals achieved respective treatment goals, while only 7.7% of individuals with T2D achieved all three goals [68].

In the ICMR-INDIAB study, 101 million individuals were estimated to have diabetes in India in 2021, with the majority having T2D [69]. In LMICs with large diabetes populations, such as India, medication affordability is a key enabler to achieving ABC goals. Using India as an example, use of newer GLDs like GLP-1 RAs requires out-of-pocket expenses as high as 70% [70]. Given their proven therapeutic and cost effectiveness, SUs and metformin remain the cornerstone of T2D treatment in most LMICs. With the recent inclusion of SGLT2is (empagliflozin, canagliflozin, dapagliflozin) and GLP-1 RAs (semaglutide, dulaglutide, liraglutide, tirzepatide) in the 2025 WHO's essential drug list [35], payors and providers must ensure that these organ-protective GLDs are made available to individuals in LMICs and under-served individuals in high-income areas.

6. Therapeutic inertia

Despite the benefits of early glycaemic control, treatment intensification is often delayed in individuals with T2D [71,72]. In the global DISCOVER study, 36% of individuals from South-East Asia and 33.9% from Eastern Mediterranean region had HbA1c ≥ 9.0% (≥75 mmol/mol) before initiation of their second GLD [72]. Therapeutic inertia in T2D management has a 'dysglycaemic legacy' effect, with long-term hyperglycaemia driving an increased risk of cardiovascular-kidney complications. In the US Diabetes and Aging cohort, delayed treatment intensification by 2–7 years in individuals with HbA1c ≥ 8.0% (≥64 mmol/mol) was associated with increased risks of microvascular and macrovascular events and mortality compared with individuals with HbA1c < 6.5% (<48 mmol/mol) during the same periods [56].

Taken together, early, intensified and multifactorial management of T2D from the time of diagnosis is needed to optimise HbA1c, BP and LDL-C goals and provide long-lasting benefits. This includes the appropriate use of conventional GLDs (e.g. metformin, SUs, insulin), newer organ-protective GLDs (i.e. SGLT2is, GLP-1 RAs) and other organ-protective treatments (e.g. statins, RAASis), as well as self-management education and an effective support programme [9,73,74].

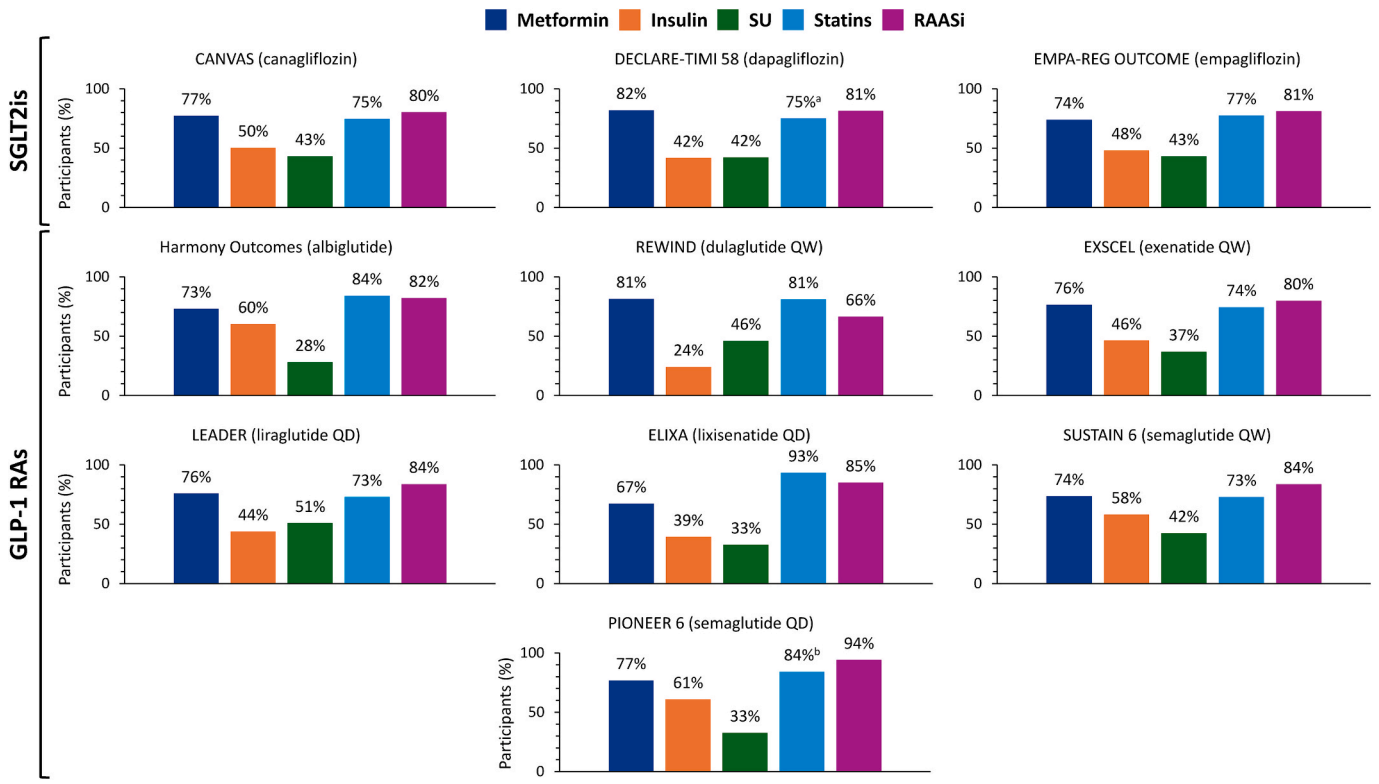

Fig. 3. Proportion of participants receiving baseline GLD and BP- and lipid-lowering medications in CVOTs of SGLT2is [29,42,43] and GLP-1 RAs [44–48,61,62]. [a]Statins or ezetimibe. [b]Any lipid-lowering therapy. BP, blood pressure; CVOT, cardiovascular outcomes trial; GLD, glucose-lowering drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; QD, once daily; QW, once weekly; RAASi, renin–angiotensin–aldosterone system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulphonylurea.

7. Strategies to optimise adherence and reduce therapeutic inertia

In the IDF guidelines, the recommended ABC goals are more stringent than those used in the ICMR-INDIAB study: HbA1c < 7.0% (<53 mmol/mol), BP < 130/80 mmHg and LDL-C < 2.6 mmol/L (for low-to-moderate CVD risk), <1.8 mmol/L (for high CVD risk) and < 1.4 mmol/L (for very high CVD risk) [6]. To achieve each of these goals, two or more medications are often needed. This increased pill burden can lead to poor treatment adherence [75]. In the International Diabetes Management Practices Study, one in three individuals with T2D reported non-adherence to treatment [76]. Multiple medications and long duration of treatment were associated with low scores on the ACCEPT© questionnaire (indicating lower overall acceptance) [76]. Simplifying treatment regimens, including the use of single-pill FDCs or single-injection FRCs, may help overcome therapeutic inertia to escalate treatment, reduce medication burden and increase treatment adherence. In a systematic review of polypharmacy for chronic medical conditions, FDC use was associated with 30% increased adherence compared with equivalent doses of individual drugs [77]. In the PolyIran pragmatic cluster-randomised study in almost 7000 individuals (15% with pre-existing diabetes, 11% with CVD and 49% with hypertension), treatment with a four-component combination pill consisting of aspirin, a RAASi (enalapril or valsartan), diuretic (hydrochlorothiazide) and statin (atorvastatin) reduced the incidence of both primary and secondary MACE compared with usual care [78].

8. Conclusions

The ADA and ADA/EASD guidelines for T2D management focus on the use of organ-protective GLDs in individuals with T2D and established ASCVD or CKD. On the other hand, the 2025 IDF guidelines emphasise a global perspective that recognises that newer organ-protective GLDs, particularly GLP-1 RAs, are either not available or not affordable in many LMICs. Depending on setting and resources, the 2025 IDF guidelines recommend either 'optimal' or 'basic' care in people with T2D, both of which represent transitional stages of treatment. The IDF guidelines highlight the importance of early intensive multifactorial intervention, including control of HbA1c, BP and LDL-C, for long-term cardiovascular-kidney protection. Treatment regimens should be modified to meet to the individual patient's needs, with dual emphasis on glycaemic control and organ protection, while taking affordability into consideration. Early and intensive glycaemic control using combination rather than sequential GLD therapy is particularly important in individuals with short disease duration and few complications. Early initiation of FDCs or FRCs may reduce therapeutic inertia, increase glycaemic durability, delay the onset of complications and avoid the need for future treatment escalation. Although early use of SGLT2is and GLP-1 RAs is supported by RCTs, there is insufficient evidence to recommend their use as first-line monotherapy in low-risk individuals with T2D, for whom metformin and SUs (particularly gliclazide and glimepiride) remain an important GLD option, especially in LMICs.

CRediT authorship contribution statement

Juliana C.N. Chan: Writing – review & editing, Writing – original draft, Resources, Investigation, Conceptualization. **Chaicharn Deerochanawong:** Writing – review & editing, Writing – original draft, Resources, Investigation, Conceptualization. **Kamlesh Khunti:** Writing – review & editing, Writing – original draft, Resources, Investigation, Conceptualization. **Mohamed Hassanein:** Writing – review & editing, Writing – original draft, Resources, Investigation, Conceptualization. **Viswanathan Mohan:** Writing – review & editing, Writing – original

draft, Resources, Investigation, Conceptualization.

Funding

The expert meeting, editorial assistance for the preparation of this article, and the article processing fee for publication were funded by Servier.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Juliana C. N. Chan has received consultancy or lecture fees and research support from Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Celltrion, Eli Lilly, Merck, MSD, Novartis, Pfizer, Powder Pharmaceuticals, Sanofi, Servier, Viatris and ZP Therapeutics; is the Chief Executive Officer (pro-bono) for the Asia Diabetes Foundation; and is the Founding Director of GemVCare. Chaicharn Deerochanawong has no conflicts of interest to declare. Kamlesh Khunti has acted as a consultant for Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Embecta, Eli Lilly, Nestle Health Science, Novo Nordisk, Pfizer, Roche, Sanofi and Servier; has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Merck, Novo Nordisk, Oramed Pharmaceuticals, Roche, Sanofi and Servier; and has participated in speaker's bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Roche, Sanofi and Servier. Kamlesh Khunti is also supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands, the NIHR Global Research Centre for Multiple Long Term Conditions, the NIHR Cross NIHR Collaboration for Multiple Long Term Conditions, the NIHR Leicester Biomedical Research Centre and the British Heart Foundation Centre of Excellence. Mohamed Hassanein had acted as a speaker or attended advisory boards for Novo Nordisk, MSD, Lilly, Sanofi, Boehringer Ingelheim, Servier, Medtronic and Abbott. Viswanathan Mohan has received honoraria or research grants from Abbott, AstraZeneca, Boehringer Ingelheim, Dr. Reddy's Laboratories, Eli Lilly, LifeScan J & J, MSD, Novartis, Novo Nordisk, Roche, Sanofi Aventis, Servier and USV.

Acknowledgments

We would like to thank Sarah Greig, PhD, CMPP, of Springer Health+, who provided assistance in preparing the first and subsequent drafts of the manuscript and with post-submission revisions. This medical writing assistance was funded by Servier.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

[1] Rawshani A, Rawshani A, Franzen S, Eliasson B, Svensson AM, Miftaraj M, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376:1407–18. https://doi.org/10.1056/NEJMoa1608664.
[2] International Diabetes Federation. Diabetes Atlas, https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/; 2025 [accessed 25 June 2025].
[3] Arnold SV, Khunti K, Tang F, Chen H, Cid-Ruzafa J, Cooper A, et al. Incidence rates and predictors of microvascular and macrovascular complications in patients with type 2 diabetes: results from the longitudinal global discover study. Am Heart J 2022;243:232–9. https://doi.org/10.1016/j.ahj.2021.10.181.
[4] American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2026. Diabetes Care. 2026;49:S61-S88. DOI: 10.2337/dc26-S004.
[5] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. 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). Diabetologia 2022;65:1925–66. https://doi.org/10.1007/s00125-022-05787-2.
[6] International Diabetes Federation. Global clinical practice recommendations, https://idf.org/what-we-do/education/idf-clinical-practice-recommendations-for-type-2-diabetes-2025/; 2025 [accessed 22 April 2025].
[7] Davies MJ, Drexel H, Jornayvaz FR, Pataky Z, Seferovic PM, Wanner C. Cardiovascular outcomes trials: a paradigm shift in the current management of type 2 diabetes. Cardiovasc Diabetol 2022;21:144. https://doi.org/10.1186/s12933-022-01575-9.
[8] Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. Circulation 2023;148:1606–35. https://doi.org/10.1161/CIR.0000000000001184.
[9] Khunti K, Zaccardi F, Amod A, Aroda VR, Aschner P, Colagiuri S, et al. Glycaemic control is still central in the hierarchy of priorities in type 2 diabetes management. Diabetologia 2025;68:17–28. https://doi.org/10.1007/s00125-024-06254-w.
[10] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89. https://doi.org/10.1056/NEJMoa0806470.
[11] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-53.
[12] ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39:701–8. https://doi.org/10.2337/dc15-2283.
[13] ACCORD Study Group, Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59. https://doi.org/10.1056/NEJMoa0802743.
[14] ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72. https://doi.org/10.1056/NEJMoa0802987.
[15] Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–406. https://doi.org/10.1056/NEJMoa1407963.
[16] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39. https://doi.org/10.1056/NEJMoa0808431.
[17] Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197–206. https://doi.org/10.1056/NEJMoa1414266.
[18] Adler AI, Coleman RL, Leal J, Whiteley WN, Clarke P, Holman RR. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). Lancet 2024;404:145–55. https://doi.org/10.1016/S0140-6736(24)00537-3.
[19] Kunutsor SK, Balasubramanian VG, Zaccardi F, Gillies CL, Aroda VR, Seidu S, et al. Glycaemic control and macrovascular and microvascular outcomes: a systematic review and meta-analysis of trials investigating intensive glucose-lowering strategies in people with type 2 diabetes. Diabetes Obes Metab 2024;26:2069–81. https://doi.org/10.1111/dom.15511.
[20] Gao Y, Peterson E, Pagidipati N. Barriers to prescribing glucose-lowering therapies with cardiometabolic benefits. Am Heart J 2020;224:47–53. https://doi.org/10.1016/j.ahj.2020.03.017.
[21] Wittbrodt E, Chamberlain D, Arnold SV, Tang F, Kosiborod M. Eligibility of patients with type 2 diabetes for sodium-glucose co-transporter-2 inhibitor cardiovascular outcomes trials: an assessment using the Diabetes Collaborative Registry. Diabetes Obes Metab 2019;21:1985–9. https://doi.org/10.1111/dom.13738.
[22] Agarwal A, Mustafa R, Manja V, Agoritsas T, Macdonald H, Li S, et al. Cardiovascular, kidney related, and weight loss effects of therapeutics for type 2 diabetes: a living clinical practice guideline. BMJ 2025;390:e082071. https://doi.org/10.1136/bmj-2024-082071.
[23] Li S, Vandvik PO, Lytvyn L, Guyatt GH, Palmer SC, Rodriguez-Gutierrez R, et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. BMJ 2021;373:n1091. https://doi.org/10.1136/bmj.n1091.
[24] Chung WK, Erion K, Florez JC, Hattersley AT, Hivert MF, Lee CG, et al. Precision medicine in diabetes: a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:1617–35. https://doi.org/10.2337/dci20-0022.
[25] Ke C, Narayan KMV, Chan JCN, Jha P, Shah BR. Pathophysiology, phenotypes and management of type 2 diabetes mellitus in Indian and Chinese populations. Nat Rev Endocrinol 2022;18:413–32. https://doi.org/10.1038/s41574-022-00669-4.
[26] Sundström J, Kristófi R, Östlund O, Bennet L, Eliasson B, Jansson S, et al. A registry-based randomised trial comparing an SGLT2 inhibitor and metformin as standard treatment of early stage type 2 diabetes (SMARTEST): rationale, design and protocol. J Diabetes Complications 2021;35:107996. https://doi.org/10.1016/j.jdiacomp.2021.107996.
[27] Eriksson JW, Fanni G, Lundqvist MH, Jansson S, Rådholm K, Sofizadeh S, et al. SGLT2 inhibitor or metformin as standard treatment in early-stage type 2 diabetes? Baseline data in SMARTEST, a novel, decentralised, register-based randomised trial on prevention of diabetic complications. Diabetes Obes Metab 2026;28:1327–38. https://doi.org/10.1111/dom.70320.
[28] Flood D, Seiglie JA, Dunn M, Tschida S, Theilmann M, Marcus ME, et al. The state of diabetes treatment coverage in 55 low-income and middle-income countries: a cross-sectional study of nationally representative, individual-level data in 680 102

adults. Lancet Healthy Longev 2021;2:e340–51. https://doi.org/10.1016/s2666-7568(21)00089-1.
[29] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57. https://doi.org/10.1056/NEJMoa1812389.
[30] American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2026. Diabetes Care. 2026;49:S183-S215. DOI: 10.2337/dc26-S009.
[31] Ohkuma T, Harris K, Woodward M, Hamet P, Harrap S, Mancia G, et al. Intensive glucose lowering and its effects on vascular events and death according to age at diagnosis and duration of diabetes: the ADVANCE trial. Diabetes Care 2025;48:279–84. https://doi.org/10.2337/dc24-1516.
[32] Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. J Am Med Assoc 2019;322:1155–66. https://doi.org/10.1001/jama.2019.13772.
[33] Wang H, Cordiner RLM, Huang Y, Donnelly L, Hapca S, Collier A, et al. Cardiovascular safety in type 2 diabetes with sulfonylureas as second-line drugs: a nationwide population-based comparative safety study. Diabetes Care 2023;46:967–77. https://doi.org/10.2337/dc22-1238.
[34] Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. Lancet Diabetes Endocrinol 2015;3:43–51. https://doi.org/10.1016/S2213-8587(14)70213-X.
[35] World Health Organization. The selection and use of essential medicines, 2025: WHO Model List of Essential Medicines, 24th list. Geneva: World Health Organization; 2025. DOI: 10.2471/B09474.
[36] Wang MT, Huang YL, Lai JH, Lee CH, Wang PC, Pan HY, et al. Association between specificity of sulfonylureas to cardiac mitochondrial KATP channels and the risk of major adverse cardiovascular events in type 2 diabetes. Diabetes Care 2022;45:1276–87. https://doi.org/10.2337/dc21-1779.
[37] Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J 2011;32:1900–8. https://doi.org/10.1093/eurheartj/ehr077.
[38] Gebrie D, Getnet D, Manyazewal T. Cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes: systematic review and meta-analysis of randomized controlled trials. Sci Rep 2021;11:137. https://doi.org/10.1038/s41598-020-80603-8.
[39] Colling C, Atlas SJ, Wexler DJ. Application of 2021 American Diabetes Association glycemic treatment clinical practice recommendations in primary care. Diabetes Care 2021;44:1443–6. https://doi.org/10.2337/dc21-0013.
[40] American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes—2026. Diabetes Care. 2026;49:S216-S45. DOI: 10.2337/dc26-S010.
[41] Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. N Engl J Med 2002;347:1342–9. https://doi.org/10.1056/NEJMcp021106.
[42] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57. https://doi.org/10.1056/NEJMoa1611925.
[43] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28. https://doi.org/10.1056/NEJMoa1504720.
[44] Hernandez AF, Green JB, Janmohamed S, D'Agostino Sr RB, Granger CB, Jones NP, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 2018;392:1519–29. https://doi.org/10.1016/S0140-6736(18)32261-X.
[45] Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2017;377:1228–39. https://doi.org/10.1056/NEJMoa1612917.
[46] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44. https://doi.org/10.1056/NEJMoa1607141.
[47] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22. https://doi.org/10.1056/NEJMoa1603827.
[48] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247–57. https://doi.org/10.1056/NEJMoa1509225.
[49] American Diabetes Association Professional Practice Committee. 5. Facilitating positive health behaviors and well-being to improve health outcomes: Standards of Care in Diabetes—2026. Diabetes Care. 2026;49:S89-S131. DOI: 10.2337/dc26-S005.
[50] Hassanein M, Al Sifri S, Shaikh S, Abbas Raza S, Akram J, Pranoto A, et al. A real-world study in patients with type 2 diabetes mellitus treated with gliclazide modified-release during fasting: DIA-RAMADAN. Diabetes Res Clin Pract 2020;163:108154. https://doi.org/10.1016/j.diabres.2020.108154.
[51] Lim LL, Shl E, Pheng Chan S, Ji L, Lim S, Sirinvaravong S, et al. Real-world evidence on health-related quality of life in patients with type 2 diabetes mellitus using sulphonylureas: an analysis of the Joint Asia Diabetes Evaluation (JADE) Register. Diabetes Res Clin Pract 2023;203:110855. https://doi.org/10.1016/j.diabres.2023.110855.
[52] Lim LL, Lau ESH, Cheung JTK, Chan SP, Ji L, Lim S, et al. Real-world usage of sulphonylureas in Asian patients with type 2 diabetes using the Joint Asia Diabetes Evaluation (JADE) register. Diabetes Obes Metab 2023;25:208–21. https://doi.org/10.1111/dom.14865.
[53] Shin JI, Echouffo-Tcheugui JB, Fang M, Grams ME, Selvin E. Trends in use of sulfonylurea types among US adults with diabetes: NHANES 1999-2020. J Gen Intern Med 2023;38:2009–10. https://doi.org/10.1007/s11606-023-08067-w.
[54] Khunti S, Khunti K, Seidu S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. Ther Adv Endocrinol Metab 2019;10:2042018819844694. https://doi.org/10.1177/2042018819844694.
[55] Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab 2021;46:101102. https://doi.org/10.1016/j.molmet.2020.101102.
[56] Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging study). Diabetes Care 2019;42:416–26. https://doi.org/10.2337/dc17-1144.
[57] Meneghini LF, Mauricio D, Orsi E, Lalic NM, Cali AMG, Westerbacka J, et al. The Diabetes Unmet need with Basal Insulin Evaluation (DUNE) study in type 2 diabetes: achieving HbA1c targets with basal insulin in a real-world setting. Diabetes Obes Metab 2019;21:1429–36. https://doi.org/10.1111/dom.13673.
[58] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12. https://doi.org/10.1136/bmj.321.7258.405.
[59] Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100. https://doi.org/10.1186/s12933-015-0260-x.
[60] Chan SP, Lim LL, Chan JCN, Matthews DR. Adjusting the use of glucose-lowering agents in the real-world clinical management of people with type 2 diabetes: a narrative review. Diabetes Ther 2023;14:823–38. https://doi.org/10.1007/s13300-023-01386-5.
[61] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–30. https://doi.org/10.1016/S0140-6736(19)31149-3.
[62] Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381:841–51. https://doi.org/10.1056/NEJMoa1901118.
[63] Gæde P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999;353:617–22. https://doi.org/10.1016/S0140-6736(98)07368-1.
[64] Gæde P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93. https://doi.org/10.1056/NEJMoa021778.
[65] Gæde P, Oellgaard J, Carstensen B, Rossing P, Lund-Andersen H, Parving HH, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia 2016;59:2298–307. https://doi.org/10.1007/s00125-016-4065-6.
[66] Oellgaard J, Gæde P, Rossing P, Persson F, Parving HH, Pedersen O. Intensified multifactorial intervention in type 2 diabetics with microalbuminuria leads to long-term renal benefits. Kidney Int 2017;91:982–8. https://doi.org/10.1016/j.kint.2016.11.023.
[67] Usman M, Khunti K, Davies MJ, Gillies CL. Association and relative importance of multiple risk factor control on cardiovascular disease, end-stage renal disease and mortality in people with type 2 diabetes: a population-based retrospective cohort study. Prim Care Diabetes 2021;15:218–26. https://doi.org/10.1016/j.pcd.2020.08.008.
[68] Anjana RM, Unnikrishnan R, Deepa M, Venkatesan U, Pradeepa R, Joshi S, et al. Achievement of guideline recommended diabetes treatment targets and health habits in people with self-reported diabetes in India (ICMR-INDIAB-13): a national cross-sectional study. Lancet Diabetes Endocrinol 2022;10:430–41. https://doi.org/10.1016/S2213-8587(22)00072-9.
[69] Anjana RM, Unnikrishnan R, Deepa M, Pradeepa R, Tandon N, Das AK, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). Lancet Diabetes Endocrinol 2023;11:474–89. https://doi.org/10.1016/S2213-8587(23)00119-5.
[70] Sofi SA, Yasmin E. Out-of-pocket health expenditure and associated factors: insights from National Health Accounts (NHA) using panel data analysis. Inquiry 2024;61:469580241309903. https://doi.org/10.1177/00469580241309903.
[71] Khunti K, Gomes MB, Pocock S, Shestakova MV, Pintat S, Fenici P, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. Diabetes Obes Metab 2018;20:427–37. https://doi.org/10.1111/dom.13088.
[72] Khunti K, Chen H, Cid-Ruzafa J, Fenici P, Gomes MB, Hammar N, et al. Glycaemic control in patients with type 2 diabetes initiating second-line therapy: results from the global DISCOVER study programme. Diabetes Obes Metab 2020;22:66–78. https://doi.org/10.1111/dom.13866.
[73] Mohan V, Mohan Anjana R, Unnikrishnan R, Gupta PK, Routary P, Jebarani S, et al. Clinical profile of elderly patients (over 90 years) with type 2 diabetes seen at a

diabetes center in South India. Diabetes Technol Ther 2020;22:79–84. https://doi.org/10.1089/dia.2019.0219.
[74] Mohan V, Shanthi Rani CS, Amutha A, Dhulipala S, Anjana RM, Parathasarathy B, et al. Clinical profile of long-term survivors and nonsurvivors with type 2 diabetes. Diabetes Care 2013;36:2190–7. https://doi.org/10.2337/dc12-1193.
[75] Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence 2016;10:1299–307. https://doi.org/10.2147/PPA.S106821.
[76] Chan JC, Mbanya JC, Chantelot JM, Shestakova M, Ramachandran A, Ilkova H, et al. Patient-reported outcomes and treatment adherence in type 2 diabetes using natural language processing: wave 8 of the observational international diabetes management practices study. J Diabetes Investig 2024;15:1306–16. https://doi.org/10.1111/jdi.14228.
[77] Wei Q, Zhou J, Li H, Wang L, Wu Y, Ma A, et al. Medication adherence with fixed-dose versus free-equivalent combination therapies: systematic review and meta-analysis. Front Pharmacol 2023;14:1156081. https://doi.org/10.3389/fphar.2023.1156081.
[78] Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. Lancet 2019;394:672–83. https://doi.org/10.1016/S0140-6736(19)31791-X.