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2022 update to the position statement by Primary Care Diabetes Europe: a disease state approach to the pharmacological management of type 2 diabetes in primary care

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ABSTRACT

Type 2 diabetes and its associated comorbidities are growing more prevalent, and the complexity of optimising glycaemic control is increasing, especially on the frontlines of patient care. In many countries, most patients with type 2 diabetes are managed in a primary care setting. However, primary healthcare professionals face the challenge of the growing plethora of available treatment options for managing hyperglycaemia, leading to difficultly in making treatment decisions and contributing to treatment and therapeutic inertia. This position statement offers a simple and patient-centred clinical decision-making model with practical treatment recommendations that can be widely implemented by primary care clinicians worldwide through shared-decision conversations with their patients. It highlights the importance of managing cardiovascular disease and elevated cardiovascular risk in people with type 2 diabetes and aims to provide innovative risk stratification and treatment strategies that connect patients with the most effective care.

1. Statement of intent

New and emerging medical therapies and evidence have changed the landscape for managing people with type 2 diabetes (T2D) with established cardiovascular disease (CVD) and those with cardiovascular risk factors. Previously, guidelines gauged good diabetes care primarily based on glycated haemoglobin (HbA_{1c}) targets [1], but recent updates have represented a major shift, now recommending a multimorbidity risk management approach, mainly based on cardiovascular outcome trials (CVOTs). Effective glycaemic control also remains an important consideration for prevention or improvement of microvascular disease. The reality of primary care necessitates an increasingly holistic and integrated care approach for optimal patient management [2,3].

This position statement, written by primary care practitioners (PCPs) and for PCPs, supports a comprehensive disease state approach to clinical decision making in management of patients with T2D. It is intended to provide a simple and effective guide to evaluate cardiovascular risk in people with T2D managed in primary care, and clear and practical treatment recommendations that can be useful for healthcare professionals (HCPs) globally who manage people with diabetes in a primary care setting. The role of primary care professionals as frontline clinicians in chronic disease management varies worldwide. While every

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country will have its own treatment realities, this position statement aims to provide a critical interpretation of the best available evidence and a unique tool to facilitate its application in primary care clinical decision making. The guiding scientific principles will be applied differently, contingent on treatment access and the financial or economic limitations of patients and their country-specific healthcare systems [4,5].

2. Introduction and rationale

The severe burden of T2D is recognised globally [6], accounting for approximately 90% of the 537 million estimated diabetes cases worldwide [5]. Diabetes can be successfully managed, and its associated complications prevented, especially if detected and treated early [7]. Understanding the complexity of the disease and the pharmacological options is critical for ensuring optimal patient care and improving outcomes.

When not treated in a timely and effective manner, poorly managed T2D is associated with life-threatening complications, including chronic kidney disease (CKD), amputations, blindness and CVD [8,9]. The presence of multimorbidity is the reality for the vast majority of patients with T2D. CVD affects about 30% of all people with T2D [10] and is a major cause of morbidity and mortality [5]. Thus, a comprehensive diabetes management plan for both the primary and secondary prevention of CVD is important for educating patients to make informed decisions that will help them succeed in reaching their glycaemic target goals and prevent the number and complexity of serious complications [11–13].

As experts in 'whole-person medicine', primary care physicians are tasked with using their generalist expertise to work with their patients to develop a comprehensive treatment plan that addresses all of their health needs and goals. Indeed, an evidence-based generalist approach has been suggested as the way forward to address the complex challenges of multimorbidity and avoid the pitfalls of treating each disease state in isolation [14]. Access to patient-centred care can significantly improve outcomes for people with T2D, and this process begins at the level of primary care. The majority of routine T2D management occurs in primary care [15], as part of the chronic care model which focuses on an integrated multidisciplinary team approach involving specialists, dieticians, nurses and other allied HCPs [2,16,17]. While nurses play a central role in primary care, their degree of professional involvement and utilisation can vary widely across different healthcare systems [18,19]. Nonetheless, patients continue to benefit from comprehensive care, as family physicians and general practitioners are able to provide timely and informed treatment recommendations based on their clinical expertise in both chronic and acute condition management and an effective patient–physician relationship enabled by continuity of care [20]. Primary care physicians are uniquely placed to adopt shared decision making models of care, where HCPs and patients co-develop treatment goals through dialogue and with reference to the benefits and risks of different treatment options [11–13,16]. These conversations should also address treatment access, drug cost, adverse events, reimbursement options and local prescribing guidelines.

In spite of this, an increasing number of HCPs struggle with therapeutic inertia when treating diabetes [21–23]. Moreover, there is room for improvement in the control of risk factors in people with T2D worldwide [24,25]. The clinical decision process in primary care is exceedingly complex, and some PCPs may struggle to maintain up-to-date knowledge in a changing scientific landscape and with limited resources available to care for their patients. Research identifies a lack of adherence to treatment guidelines among these challenges, resulting in delayed or inappropriate therapy advancement [26] and failure to meet guideline-recommended targets [27]. Patients often lack clear and personalised healthcare agendas because of clinicians' concerns related to medication issues, the complexity of creating tailored treatment plans for patients with multimorbidity, and in some instances, budget constraints. Patients also struggle with adherence to medication regimens, particularly when treated with multiple agents [28]. Other issues, such as social determinants of health, remain significant barriers to treatment improvement and access [29]. Despite these challenges, high-quality diabetes care has been shown to be achievable in the primary care setting [30,31]. As such, training in optimal use of available therapies and primary care-specific treatment guidelines are necessary to overcome therapeutic inertia, improve T2D control and prevent complications.

The paucity of randomised controlled trials (RCTs) carried out in primary care populations has served as a potential barrier for the development of treatment guidelines and tools specific for primary care [32]. Even though there has been an increase in the proportion of diabetes research outputs from primary care in recent years, this still lags significantly behind the total research output in diabetes (0.5% in 1996 and 2.2% in 2016) [33].

Moreover, the full patient population treated in primary care often differs widely from those who meet the inclusion criteria of clinical trials, with the relevant primary care population typically being older and displaying greater multimorbidity than patients included in RCTs [34–37], making it challenging to apply these data to everyday practice. Thus, more research is needed to strengthen the capacity of primary care teams to overcome the diabetes epidemic.

2.1. Purpose of position statement

A tremendous volume of high-quality, evidence-informed treatment guidelines for the management of T2D exist and have been widely distributed. While these guidelines have had a profound influence in promulgating clinical practice decisions, they may be too detailed and exhaustive for primary care clinicians. Recent consensus guidelines with complex treatment algorithms for people with T2D and established or risk of CVD have shown greater focus towards a target audience of secondary care specialists, rather than frontline clinicians [11–13,38,39]. In addition, most guidelines lack specific recommendations for patient referral to secondary care [40]. Significant strides have been made in some countries to include the primary care perspective in guideline development, and this position statement aims to complement these efforts and to provide useful guidance for regions where primary care guideline input is lacking.

This position statement aims to provide a simple and pragmatic tool for primary care clinicians and other HCPs worldwide for the pharmacological management of people with T2D and other comorbidities in their role as first point of contact in healthcare. This document will also include a selection of some useful online resources on how to manage T2D in the virtual consultation setting in response to the COVID-19 pandemic impact on the delivery of care. This patient-centred clinical decision-making approach is unique from most of the existing national and international guidelines. It offers a novel risk stratification approach and practical recommendations that can be widely implemented through various primary care systems to help link patients with the appropriate care and prevent diabetes-associated complications. It is not intended to supplant well-established national and international guidelines, but rather to provide additional direction and focus to reflect primary care in high-risk patients with T2D. In addition, this consensus paper draws increasing attention to heart failure and cardiorenal syndrome as serious comorbidities associated with T2D.

Box 1 summarises suggestions on how primary care physicians can use this position statement to drive shared decision-making conversations with their patients. Box 2 introduces new, evidence-based criteria for cardiovascular risk stratification of patients with T2D in primary care. Throughout the paper, the key recommendations are collected in callout boxes for easy reference.

Box 1
How to use this position statement.

This position statement summarises the current evidence for glycaemic efficacy, cardiovascular and renal risk, and side effects for a wide variety of therapies for T2D.

Box 2 suggests a simple and pragmatic cardiovascular risk assessment to help inform patient-centred treatment decisions.

Boxes 3–8Box 3 summarise the treatment recommendations by cardiovascular/renal disease or risk factor.

Table 1 summarises the prescribing tips and side effects related to each drug class discussed.

Box 2
Cardiovascular risk stratification in patients with T2D

Patients with T2D are considered to be at *very high cardiovascular risk* if they have any of the following:

1 History of CVD (A)
2 Multiple uncontrolled CVD risk factors, including hypertension, hyperlipidaemia, obesity, smoking and/or physical inactivity (A)
3 Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (B)
4 Albuminuria (B)
5 Age at diagnosis <40 years (C)

All other patients with T2D, including patients ≥65 years, are considered to be at *high cardiovascular risk*

Letters (A–C) denote level of evidence based on the American Diabetes Association grading system: A, clear evidence from well-conducted, generalisable RCTs, that are adequately powered, including 1) evidence from a well-conducted multicentre trial or meta-analysis that incorporated quality ratings in the analysis, 2) compelling nonexperimental evidence, 3) supportive evidence from well-conducted RCTs that are adequately powered; B, supportive evidence from a well-conducted cohort study or case-control study; C, supportive evidence from poorly controlled or uncontrolled studies, or conflicting evidence with the weight of evidence supporting the recommendation; E, expert opinion.

3. Methods

This position statement is authored by a group of PCPs convened by Primary Care Diabetes Europe. A comprehensive review of international diabetes guidelines was conducted at a roundtable consensus conference in February 2019, following which the evidence was updated in 2021. The overall author group consisted of 9 primary care clinicians and 1 nurse with expertise in diabetes representing the European and North American regions. Facilitated by an independent moderator, consensus was reached between all members of the author group on the focus of the position statement and its general framework by using a nominal group technique [41]. Using a Likert scale (of ‘strongly disagree’, ‘disagree’, ‘agree’, and ‘strongly agree’), a consensus was achieved when agreement exceeded 90% of the votes.

To assess the currently available research on people with diabetes in primary care, a PubMed literature search was conducted in advance of the consensus conference on epidemiological studies carried out in primary care populations and with the involvement of primary care clinicians within the last 5 years. These results were shared at the consensus conference, followed by a series of presentations organised by drug family [42]. Each individual presentation replicated a common format, from discussing the different compound options available within each family, to a detailed review of current evidence supporting the use of each compound/drug family in the primary and secondary prevention of CVD in patients with T2D. These presentations helped to lay the foundational knowledge for further discussion on the gaps in existing guidelines and the need for specific treatment recommendations for primary care clinicians.

3.1. Synthesis of the position statement

To assess the most recent data on optimal treatment of T2D, a detailed and focused literature review (Medline, Web of Science, Google Scholar, and Ebsco CINAHL. EMBASE was not included in this search) was undertaken to identify English language articles published since 2015. Search terms included, but were not limited to, ‘type 2 diabetes’, ‘cardiovascular disease’, ‘global health’, ‘prevalence’, ‘primary care’, ‘therapeutic adherence’ and ‘therapeutic inertia’. Given the breadth of this consensus statement, review articles were also included. Recommendations are based on rigorous and careful review of the evidence regarding the efficacy on clinically important outcomes and adverse effects of available medications. Additional landmark studies and publications were suggested by the authors. The authors discussed the identified literature and assessed its relevance using the consensus approach outlined above.

This consensus statement was drafted with the support of a writing group, followed by cycles of review and revision of the manuscript. The focus of the position statement and section headings were further refined through various rounds of correspondence until consensus was reached between all members of the author group. A draft was reviewed at a second author group meeting in September 2019 to discuss and collect additional feedback. Review of the updated draft was then invited by a diabetologist and a primary care physician external to the consensus statement process and their comments considered by the authors. In May 2021, substantial new evidence had come into light since the initial publication of this position statement. This evidence was compelling enough to demand an additional round of review and discussion and led to the update of this consensus statement, which includes a summary of the recently published evidence.

4. Visual patient assessment checklist and prescribing tips by drug class

Fig. 1 shows a visual summary of the recommendations of this position statement. More information for the summarised recommendations can be found in Section 6.

Some general principles, such as avoiding hypoglycaemia, focusing on cardiovascular prevention, individualising control targets, assessing therapeutic adherence, avoiding therapeutic inertia, acknowledging the importance of patient-perceived outcomes (e.g., weight loss), and considering patients' preferences and values, should be considered when treating patients with T2D [43].

Side effects are major factors influencing treatment choice and medication adherence [44]. Patients will have their personal needs, preferences, and tolerances regarding the route of administration (injectable or oral), discomfort, side effects, and the price they are willing to pay out of pocket. Shared decision making is an approach in which patients and clinicians work together and engage in a deliberate dialogue about reasonable treatment options. In this process, the HCP is the expert in evidence-based medicine and should suggest the most clinically appropriate and safe medications. This approach is feasible in primary care [16]. Table 1 summarises the most common and serious side effects that should be taken into consideration when choosing the most appropriate treatment regimen, as well as relevant prescribing tips to ensure minimal occurrence or impact of these side effects.

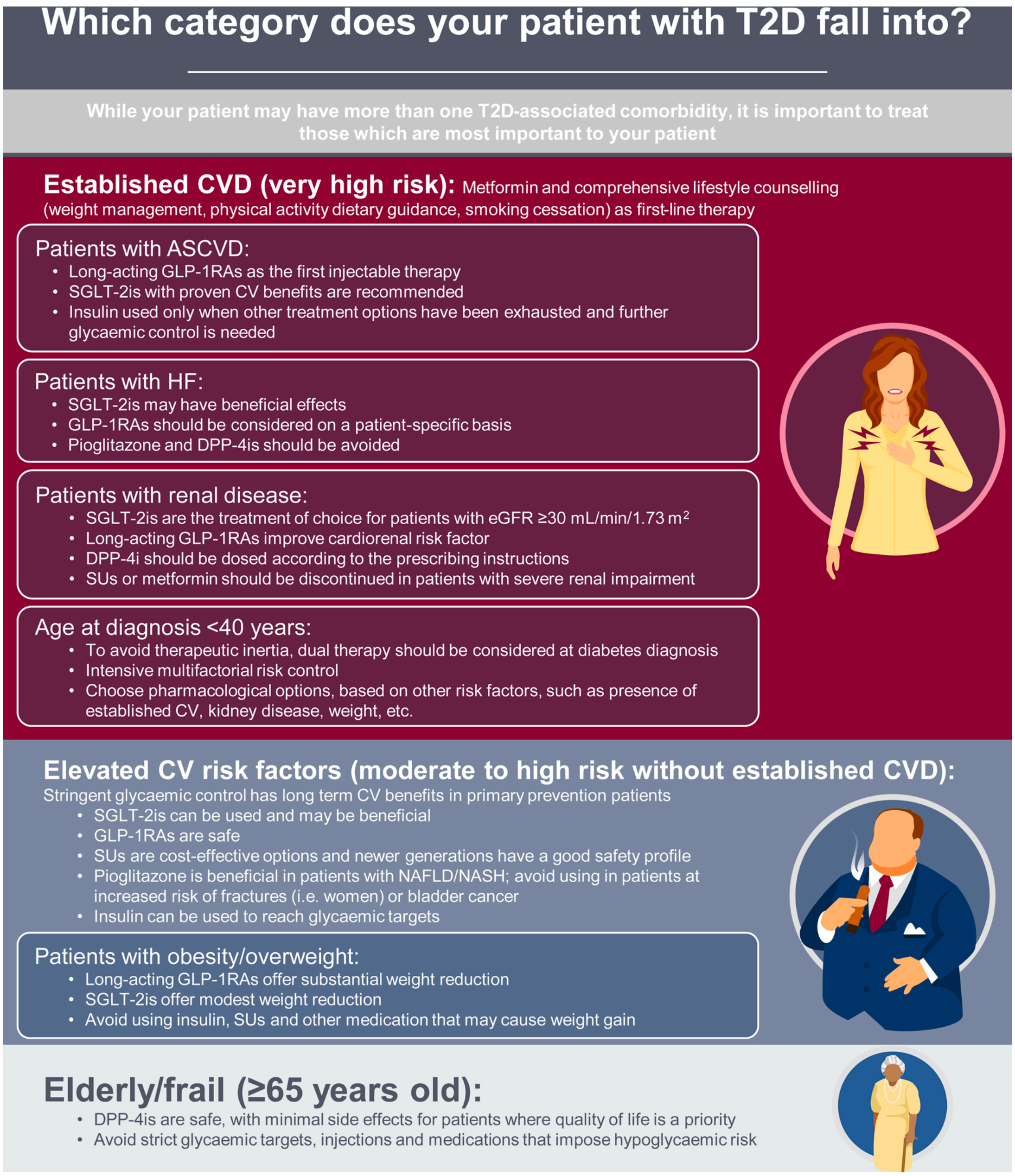

Fig. 1. Visual patient assessment checklist.
Reference in support of these recommendations can be found in Section 6. Treatment recommendations stratified by disease condition. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular, CVD, cardiovascular disease; DPP-4is. dipeptidy peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HF, heart failure; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatis; SGLT-2is, sodium-glucose co-transporter-2 inhibitors; SUs, sulphonylureas; T2D, type 2 diabetes.

Table 1
Side effects of concern and prescribing tips for the use of antidiabetic medications in the treatment of type 2 diabetes.

Chemical substance or chemical subgroup	Physiological mode of action	Side effects of concern	Prescribing tips
Metformin	Decreases hepatic glucose production [11–13]	GI symptoms [11–13]	GI symptoms during therapy initiation appear to be dose-related, and they may be decreased by gradual dose escalation and by taking the medicine with meals [257]
Glinides	Increase insulin secretion [11–13]	Modest weight gain, low risk of hypoglycaemia [197]	
GLP-1 receptor agonists	Enhance glucose-dependent insulin production, suppress glucose-dependent glucagon secretion, slow gastric emptying, suppress appetite [11–13]	GI symptoms including nausea, diarrhoea, vomiting, decreased appetite, abdominal pain, constipation. These may also include a possible increased risk of acute pancreatitis (which is listed as very rare or uncommon) [216, 217] An increased risk of diabetic retinopathy was observed with semaglutide in SUSTAIN 6 trial [100]	GI symptoms may happen initially, but they are transitory and often mild to moderate. If patients do not tolerate a gradual dose escalation, consider returning the patient to a lower dose for one week or more before trying again to increase the dose. It is also recommended to have healthy, non-spicy, and smaller meals to reduce the risk of nausea [258] Patients are advised to use a different injection site each week to avoid injection site reactions [259]
SGLT-2 inhibitors	Enhance excretion and prevent reabsorption of urinary glucose [11–13]	Urogenital tract infections (with higher risk in women and potential greater impact on quality of life in the elderly). Dehydration, hypotension from increased urination, and risk of lower limb amputations are considered uncommon, except for volume depletion with ertugliflozin, which is listed as common [133–136, 260–262]	Monitor and treat urogenital infections as needed In conditions of reduced oral intake, or potential fluid losses, such as gastrointestinal illness, carefully monitor volume status and discontinue treatment until fluid loss is corrected [134–136,262,263] If administering canagliflozin, be cautious of other pre-existing factors that could increase fracture risk, such as history of fractures and higher risk of falls, as bone fracture is listed as uncommon for this chemical substance [134] Encourage proper hygiene in both female and male patients to avoid genital mycotic infections [133]
DPP-4 inhibitors	Enhance glucose-dependent insulin production, suppress glucose-dependent glucagon secretion [11–13]	Upper respiratory tract infection, urinary tract infection, nasopharyngitis and headache [264–266], neutral effect on macrovascular and microvascular complications, with the exception of saxagliptin, which may increase the risk for HF hospitalisations [267]	
Sulphonylureas	Increase insulin secretion [11–13]	Hypoglycaemia, weight gain [268]	Hypoglycaemia usually occurs due to excessive dosage; use with caution in situations in which hypoglycaemia is most likely to occur. Weight gain is usually countered by the concurrent administration of metformin [268] Only gliclazide may be used in CKD stage 3 or worse. For all others, dose should be reduced in subjects with eGFR 60–90 mL/min/1.73 m^2. Contraindicated in subjects with eGFR <60 mL/min/1.73 m^2[269]. Even in the case of gliclazide, a hypoglycaemic episode occurring in these patients may be prolonged, so appropriate management should be initiated
Acarbose	Reduces rate of absorption of carbohydrates	Flatulence, mild diarrhoea	Side effects may be mitigated if the dose is increased slowly [215]
Pioglitazone	Enhances insulin sensitivity [11–13]	Weight gain, swelling, risk of bone fracture, bone loss [11–13, 270] Should not be used in patients with history of or active bladder cancer [210] or those at risk of HF [207]	
Insulin	Stimulates insulin receptor leading to increased insulin disposal and decreased production of glucose [11–13]	Hypoglycaemia, weight gain [11–13]	If hypoglycaemia develops, consider reducing dose or modifying timing of injection. Patients should be encouraged to rotate injection sites

DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HF, heart failure; SGLT-2, sodium-glucose co-transporter-2.

4.1. Managing T2D in the virtual consultation setting

Telemedicine has emerged as a must-use method in the delivery of care during the COVID-19 pandemic. It has shown that remote consultation can improve the quality of primary care and be effectively used for forwarding patients to COVID-19 triage before face-to-face consultation [45,46]. On the other hand, the experience during the pandemic also pointed out possible pitfalls of the virtual consultation setting. Negligence of the essential first-contact role with primary care professionals happened due to the hegemony of pandemic health services. This led to missed opportunities for preventative care not related to COVID-19, as well as an increase in the post-pandemic chronic disease burden. Also, safety (e.g., physical examination effectiveness) and equity issues (e.g., insufficient proactive outreach to vulnerable populations) were identified in the remote consultation setting [46,47]. Thus, there is a need for a patient-centred telemedicine approach to people with chronic diseases, including those with T2D, and treatment options should be suitable for this scenario [48]. A selection of some online resources about the virtual consultation setting can be found below.

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5. Treatment recommendations stratified by risk

5.1. Treatment adherence

Treatment adherence in patients with T2D is extremely important, since improved adherence is associated with better glycaemic control, mortality and hospital admissions [49]. A meta-analysis of studies evaluating treatment adherence, persistence, and discontinuation of oral antidiabetic drugs reported that adherence was suboptimal with the pooled proportion of adherent patients of 67.9% (59.6%; 76.3%) in a total of 12 studies evaluated. The discontinuation rate in RCTs was 31.8% (17.0%; 46.7%) in a total of 7 studies evaluated and the mean persistence rate was 56.2% (46.1%; 66.3%) in a total of 6 studies evaluated [50]. In another systematic review and meta-analysis that included 34 cohort studies involving almost 600,000 patients with T2D receiving oral an antidiabetic drug, 56.9% (49.3%; 64.4%) of patients with T2D were adherent at one year (proportion of days covered or medication possession ratio $\geq$0.80) and 44.2% (36.4%; 52.1%) at two years [51]. A third systematic review and meta-analysis comprising 48 studies showed that adherence was better for sulphonylureas (SUs) and thiazolidinediones when compared with metformin. Patient-oriented outcomes like treatment satisfaction (measured by Diabetes Treatment Satisfaction Questionnaire scores), when correlated with adherence and persistence, have shown to be significantly higher with glucagon-like peptide-1 receptor agonists (GLP-1RA) drugs as compared with placebo or other active comparators (e.g. metformin, insulin) [52–54]. A study comparing persistence among new antidiabetic drugs showed differences between drug classes, favoring dipeptidyl peptidase-4 inhibitors (DPP-4is) vs. sodium-glucose co-transporter-2 inhibitors (SGLT-2*is*) and GLP-1RAs [55]. Schlesinger and colleagues reported in their systematic review and meta-analysis of 19 prospective studies that adhering to a healthy lifestyle (such as mostly favourable diet, physical activity, non-smoking, moderate alcohol intake, and normal weight) reduced the risk of T2D by 78% (14 studies evaluated) and of mortality by 57% (5 studies evaluated) when compared with low adherence to a healthy lifestyle. A reduction in the risk for T2D by 32% (28%; 36%) and for mortality by 21% (15%; 26%) can be attributed to the adherence to every additional healthy lifestyle factor [56]. In their meta-analysis study, Khunti et al. found that individuals with good adherence had a significant 10% lower rate of hospitalisation events and a significant 28% lower rate of all-cause mortality when compared with a group with poor adherence [49]. Another study by Anderson et al. showed that patient drug preferences are guided by factors of convenience rather than effectiveness and safety. The study results showed the relative importance for the attributes in rank order as follows: dosing frequency' (41.6%), 'type of delivery system (35.5%), 'frequency of nausea' (10.4%), 'weight change' (5.9%), 'HbA_{1c} change' (3.6%), and 'frequency of hypoglycemia' (3.0%) [57].

5.2. Lifestyle modifications

As part of their first-line therapy, all patients with T2D should be offered individualised and comprehensive lifestyle counselling including weight management, physical activity, dietary guidance, and smoking cessation. All glycaemic and lifestyle goals should be co-developed and agreed to by the patient and physician. For patients who find it challenging to meet their glycaemic goals, therapeutic lifestyle modifications and adherence to these measures should be discussed at ongoing follow-up visits every 3–6 months. Self-management education and support are pivotal to help patients achieving good results in diabetes control [54,58,59].

5.3. Metformin

In addition to healthy lifestyle management, newly diagnosed patients with T2D should also be treated with metformin at diabetes diagnosis as the first-line pharmacological therapy of choice. A systematic review and meta-analysis published in 2021 reported that longer-acting metformin (i.e., extended-release and delayed-release formulations) were equally efficient for glycaemic control when compared to the immediate-release formulation, but delayed-release metformin was strongly associated with reduced gastrointestinal effects, and extended-release metformin was associated with reduced serum low-density lipoprotein (LDL) cholesterol concentrations [60]. Clinicians have over 60 years of experience using metformin [61], thus its risks and benefits are well understood. Metformin is a cost-effective option for glucose lowering, associated with weight loss and fewer hypoglycaemic episodes when compared to insulin or SUs [11–13,62]. Some evidence suggests it has cardiovascular benefit with respect to myocardial infarction (MI) [58,63], but the paucity of data from long-term CVOTs creates uncertainty around the effect of metformin in reducing CVD in patients with T2D [64]. Importantly, metformin has been shown to be associated with gastrointestinal side effects, affecting nearly 25% of patients, among whom 5% develop complete intolerance [65]. Women and elderly were more likely to be intolerant to metformin [57]. These side effects can often be successfully mitigated in many patients with careful dose titration [66].

Evidence is emerging to support the initiation of a second therapeutic agent along with metformin, rather than waiting for treatment failure with metformin before intensification [67–69]. A Cochrane systematic review published in 2020 evaluated 18 RCTs involving more than 10,000 patients in multiple study arms. Approximately 58% of patients finished the trials in all groups, and the treatment duration varied from one to 10.7 years. The systematic review concluded that metformin monotherapy versus other glucose-lowering drugs, no intervention, or behaviour changing interventions had no apparent influence on the main outcomes of interest such as all-cause mortality, CV mortality, health-related quality of life, serious adverse events, non-fatal MI, non-fatal stroke, and end-stage renal disease (ESRD) [70]. These data are supported by evidence of 'glycaemic legacy', whereby reduced risk of complications is seen in some studies where patients are treated intensively early in their disease progression, even if this stringent glycaemic control is eventually relaxed [71,72]. It should be noted, however, that evidence for this glycaemic legacy effect is not supported by all follow-up studies [73]. To avoid therapeutic inertia, dual therapy may be considered three months after starting metformin treatment in patients who are likely to benefit from better glycaemic control, particularly those with a high baseline HbA_{1c}. The decision of whether to initiate dual therapy should consider individual patient characteristics and treatment goals. If a dual therapy approach is used, patients with cardiovascular or renal disease could gain the benefits of agents shown to reduce risk of cardiovascular events or improve renal parameters (outlined below) earlier in their treatment progression. If metformin monotherapy is chosen at diagnosis, patients should be monitored closely and treatment should be intensified three months after starting metformin, if individualised glycaemic targets are not met and to avoid therapeutic inertia [74]. For patients on dual therapy who are not meeting treatment goals, additional intensification should be strongly considered to better glycaemic control and avoid therapeutic inertia.

5.4. Assessing risk in patients with T2D

CVD represents one of the most prevalent comorbidities of T2D [5], affecting nearly one-third of all patients globally [10]. The World Health Organization defines CVD as a group of conditions related to the heart and blood vessels, including coronary heart disease, cerebrovascular disease, and peripheral arterial disease [75].

Understanding the intricate pathophysiological link between CVD and T2D is useful for clinicians when choosing the most suitable and effective treatment for their patients. The physiological mechanisms driving diabetic cardiomyopathy can be used to explain the profound impact of T2D on the cardiovascular system. Most people with T2D have hyperglycaemia, hyperlipidaemia, hypertension, and overweight, all of which confer substantial CVD risk. Diabetes guidelines and intervention strategies therefore mandate an intensified treatment approach to reduce the risk for diabetes-related complications [11–13,76].

Awareness and knowledge of all cardiovascular risk factors are critical in determining CVD risk. When primary prevention strategies fail due to pervasive or unmodifiable risk factors, secondary prevention efforts become important, with focus on early detection to preserve quality of life of the patient [77].

We propose here a pragmatic, evidence-based cardiovascular risk stratification tool intended to complement the tool provided by the American College of Cardiology (ACC)/American Heart Association (AHA) and endorsed by the American Diabetes Association (ADA) [78, 79], and guide primary care physicians in their choice for the treatment of patients with T2D (Box 2).

6. Rationale for risk stratification criteria

History of established CVD is one of the most widely recognised and important predictors of future major adverse cardiovascular events (MACE) [80]. Similarly, both decreased estimated glomerular filtration rate (eGFR) and albuminuria are strong independent predictors of MACE in patients with T2D [81]. Finally, there is evidence to suggest that early-onset T2D represents an aggressive form of the disease in terms of cardiovascular risk [82], reflected in the fact that patients with a younger age at diagnosis have a much higher cardiovascular risk than that of age-matched controls [83]. Thus, patients with any of these characteristics are considered to be at very high cardiovascular risk.

Since T2D itself is considered a major risk factor for CVD, the remaining patients who do not fit these criteria are considered to be at high cardiovascular risk.

6.1. Patients at very high cardiovascular risk

The relationship between glucose lowering and CVD in diabetes has been investigated [84]. The ACCORD trial demonstrated that intensive glucose lowering therapy alone did not translate into a statistically significant or clinically relevant reduction in adverse cardiovascular outcomes. Results from this study suggested a lesser benefit in the first occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular causes in patients who had previously experienced a cardiovascular event [85]. Although some studies observed that intensification of antidiabetic treatment increased the risk of CV events in patients with diabetes (many of them treated with insulin), more recent studies demonstrated an association between the reduction of HbA_{1c} and the decrease in the incidence of CV events (potentially due to the use of drugs that cause less hypoglycaemia) [86–92]. Episodes of severe hypoglycaemia, which can sometimes occur as a consequence of stringent glycaemic targets, are a strong predictor of adverse cardiovascular events and mortality [93]. However, other meta-analyses and long-term follow-ups do suggest a modest risk reduction for certain macrovascular events for patients treated using long-term intensive glucose-lowering strategies [66,94,95]. An epidemiological study based on the Swedish National Diabetes Register supports that glucose control is valuable to reduce the risk of macrovascular complication (i.e., MI and stroke) [96].

Given these conflicting results, patients at very high cardiovascular risk, and particularly those prone to hypoglycaemia, may benefit from a treatment regimen that balances moderate glycaemic targets with use of agents with proven benefits to cardiovascular risk and renal parameters, as outlined below. A summary of outcome trials and their results examining the cardiovascular and renal effects of various anti-glycaemic treatments is shown in Table 2.

6.2. Patients with atherosclerotic cardiovascular disease (ASCVD)

ASCVD is the primary cause of morbidity and mortality in individuals with T2D [97]. ASCVD is broadly defined as atherosclerosis leading to coronary artery disease, cerebrovascular disease, or peripheral arterial disease [97]. While differences exist in how ASCVD is reported across clinical trials, all CVOTs have enrolled some proportion of patients with established CVD (prior MI, stroke, or arterial revascularisation), and a range of patients with clinically significant atherosclerosis (prior transient ischaemic attack, hospitalised unstable angina, amputation, congestive heart failure [HF] New York Heart Association class II–III, $>$50% stenosis of any artery, symptomatic or asymptomatic

Table 2
Summary of outcome trials.

Chemical substance	Outcome Trial	Comparator	Population	Prior CVD	Median follow up	Primary composite endpoint	Primary endpoint HR (95% CI) *p*-value	All-cause mortality HR (95% CI) *p*-value	Number needed to treat to prevent 1 event
GLP-1RAs									
Lixisenatide	ELIXA **E**valuation of **LIX**isenatide in **A**cute coronary syndrome	Placebo	6,068	100%	25 months	4-point MACE	1.02 (0.89; 1.17) $p<0.001$ for non-inferiority; $p = 0.81$ for superiority [105]	0.94 (0.78; 1.13) $p = 0.50$	-
Exenatide	EXSCEL **EX**enatide **S**tudy of **C**ardiovascular **E**vent **L**owering	Placebo	14,752	73%	3.2 years	3-point MACE	0.91 (0.83; 1.00) $p<0.001$ for non-inferiority; $p = 0.06$ for superiority [106]	0.86 (0.77; 0.97) $p = 0.016$	-
Liraglutide	LEADER **L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of Cardiovascular Outcomes **R**esults	Placebo	9,340	81%	3.8 years	3-point MACE	0.87 (0.78; 0.97) $p<0.001$ for non-inferiority $p = 0.01$ for superiority [99]	0.85 (0.74; 0.97) $p = 0.02$	Primary outcome (over 3 years): 66 Death from any cause (over 3 years): 98
Semaglutide	SUSTAIN-6 Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes	Placebo	3,297	83%	2.1 years	3-point MACE	0.74 (0.58; 0.95) $p<0.001$ for non-inferiority; $p = 0.02$ for superiority [100]	1.05 (0.74; 1.50) $p = 0.79$	Primary outcome (over 24 months): 45 Risk of major CV event (over 3 years): 31 [271]
Oral semaglutide	PIONEER 6 Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes	Placebo	3,183	84.6%	15.9 months	3-point MACE	0.79 (0.57; 1.11) $p<0.001$ for non-inferiority; $p = 0.17$ for superiority [101]	0.51 (0.31; 0.84) no *p*-value reported	-
Albiglutide	HARMONY Outcomes Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease	Placebo	9,463	100%	1.5 years	3-point MACE	0.78 (0.68; 0.90) $p<0.0001$ for non-inferiority; $p = 0.0006$ for superiority [103]	0.95 (0.79; 1.16) $p = 0.644$	Primary event outcome (over 1.6 years): 50
Dulaglutide	REWIND **R**esearching Cardiovascular **E**vents with a **W**eekly **I**ncretin in **D**iabetes	Placebo	9,901	31%	5.4 years	3-point MACE	0.88 (0.79; 0.99) $p = 0.026$ for superiority [104]	0.90 (0.80; 1.01) $p = 0.067$	For people with a previous CV event (over 5 years): 18
SGLT-2i									
Empagliflozin	EMPA-REG OUTCOME Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes	Placebo	7,020	99%	3.1 years	3-point MACE	0.86 (0.74; 0.99) $p<0.001$ for non-inferiority; $p = 0.04$ for superiority [108]	0.68 (0.57; 0.82) $p < 0.001$	Risk of MACE (over 3.1 years): 63 [272] Risk of death from any cause (over 3 years): 39
Empagliflozin	EMPEROR-Reduced Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction	Placebo	3,730	100%	16 months	CV death/ HHF	0.76 (0.67; 0.87) $p<0.0001$ [126]	0.92 (0.77 to 1.10) No *p*-value reported [172]	Primary outcome: 19 [172]
Canagliflozin	CANVAS Canagliflozin Cardiovascular Assessment Study	Placebo	10,142	66%	126.1 weeks	3-point MACE	0.86 (0.75; 0.97) $p<0.001$ for non-inferiority; $p = 0.02$ for superiority [109]	0.87 (0.74; 1.01) $p = 0.24$ for superiority	Additional major CV event (over 3 years): 179 [271]
Canagliflozin	CREDENCE **C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation	Placebo	4,401	50.4%	2.62 years	ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59; 0.82); $p = 0.00001$ [168]	0.83 (0.68; 1.02) no *p*-value reported	Primary outcome: 22 (15; 38) Composite outcome of ESKD, doubling of serum creatinine, or renal death (over 2.62 years): 28 ESKD events (over 2.62 years): 43 HHF: 45 Composite events of CV

(*continued on next page*)

Table 2 (*continued*)

Chemical substance	Outcome Trial	Comparator	Population	Prior CVD	Median follow up	Primary composite endpoint	Primary endpoint HR (95% CI) *p*-value	All-cause mortality HR (95% CI) *p*-value	Number needed to treat to prevent 1 event
									death, MI, or stroke (over 2.62 years): 40
Dapagliflozin	DECLARE-TIMI 58 Dapagliflozin Effect on Cardiovascular Events –Thrombolysis in Myocardial Infarction 58	Placebo	17,160	41%	4.2 years	3-point MACE	0.93 (0.84; 1.03) $p = 0.17$ for superiority [110]	0.93 (0.82; 1.04) No *p*-value reported	CV death or HHF in patients with prior MI (over a period of 4 years): 53 [272]
Dapagliflozin	DAPA-HF **D**apagliflozin **A**nd **P**revention of **A**dverse-outcomes in **H**eart **F**ailure)	Placebo	4,744	100%	18.2 months	Worsening HF or death from CV causes	0.74 (0.65; 0.85) $p<0.001$ for superiority [125]	0.83 (0.71; 0.97) No *p*-value reported	Primary outcome: 21
Dapagliflozin	DAPA-CKD Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease	Placebo	4,304	37.4%	2.4 years	Sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes	0.61 (0.51; 0.72) $p<0.001$ [171]	0.69 (0.53; 0.88) $p = 0.004$	Primary outcome: 19
Ertugliflozin	VERTIS CV Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial	Placebo	8,246	100%	3.5 years	3-point MACE	0.97 (0.85; 1.11) $p<0.001$ for noninferiority [112]	0.93 (0.80; 1.08) No *p*-value reported	-
Sotagliflozin	SOLOIST-WHF Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure	Placebo	1,222	100%	9.2 months	Total number of CV deaths, hospitalisations, and urgent visits for HF (first and subsequent events)	067 (0.52; 0.85) $p<0.001$ [127]	0.82 (0.59; 1.14) No *p*-value reported	-
Sotagliflozin	SCORED Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk	Placebo	10,584	31%	16.0 months	Total number of CV deaths, hospitalisations for HF, and urgent visits for HF	HR: 0.74 (0.63; 0.88) $p<0.001$ [128]	0.99 (0.83; 1.18) No *p*-value reported	-
DPP-4i									
Alogliptin	EXAMINE Examination of Cardiovascular Outcomes with Alogliptin Versus Standard of Care	Placebo	5,380	100%	18 months	3-point MACE	0.96 ($\leq$1.16) $p<0.001$ for non-inferiority; $p = 0.32$ for superiority [273]	0.88 (0.71; 1.09) $p = 0.23$	
Saxagliptin	SAVOR-TIMI 53 Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction	Placebo	16,492	90.9%	2.1 years	3-point MACE	1.00 (0.89; 1.12) $p = 0.99$ for superiority; $p<0.001$ for non-inferiority [274]	1.11 (0.96; 1.27) $p = 0.15$	-
Linagliptin	CARMELINA **CA**rdiovascular safety and **R**enal **M**icrovascular Outcom**E** with **Lina**gliptin in Patients With Type 2 Diabetes	Placebo	7,003	57%	2.2 years	3-point MACE	1.02 (0.89; 1.17) $p<0.001$ for non-inferiority; $p = 0.74$ for superiority [146]	0.98 (0.84; 1.13) $p = 0.74$	-
Linagliptin	CAROLINA **CAR**diovascular **O**utcome Study of **LINA**gliptin Versus Glimepiride in Patients with Type 2 Diabetes	Glimepiride	6,033	35%	6.3 years	3-point MACE	0.98 (0.84; 1.14) $p<0.0001$ for non-inferiority; $p = 0.76$ for superiority [147]	0.91 (0.78; 1.06) *p*-value not significant	-
Insulin									
Insulin degludec	DEVOTE Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events	Insulin glargine U100	7,637	85.2%	1.83 years	3-point MACE	0.91 (0.78; 1.06) $p<0.001$ for noninferiority [113]	0.91 (0.76; 1.11) $p = 0.35$	-

CV, cardiovascular; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction.

coronary artery disease documented by imaging, CKD with eGFR <60 mL/min/1.73 m^2) [11–13].

When deciding on the most appropriate and effective antidiabetic medication to add after or with metformin, it is important to consider the presence of other diabetes-associated comorbidities. The presence of ASCVD in people with T2D strongly advocates choosing a glucose-lowering therapy that not only reduces HbA_{1c} but also controls and prevents worsening of ASCVD, hospitalisation for HF, renal disease, and mortality. Therapy in patients at increased risk of stroke should also be focused on lowering blood pressure, which has been shown to dramatically lower the risk [98].

6.2.1. Glucagon-like peptide-1 receptor agonists

There is substantial evidence from large CVOTs corroborating the use of some GLP-1RAs in patients with T2D and established ASCVD. GLP-1RAs are recommended for initial intensification. Among the list of trials that investigated this drug class, the LEADER trial demonstrated superiority of liraglutide compared to placebo in reducing the risk of death from cardiovascular causes, nonfatal (including silent) MI, or nonfatal stroke [HR: 0.87 (0.78; 0.97), Number needed to treat (NNT): 66–67 over 3 years] [99]. In the SUSTAIN 6 trial that compared the injectable GLP-1RA semaglutide to placebo, the rate of cardiovascular death, nonfatal MI, or nonfatal stroke was 26% lower among patients receiving semaglutide than among those receiving placebo [HR: 0.74 (0.58; 0.95), NNT: 45 over 24 months]. Based on the design of the study, this result reflects noninferiority of semaglutide compared to placebo. Semaglutide had a neutral effect on the number and rate of occurrence of severe hypoglycaemic episodes [100]. The oral formulation of semaglutide also demonstrated noninferiority to placebo in the PIONEER 6 trial, achieving its primary objective of no excess cardiovascular risk [HR: 0.79 (0.57; 1.11)] [101]. Although the overall number of retinopathy events was low, there was an unexpected higher rate of retinopathy complications (vitreous haemorrhage, blindness, or the need for treatment with an intravitreal agent or photocoagulation) in the semaglutide group in both studies [100,101]. Most cases were non-proliferative, were identified during routine examination, and resulted in no new treatment. In addition, the increase was observed only in patients with previous retinopathy and in patients with the greatest and most rapid reduction in HbA_{1c}, similar to effects seen with insulin and in patients with type 1 diabetes [102].

To further add to the repertoire of CVOTs in patients with T2D and established CVD, the Harmony Outcomes trial confirmed albiglutide (not commercially available) was superior to placebo in reducing MACE [HR: 0.78 (0.68; 0.90), NNT: 50 over 1.6 years] [103]. More recently, results from the REWIND trial showed the addition of dulaglutide to existing diabetes treatment reduced the primary composite of cardiovascular outcomes over 5 years in a broad range of people with T2D [HR: 0.88 (0.79; 0.99), NNT for patients with a prior cardiovascular event: 18 over 5 years]. REWIND differed from preceding CVOTs with GLP-1RAs in that only 31% of participants had established CVD. Of note, in the REWIND trial, the risk of eye outcomes was numerically higher with dulaglutide compared with the placebo group [104].

Despite the well-recognised benefit of GLP-1RAs in effectively altering the rate of MACE, it is also important to address that some drugs of this class have not been shown to significantly improve cardiovascular outcomes. Neither lixisenatide [HR: 1.02 (0.89; 1.17)] nor exenatide [HR: 0.91 (0.83; 1.00)] showed significant improvements in risk of MACE [105,106]. Overall, a recent systematic review of GLP-1RA CVOTs identified a class effect for risk reduction of MACE, cardiovascular mortality, and all-cause death [107]. Patients and HCPs should also discuss the considerable inter-individual variation in magnitude of effect on HbA_{1c} and weight loss in patients treated with GLP-1RAs, and continued treatment with these therapies should be evaluated after 6 months.

6.2.2. Sodium-glucose co-transporter-2 inhibitors

Among the SGLT-2*is*, empagliflozin and canagliflozin have demonstrated beneficial effects in reducing MACE in patients with T2D and ASCVD. Almost all patients included in the EMPA-REG OUTCOME trial had previous CVD, and treatment with empagliflozin was shown to reduce risk of the primary MACE endpoint by 14% compared to placebo [HR: 0.86 (0.74; 0.99), NNT: 63 over 3.1 years]. While this trial showed no significant differences in the rates of MI or stroke when treated with empagliflozin, this treatment did lead to significant reductions in rates of death from cardiovascular causes, hospitalisation for HF, and death from any cause [108]. Results from the CANVAS Program, which included a broad patient population of whom more than 65% had a history of CVD, confirmed the superiority of canagliflozin compared with placebo in significantly lowering the rate of the primary outcome, which was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke [HR: 0.87 (0.75; 0.97), NNT for patients with a prior cardiovascular event: 179 over 3 years] [109]. More recently, the DECLARE-TIMI 58 study (with ~40% of patients with established CVD) did not demonstrate significantly decreased risk of MACE for dapagliflozin compared to placebo [HR: 0.93 (0.82; 1.04)], but did result in decreased rates of cardiovascular death or hospitalisation for HF [HR 0.83 (0.73; 0.95), NNT: 53 over 4 years] [110]. These results were corroborated by a subsequent meta-analysis that confirmed moderate benefits of SGLT-2is on atherosclerotic events in patients with established CVD [111]. In the CVOT VERTIS trial, the fourth SGLT-2i, ertugliflozin, was non-inferior to placebo for reducing cardiovascular events in patients with T2D and established CVD. There seems to be a consistent chemical subgroup effect regarding reductions in HF hospitalisations [HR: 0.70 (0.54; 090)], but reductions in major adverse cardiac events were only statistically significant for canagliflozin and empagliflozin [112].

6.2.3. Insulin

Importantly, insulin should only be used in patients with T2D and ASCVD when other options have been attempted and co-developed glycaemic goals have not been met. Apart from the DEVOTE trial, which demonstrated non-inferiority of insulin degludec to insulin glargine U100 on cardiovascular outcomes [113], there have been no other trials to date that have investigated the cardiovascular safety of insulin in patients with T2D established CVD. Thus, GLP-1RAs are recommended before insulin as the first injectable treatment by a number of clinical practice guidelines [11–13,39].

Ultimately, SGLT-2is (empagliflozin, canagliflozin, and dapagliflozin) and GLP-1RAs (liraglutide, semaglutide, albiglutide, and dulaglutide) have been the only chemical subgroups to show proven CV benefit in patients with T2D and ASCVD, with the exception of ertugliflozin, considering the CVOT VERTIS trial results [114].

6.3. Patients with HF

HF is an increasingly common comorbidity associated with T2D, with up to 40% prevalence in patients with T2D and a median patient survival rate of only around 4 years [115–117]. Increased risk of HF in patients with T2D has been shown to be associated with greater insulin use and poor glycaemic control [118]. Despite the poor prognosis and high medical demand for effective therapies for patients with diabetes and HF, treatment options remain scarce [109,119,120].

6.3.1. Sodium-glucose co-transporter-2 inhibitors

There is good evidence supporting the use of SGLT-2is in patients with T2D and heart failure with reduced ejection fraction (HFrEF), with demonstrated favourable effects on cardiovascular outcomes, in addition to reducing hyperglycaemia [121]. SGLT-2is are now indicated in adults for the treatment of HF with HFrEF in different parts of the world, including Europe [122,123]. The first drugs of this class available for the treatment of T2D that were shown to improve the risk of hospitalisation for HF were empagliflozin and canagliflozin [103,114,124]. *Post hoc* analyses of data from the EMPA-REG OUTCOME showed that empagliflozin resulted in significant reductions in hospitalisation for HF, as well as in death from cardiovascular causes, for patients with and without HF at baseline [115]. Results from the CANVAS Program suggest that the significant reduction in the risk of hospitalisation for HF with canagliflozin may be greater in patients with prior history of HF compared to those without [116]. Furthermore, dapagliflozin was more recently shown to lower the rates of cardiovascular death and hospitalisation for HF in a broad patient population. Although similar reductions were seen in patients regardless of history of ASCVD or HF, only 10% of patients had a history of HF [110]. The DAPA-HF study sought to further examine the patient population with established HF and showed benefits in reduced hospitalisation for HF and mortality in patients with HF with and without diabetes. This trial is the first to show benefits specifically in patients with prior HF without diabetes and reinforces the use of these drugs in this population. The primary endpoint of the study, the composite of a first episode of worsening HF or cardiovascular death, occurred in 16.3% in the dapagliflozin group and in 21.2% in the placebo group [HR: 0.74; (0.65; 0.85), NNT: 21]. The results were consistent in the prespecified subgroup of patients with T2D at baseline [HR: 0.75 (0.63; 0.90)] [125]. More recently, the EMPEROR-Reduced trial revealed that empagliflozin reduced HF hospitalisations [HR 0.70 (0.63; 0.78)] in patients with HFrEF. The magnitude of the observed benefits was comparable in patients with and without diabetes at enrolment [126]. In the SOLOIST-WHF trial, patients with T2D and recent worsening HF received placebo or sotagliflozin, which is not approved for patients with T2D yet. The rate of the total number of CV deaths, hospitalisations, and urgent visits for HF was 51.0 per 100 patient-years in the sotagliflozin group and 76.3 per 100 patient-years in the placebo group [HR: 067 (0.52; 0.85)]. The authors mentioned that the trial was ended early due to funding loss, which led to a significant reduction in power to test the original primary endpoint [127]. The SCORED trial compared sotagliflozin with placebo in reducing CV events in patients with T2D, CKD (eGFR rate, 25–60 mL/min/1.73 m^2 of body-surface area), and risks for CV disease. The primary endpoint, a composite of the total number of CV deaths, hospitalisations for HF, and urgent visits for HF, was lower to sotagliflozin when compared to placebo [(5.6 vs. 7.5 events per 100 patient-years; HR: 0.74 (0.63; 0.88)]. The authors indicated that the original co-primary endpoint was the first occurrence of MACE (defined as CV deaths, non-fatal MI, or non-fatal stroke) and the first occurrence of CV deaths or hospitalisation for HF, but it had to be changed due to funding loss [128]. These studies, DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF, and SCORED, confirm the role of SGLT-2i agents for the management of HF or CKD even in patients without diabetes [117–120]. Also, in patients with HFrEF, the aim should be to up-titrate renin-angiotensin-aldosterone system inhibitors and beta-blockers to the target or maximum-tolerated doses in a timely fashion. Mineralocorticoid receptor antagonists can be added before achieving the maximally tolerated or target doses of the other medications [129].

While these clinical trial data examine patients with HFrEF, heart failure with preserved ejection fraction (HFpEF) has been less well studied, despite its common association with T2D. However, the CVD-REAL real-world evidence study showed reduced risk of hospitalisation for any HF and mortality in patients taking SGLT-2is [122]. Clinical trials examining SGLT-2i treatment specifically in patients with HFpEF indicate that empagliflozin reduced the combined risk of cardiovascular death or hospitalisation for HF in patients with HF and a preserved ejection fraction, regardless of the presence or absence of diabetes [123].

Despite their benefits, patients and physicians should be aware that an increased risk of lower limb amputation was observed in patients treated with canagliflozin in the CANVAS Program, but not in other trials with SGLT-2is, including several observational studies [130]. A more recent study (CREDENCE) did not observe the increased risk for bone fractures and lower-limb amputations previously reported in CANVAS. Globally, these two studies reinforce a favourable risk-benefit balance of canagliflozin in a T2D population with CV or renal risk [131, 132]. That said, patients should be cautious of other pre-existing factors that increase fracture risk. Physicians should also encourage proper hygiene in both female and male patients to avoid genital mycotic infections common with this class of drug (and which may affect treatment adherence) [133–136]. Patients should also be counselled to maintain adequate fluid intake to prevent dehydration and hypotension from increased urination. Physicians should also be aware of the risk of uncommon but severe side effects as diabetic ketoacidosis and the rarer but highly severe Fournier gangrene. A few cases of diabetic ketoacidosis have been reported in patients who had recently undergone major surgery, decreased or discontinued insulin, or were diagnosed with T2D and subsequently found to have latent autoimmune diabetes of adulthood [137].

6.3.2. *Thiazolidinediones*

Certain drug families should also be particularly avoided when treating patients with T2D and HF. The PROactive trial demonstrated that the thiazolidinedione pioglitazone (commercial availability varies from country to country) was associated with a 50% increase in hospitalisation for HF compared to patients treated with placebo [138]. A meta-analysis of RCTs studying the effect of pioglitazone in secondary prevention of established CVD showed increased risk of HF despite lowered risk of recurrent MACE, stroke, and MI [139]. Direct comparison trials assessing the incidence of cardiovascular events between pioglitazone and other antidiabetic medications is limited to the TOSCA. IT trial, which compared pioglitazone with SUs (mostly glimepiride and gliclazide) which showed a non-statistically significant but numerically higher risk of HF in patients treated with pioglitazone [140]. Thus, pioglitazone is not recommended in the treatment of patients with T2D and HF, due to its demonstrated increased risk in HF-associated adverse cardiovascular effects, as well as the inadequacy of robust data from multiple dedicated trials.

6.3.3. *Dipeptidyl peptidase-4 inhibitors*

To date, there are no demonstrated benefits on CV outcomes of DPP-4is, and caution may be warranted when using saxagliptin in T2D patients with HF [141,142]. In the SAVOR-TIMI 53 trial, saxagliptin was associated with an increased relative risk of hospitalisation for HF, which was higher among patients with prior HF [143]. Furthermore, in a *post hoc* analysis, a small increase in hospitalisation for HF was observed in patients without a history of HF randomised to receive alogliptin in the EXAMINE trial, compared to those assigned to placebo; however, an interaction between treatment and history of HF was not found in the analysis, and there was no statistically significant difference between the two treatment groups in all-cause death and hospitalisation for HF, irrespective of history of HF [144]. The two other CVOTs examining DPP-4is, TECOS examining sitagliptin and CARMELINA evaluating linagliptin, failed to demonstrate any significant difference in the rate of hospitalisation for HF between the DPP-4i and placebo groups [145, 146]. The CAROLINA trial sought to further examine the noninferiority of linagliptin compared with glimepiride in preventing CV events. One of the secondary endpoints of the study, hospitalisation for HF, occurred in 3.7% in the linagliptin group and in 3.1% in the glimepiride group [HR: 1.21 (0.92; 1.59)] [147].

6.3.4. *Insulin*

Insulin treatment has been associated with renal sodium retention and oedema, particularly when used in combination with thiazolidinediones [148,149]. Assessing whether insulin treatment worsens HF has been difficult, given that patients treated with insulin typically have more advanced T2D and a greater degree of comorbidity and thus, clinical severity. However, a recent meta-analysis showed that insulin treatment in patients with HF was associated with a higher risk of death and hospitalisation for HF, irrespective of diabetes duration [150]. For those with HF, patients and HCPs should carefully weigh the benefits of stricter glycaemic control against the risks of worsening HF, with reduced insulin intensification given serious consideration.

In conclusion, SGLT-2is may be beneficial and are recommended for the treatment of patients with T2D and HF. Insulin treatment should be used with caution in patients who develop or have a history of HF. Saxagliptin or pioglitazone should be used only when there are no other therapeutic options available. GLP-1RAs and DPP-4is, other than saxagliptin, have not shown any benefits or harms in the risk for HF in patients with T2D.

6.3.5. Glucagon-like peptide-1 receptor agonists

A meta-analysis published in 2020 evaluated the effects of GLP1-RAs on HF, and reported that GLP1-RAs did not increase the HF risk [Mantel-Haenszel odds ratio 0.93 (0.85; 1.01), $p = 0.09$] with no discrepancy between different groups. Independent comparison between trials with and without cardiovascular endpoints showed that there was no significant between-group difference. No significant trend toward a reduction in HF was observed after adding non-cardiovascular outcomes to the analysis. The authors concluded that GLP1-RAs do not have the same stellar effects as other drug classes, and their effects on HF remain unclear, although they highlighted that one of the limitations of the meta-analysis was that the definition of HF was heterogeneous across trials [151].

6.4. Patients with CKD

Diabetes is the leading cause of CKD, and 25–40% of people with T2D also have CKD [152,153]. The kidney microvasculature is particularly sensitive to the damaging effects of hyperglycaemia, leading to impaired renal function [154]. Importantly, CKD puts limitations on the glucose-lowering therapies that can be used [155], making good glycaemic control increasingly difficult. Although these patients are at very high cardiovascular risk, patients and physicians are encouraged to choose as stringent glycaemic targets as are deemed safe to limit the worsening of microvascular disease [156]. Patients with diabetes with lower eGFR levels had a higher percentage of avoidable deaths and cardiovascular hospitalisations than those with other cardiovascular risk factors [157].

6.4.1. Metformin

Patients with established CKD should use metformin cautiously, and it should be discontinued entirely if eGFR falls below 30 mL/min/1.73 m^2 [158].

6.4.2. Sulphonylureas

The use of SU in individuals with CKD is dependent on the level of renal impairment and risk of hypoglycaemia. Due to the high hypoglycaemia rates of glibenclamide, higher risk of hypoglycaemia in patients with renal disease, and the availability of safer sulphonylureas as well as other therapeutic options, glibenclamide should not be recommended in these patients.” [155]. In the ADVANCE study, intensive glucose lowering with gliclazide modified release (MR) significantly reduced the risk of new-onset microalbuminuria by 9%, macroalbuminuria by 30%, new or worsening nephropathy by 21% and end-stage renal disease by 65% [159]. A persistent benefit of this intensive glucose control with respect to ESRD was observed for 10 years after initiation of therapy [160]. Gliclazide and gliclazide MR, with their lower risk of hypoglycaemia, does not require dose reduction in patients with eGFR >30 mL/min/1.73 m^2 [161]. Compared to other SUs, gliclazide treatment has been associated with lower risk of CVD and with weight neutrality [162].

6.4.3. Glinides

The insulin secretagogue glinides can also be used in patients with CKD as they are largely metabolised by the liver, though reduced dosages are suggested to limit the risk of hypoglycaemia [163]. Repaglinide requires a greater number of tablets per day than other drugs, which hinders adherence to treatment in patients who are usually polymedicated, especially those with CKD.

6.4.4. Dipeptidyl peptidase-4 inhibitors

DPP-4is are an important option in patients with CKD who are not meeting their glycaemic targets. The different available DPP-4is are metabolised and eliminated in different ways and decreased doses in patients with varying levels of decreased kidney function may be required according to the prescribing instructions [155]. Of note, linagliptin is excreted almost entirely through a hepatic route and can be used at all stages of CKD without dose adjustment [155].

6.4.5. Glucagon-like peptide-1 receptor agonists

The GLP-1RA CVOTs have shown this drug family to have positive effects on renal function, particularly reducing albuminuria [164]. GLP-1RAs are therefore of benefit to patients with even severely impaired renal function, particularly those at high risk for CVD, although there is currently no evidence in patients with ESRD, and therefore GLP-1RAs are not recommended in these patients. No dose reduction is required for the long-acting GLP-1RAs liraglutide, dulaglutide, and semaglutide in patients with eGFR >15 mL/min/1.73 m^2 as they are not excreted renally.

6.4.6. Sodium-glucose co-transporter-2 inhibitors

For prevention and treatment of diabetic nephropathy with eGFR ≥30 mL/min/1.73 m^2, the SGLT-2is are recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease as first-line treatment with metformin [165]. Although that is the recommendation from KDIGO, primary care professionals should always follow the instructions and the eGFR range found in the local labels of these chemical substances. At first, there was concern regarding the use of SGLT-2is in patients with reduced renal function due to their mechanism of action of inhibiting renal glucose transport [166]. However, EMPA-REG OUTCOME (testing empagliflozin), CREDENCE (testing canagliflozin), and DECLARE-TIMI 58 (testing dapagliflozin), along with several meta-analyses, have demonstrated that SGLT-2is reduce the risk of overall nephropathy events, creatinine doubling, and initiation of renal replacement therapy [111,167–170]. More recently, in the DAPA-CKD trial, dapagliflozin reduced the primary endpoint (composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or CV causes) by 39% [0.61 (0.51; 0.72)]. There was no statistical interaction for the primary endpoint based on T2D status, so the benefits were independent of glycaemic status. In addition, the composite of CV death or hospitalisation for HF was reduced by 29% [0.71 (0.55; 0.92)], and overall mortality by 31% [0.69 (0.53; 0.88)]. Finally, there were no new safety signals reported in the DAPA-CKD trial, in particular, no imbalances related to fracture, amputation, diabetic ketoacidosis, or serious renal events [171]. In the EMPEROR-Reduced trial, one of the secondary outcomes was the decline rate in eGFR. The empagliflozin group showed a slower annual decline rate in eGFR than the placebo group (–0.55 vs. –2.28 mL/min/1.73 m^2 of body-surface area per year) and a lower risk of serious renal outcomes [172]. The evidence for renal benefit is sufficient to warrant prioritising SGLT-2i treatment in patients with eGFR 30–60 mL/min/1.73 m^2, especially in the presence of microalbuminuria, even when these patients already exhibit good glycaemic control, as SGLT-2is have shown to be renoprotective. Accordingly, it is crucial to highlight the importance of measuring albumin-to-creatinine ratio (ACR) routinely to reduce progression to ESRD in patients with elevated ACR.

As outlined here, treatment options vary significantly by CKD stage, with significant variations of suggested dose reduction/discontinuation even within drug classes, so physicians are encouraged to consult prescribing instructions for specific agents.

6.5. Patients at high cardiovascular risk

Since T2D itself is considered a major risk factor for CVD, the remaining patients with T2D but without established CVD, with eGFR >60 mL/min/1.73 m^2, with normoalbuminuria and aged >40 years at diagnosis are considered to have high cardiovascular risk. In addition, patients with T2D are also likely to have additional cardiovascular risk factors, including overweight/obesity [173]. These patients with diabetes and without CVD but at high cardiovascular risk represent about half of those with T2D treated in primary care.

Lifestyle and nutrition changes in recent decades have led to a global increase in obesity and a cluster of related and interdependent conditions including dyslipidaemia, hypertension, non-alcoholic fatty liver disease (NAFLD), and insulin resistance leading to T2D. Together, this cluster of conditions is sometimes referred to as the metabolic syndrome [174,175]. Increased insulin resistance has been implicated as a precursor to many of these metabolic complications [176]. However, there is a growing appreciation for the heterogeneity of T2D, with only a subset of patients showing very high insulin resistance [177].

As in all patients, understanding the personal health goals and priorities of patients with T2D and without established CVD is critical. That said, there is evidence that patients with T2D are at much higher risk for ASCVD than those without diabetes [178], and CVD remains the most common cause of death in patients with T2D [179], making primary CVD prevention of great importance. In patients with T2D and established CVD, stringent HbA_{1c} targets may not be appropriate given the association between severe hypoglycaemia and increased risk of adverse macrovascular events [180], but in patients without established CVD, with their longer life expectancy, may experience microvascular benefits on a regimen of tighter glycaemic control [181]. As noted previously, some studies show that intensive treatment intervention early in the course of disease is associated with long-lasting benefits in reducing diabetes complications, known as a legacy effect. [67,71,72].

6.5.1. Sulphonylureas

Despite being one of the first oral antidiabetic drug classes available, SUs remain some of the most potent agents for lowering HbA_{1c} [182]. In terms of treatment durability, the ADOPT study showed that treatment with the SU glibenclamide resulted in faster progression to treatment failure than with other glucose-lowering agents [183], but more recent studies demonstrated similar treatment durability for SUs compared to newer drugs, although with a higher incidence of hypoglycaemias, weight gain, and higher proportion of patients needing treatment intensification [184,185].

Despite contradictory results with first-generation therapies, recent analyses on second- and third-generation SUs show they do not increase cardiovascular mortality or macrovascular events in comparison to other commonly used treatments [186]. These results are corroborated by the findings of the CAROLINA trial, which showed no difference in MACE with the SU glimepiride compared to the DPP-4i linagliptin in patients at elevated cardiovascular risk, although the risk of hypoglycaemia was significantly higher with SU than with DPP-4i [147]. Notably, the UK Prospective Diabetes Study (UKPDS) and follow-up studies of its cohort suggested SUs may also have microvascular benefits [71,187]. Because of their robust effects on glycaemic control and established cardiovascular safety, along with the lower cost of SUs compared to other classes of glucose-lowering drugs [188], these agents have a continued role in management of patients with T2D.

Gliclazide is preferable to others in the class [158] due to its improved treatment durability [189] and reduced risk of hypoglycaemia [190]. Additionally, its neutral effects on mortality and CVD were confirmed in the ADVANCE trial [191]. Glimepiride, which can be used when gliclazide is not available, can be considered as the next-best choice, with effective glycaemic control and lower rates of hypoglycaemia compared to glibenclamide [192]. While glibenclamide is the only SU available in many pharmacies in low-income countries [193], it is associated with increased mortality [194] and risk of severe hypoglycaemia [195] compared to other drugs in the class and should not be used unless no other options exist.

Drug access and economic factors will necessarily constrain treatment. If access and cost are no issue, DPP-4is, SGLT-2is, or GLP-1RAs are all preferable to SUs as second-line treatment of T2D. However, newer SUs remain important low-cost treatment options for many patients [11–13,196].

6.5.2. Glinides

The glinides, nateglinide and repaglinide, are insulin secretagogues with a similar mode of action to SUs, but a shorter duration of action [197]. Although they are not widely used, they remain treatment options in some countries, and have a role to play in managing glycaemia in patients with CKD. Although the cardiovascular effects of these treatments have not been extensively examined, repaglinide appears to have a cardiovascular and all-cause mortality profile similar to that of metformin [198]. Glinide therapy is associated with low risk of hypoglycaemia, with some studies showing a lower risk than SUs. Similarly, most studies show that glinide use is associated with modest weight gain, but perhaps less than that seen with SU therapy [197].

6.5.3. Pioglitazone

The insulin sensitiser pioglitazone is an option for patients without established CVD and who are not reaching their HbA_{1c} targets, particularly for patients with a metabolic syndrome profile where insulin resistance predominates. It provides HbA_{1c} reduction similar to metformin [199] with better treatment durability than SUs [200]. In addition to improvements in insulin resistance and therefore glycaemic control, pioglitazone also has beneficial effects on lipid profile [201].

As mentioned previously, pioglitazone treatment has been shown to reduce ASCVD in patients with established CVD, and data exists to suggest it has a similar effect in populations without established CVD [202]. The mechanism behind this cardioprotection may be attenuation of atherosclerosis, demonstrated in patients treated with pioglitazone compared with those taking glimepiride [203,204].

In addition to cardiovascular benefits, pioglitazone has also been shown to be beneficial in treatment of NAFLD and the more severe non-alcoholic steatohepatitis (NASH) by reducing liver fat content and hepatic fibrosis [205]. The pathophysiology of NAFLD/NASH is intimately related to insulin resistance [206], so the beneficial effect of pioglitazone is unsurprising.

Despite its benefits, pioglitazone use is cautioned in some patients. As mentioned previously, it should not be used in patients with symptomatic HF, since treatment with pioglitazone is associated with fluid retention and oedema in some patients, especially when used in combination with insulin or SUs [207]. It is also associated with weight gain [208] and so must be carefully considered in patients focused on weight loss. Pioglitazone treatment has been linked to increased risk of bone fracture, particular in postmenopausal women [209], so should be avoided in these patients and those with previous fracture. Some studies suggest prolonged pioglitazone use may be associated with an increased risk of bladder cancer [210], so its use in patients with history of or active bladder cancer should be avoided.

6.5.4. α-glucosidase inhibitors

The α-glucosidase inhibitor acarbose slows the rate of digestion and absorption of complex carbohydrates, decreasing postprandial hyperglycaemia [211]. Acarbose has a modest HbA_{1c} lowering effect that is more pronounced in patients with diets higher in carbohydrates [212]. Most RCTs of acarbose treatment have included patients with impaired glucose tolerance rather than T2D. The results of the effects on acarbose are mixed, with the STOP-NIDDM study showing significantly decreased risk of cardiovascular events in patients with impaired glucose tolerance treated with acarbose compared to placebo, while the ACE trial showed no significant difference in cardiovascular events between patients with established CVD treated with acarbose compared to placebo [213,214]. A Cochrane systematic review did not find evidence for an effect of acarbose on mortality or morbidity [215]. Acarbose is generally safe, with side effects largely limited to flatulence and mild diarrhoea [211] and requires a greater number of tablets per day than other drugs, which hinders adherence to treatment in patients who are usually polymedicated. Despite its relatively modest effects on glycaemic control, acarbose remains a popular option in some parts of the world, particularly in cultures with diets rich in carbohydrates.

6.5.5. Glucagon-like peptide-1 receptor agonists

As mentioned previously, data from CVOTs demonstrate that the long-acting GLP-1RAs liraglutide, semaglutide, and dulaglutide are cardioprotective [99,100,104]. Although LEADER and SUSTAIN 6 included both primary and secondary CV prevention patients, more than 80% of patients included in both trials had established CVD [99,100]. Thus, there is limited evidence for a protective role in patients without established CVD for liraglutide and subcutaneous semaglutide. However, nearly 70% of patients in the REWIND trial did not have established CVD, and dulaglutide treatment was still found to reduce the incidence of MACE [HR: 0.88 (0.79; 0.99), $p = 0.026$], so the evidence for dulaglutide in primary prevention of adverse cardiovascular events is somewhat stronger [104]. GLP-1RAs are safe in this population, and their effective glycaemic control without risk of hypoglycaemia makes them an attractive option for glucose control in patients without CVD.

The main adverse effects associated with the use of GLP-1RAs are gastrointestinal symptoms including nausea, diarrhoea, vomiting, decreased appetite, abdominal pain, and constipation [216,217]. In a recent *post hoc* analysis of the LEADER trial, an increase in the risk of gallstones and related complications was observed in the liraglutide-treated patients compared to the placebo control group, with consistent trends across all four categories of events (uncomplicated gallbladder stones, complicated gallbladder stones, cholecystitis, and biliary obstruction) [218]. Although prescribing guidelines note a possible, but uncommon or very rare, increased risk for acute pancreatitis, recent analyses of the effects of GLP-1RA treatment have argued against an association [219]. Importantly, GLP-1RA therapy is associated with a small but consistent reduction in blood pressure and an increase in heart rate [220].

6.5.6. Sodium-glucose co-transporter-2 inhibitors

As with the seminal GLP-1RA trials, the majority of patients treated with SGLT-2is in the EMPA-REG OUTCOME trial (>99%) and the CANVAS Program (>60%) had established CVD at baseline, making it difficult to confirm whether the cardioprotection seen in these trials extends to patients without established CVD [108,109]. However, the DECLARE-TIMI 58 trial explored dapagliflozin vs. placebo in a population in which only 40.6% had established ASCVD and demonstrated a lower risk of CV death and hospitalisation for HF [110].

SGLT-2is are associated with a clinically relevant decrease in blood pressure, which may be of benefit to the many patients with T2D who also have hypertension [221].

6.5.7. Insulin

If other treatment options have been explored and a patient is still not reaching glycaemic target, insulin should be used to avoid hyperglycaemia-associated microvascular complications. The risk for hypoglycaemia is higher for patients with T2D on insulin than on other glucose-lowering therapies [222]. For patients who have experienced hypoglycaemia, basal insulin analogues may be preferred. First-generation insulin analogues, including insulin glargine and insulin detemir demonstrate reduced risk of nocturnal hypoglycaemia compared to older generation insulins [223,224]. In turn, second-generation insulin analogues such as insulin degludec and insulin glargine U300 show reduced overall hypoglycaemia compared to their first-generation counterparts [225,226]. The choice of basal insulin should be made in a patient-centred manner in the context of informed discussions between patient and physician, considering issues of cost and drug access, as well as risk of hypoglycaemia and its impact on quality of life.

Full basal-bolus therapy should only be considered as a last resort when no other options are available, and it is expected to be needed in very few patients. For patients who remain above target after initiation of basal insulin, insulin/GLP-1RA combination therapies may be an attractive alternative to full basal-bolus therapy, leading to reduced weight gain compared to insulin therapy at equivalent or better glycaemic control [227,228].

Because the safety of most glucose-lowering therapies has not been confirmed in pregnancy, metformin and insulin treatment should be considered in women with T2D of childbearing potential [229].

6.6. Patients with obesity

The vast majority of patients with T2D have obesity or are overweight, and approximately 45% of patients with T2D have obesity [173]. Abdominal obesity in particular is the main driver of increasing insulin resistance which causes metabolic syndrome [230]. While some weight loss studies fail to confirm CV benefits [231,232], weight loss between 5 and 10% of starting body weight has been shown to be beneficial and should be a healthy lifestyle goal for most patients with T2D [233]. Also, patient-perceived outcomes, such as weight loss, can be helpful to keep patients motivated in improving adherence and diabetes control.

The ADA Standard of Care treatment guidelines include substantial evidence-based advice on weight control through diet and lifestyle and should be consulted when treating patients with obesity [11–13]. Evidence-based patient education programmes are recommended to assist patients and their families to pursue goals of weight management and healthy lifestyle.

It is important to keep in mind that many glucose-lowering agents cause weight gain, including most SUs, glinides, pioglitazone, and insulin [234].

Where possible, glucose-lowering therapies that promote weight loss should be used in patients who would benefit from weight management. Modest weight reductions are seen in patients treated with SGLT-2is [108–110]. Small but significant weight reductions are seen in patients treated with the GLP-1RAs lixisenatide (0.7 kg difference compared to the placebo group) and dulaglutide (1.5 kg compared to placebo) [104,105]. More substantial weight loss is seen in patients treated with the GLP-1RAs liraglutide (–2.3 kg vs. placebo) and subcutaneous and oral semaglutide (–4.3 and –3.4 kg vs. placebo, respectively) [99,100]. Some trials show greater reductions in HbA_{1c} and weight using higher doses of some GLP1-RAs (dulaglutide, liraglutide, and semaglutide), although there was only a small incremental improvement in glycaemic parameters when compared with the standard doses in the sub-cohorts of patients with T2D in these trials [235–237]. Overall, GLP-1RAs and SGLT-2is are recommended for patients whose weight loss is a treatment goal for risk reduction. For patients who require insulin treatment, fixed-ratio insulin/GLP-1RA combinations have been shown to mitigate insulin-associated weight gain [227,228]. The PIONEER programme included a diverse group of patients with T2D who had different disease durations, background therapies, and comorbidities (CVD or CKD). Data from this programme showed that oral semaglutide was effective for glycaemic control, as, at the end of treatment, at least 50% of the participants treated with oral semaglutide 14 mg had HbA_{1c} below the ADA target of 7.0%. In the global trials, up to 69% reached the outcome, a composite of HbA_{1c} <7.0% with no weight gain or severe or blood glucose-confirmed hypoglycaemia [238].

Overall, it is the role of the primary care physician to view the patient as a whole. To this end, patients with T2D at high cardiovascular risk should also be assessed and treated for non-diabetes-related risk factors such as smoking cessation, dyslipidaemia, and hypertension.

6.7. Elderly/frail patients

Due to the growing aging population in many countries, as well as the progressive nature of T2D, increasing numbers of patients with diabetes are elderly (≥65). Elderly patients are at greater risk of developing T2D complications due to the longer duration of disease and increasing physical and mental frailty further exacerbates this risk [239]. Age is also a major risk factor for CVD, especially after 65 years of age; therefore, good control in maintaining CV health is beneficial for the elderly [240–243]. A prospective study of elderly patients (≥70 years) with T2D investigated the relationship between HbA_{1c} levels and the risk of MACE by evaluating electronic health records from the universal public healthcare system in the Valencian Community, Spain. The study included more than 5,000 patients and showed that the MACE incidence was 20.6 per 1,000-person-years. Oral antidiabetic treatment was significantly associated with MACE incidence [HR: 0.74 (0.62; 0.89); $p = 0.001$], while age and HbA_{1c} were time-dependent [244]. Since older people are very heterogenous, if the goal of treatment is to prevent CV events, appropriate evidence-based treatments such as SGLT2-i or GLP1-RA should be considered. Nevertheless, we acknowledge that good quality of life is the primary goal of treatment for most elderly people with T2D, rather than CV event prevention per se.

Quality of life should be a priority focus for patients who are elderly/frail. Stringent glycaemic targets are unlikely to be appropriate in this population due to the reduced life expectancy in which to accrue microvascular benefits, and because of the increased risk of hypoglycaemia [245]. Polypharmacy is also challenging for patients who may be experiencing cognitive decline or limited independence, necessitating simple glucose-lowering regimens [246]. That said, poor glycaemic control is a risk factor for sarcopenia, which is a major contributor to age-related frailty [247]. This may be part of what drives the 'obesity paradox,' the epidemiological finding that higher body mass index is related to improved survival in patients who do suffer an adverse cardiovascular event [248]. Quality of life is also negatively affected by such short-term symptoms of hyperglycaemia as recurrent cystitis, mycosis, itching, drowsiness, nocturia and increasing incontinency [249,250]. Defining adequate glycaemic control should include consideration of these issues, which may increase a patient's dependence on caregivers. Diabetes management in the elderly/frail population must balance treatment-related safety, personalised quality of life and adequate glycaemic control [3].

Evidence in support of individual treatments in elderly/frail populations is somewhat limited, though treatment guidelines have been formulated for this population [251,252].

If possible, multiple daily injectable treatments and pre-mixed insulin should be avoided in this population. Insulin must be prescribed cautiously, and most SUs should also be avoided due to increased risk of hypoglycaemia. If insulin is to be used, care should be taken to choose a treatment which reduces this risk [253]. When frailty is associated with weight loss that adversely affects health, treatments that further decrease weight may not be appropriate. Physicians should also consider assessing executive function of the patient as part of deciding on therapeutic strategy. Adherence to medication should be regularly assessed in elderly patients and regimens simplified as needed. In patients with cognitive impairments, treatments with once-weekly dosing, such as some long-acting GLP-1RAs, could be a good option to facilitate adherence as they can be administered conveniently by caregivers. Medications such as metformin that are taken more than once per day may not be appropriate for patients who struggle with adherence. SGLT-2is should also be used with caution in frail patients due to the risk of volume reduction and potential falls.

DPP-4is can be important treatment options in the elderly/frail population, as they are well-tolerated with few side effects and associated with only modest HbA_{1c} reductions without increased risk of hypoglycaemia [254].

A systematic review and meta-analysis comprising 11 studies and involving almost 94,000 patients aimed to evaluate the CV effects of GLP1-RAs and SGLT-2is in elderly patients (≥65 years) with T2D. The authors reported that GLP1-RAs decreased MACE [HR: 0.86 (0.80; 0.92)], MI, stroke, and CV death, which is consistent with their effect in the overall population. SGLT-2is also reduced MACE [HR: 0.90 (0.83; 0.98)] but had no effect on its components. They also reduced the composite renal endpoint [HR: 0.57 (0.43; 0.77)], and HF hospitalisation [HR: 0.62 (0.51; 0.76)] [243]. Another systematic review and meta-analysis including three CVOTs and two subgroup analyses and involving a total of 17,105 elderly patients (≥65 years) with T2D proposed to assess the effect of SGLT-2is on MACE risk. The results showed that the MACE risk did not change with age in patients receiving SGLT-2i (no subgroup difference; $p = 0.15$). The HR for elderly patients was 0.83 (0.71; 0.96) [255].

7. Conclusions

Recent years have seen an explosion of new treatment options for T2D, and while detailed guidelines exist to guide specialists in the nuances of treating T2D, few guidelines are targeted to help the primary care physicians navigate the growing number of options. This updated position statement has been designed to provide practical advice to primary care physicians globally to give the best possible care to their full range of patients with T2D.

The author group used a consensus approach to arrive at the specific treatment recommendations for patients with T2D in various categories of comorbidity. To aid the busy primary care physician, these recommendations have been distilled to a visual tool (Box 1). A simple, evidence-based scheme has been proposed to stratify for cardiovascular risk in patients with T2D (Box 2). Specific recommendations are given for patients with very high cardiovascular risk (including those with ASCVD, HF and CKD; Boxes 3–5Box 3 , respectively), for patients with high cardiovascular risk (Box 6), for patients with obesity (Box 7) and for elderly/frail patients (Box 8). Lifestyle modifications and adequate glycaemic control should always be considered when treating patients with T2D to prevent or mitigate severity of microvascular complications.

CVD is one of the most prevalent comorbidities causally associated with T2D and is the primary reason for mortality in these patients [78]. A wealth of data exists and is still being generated on how to minimise CV risk and other complications in patients with T2D. Navigating the data associated with the myriad of available treatment options can be daunting and necessitates the synthesis of easy-to-use treatment guidelines. Despite the extensive specialist-generated literature, more research is required specifically on the outcomes of the majority of patients with T2D treated in primary care. Primary care physicians, as the first point of contact in the healthcare system, represent the 'front lines' of T2D care and are uniquely placed in a continuity of care setting to take a patient-centred, whole-patient approach to T2D management [256].

Conflict of interest

SS has received consultancy and speaker fees from Amgen, Boehringer Ingelheim, Napp Pharmaceuticals, Novartis and Roche; advisory board, consultancy and speaker fees from AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi; and trial grant funding from AstraZeneca, Janssen Pharmaceutica, Sanofi and Servier Laboratories. XC has received consultancy and speaker fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche and Sanofi; and grant funding from AstraZeneca, Boehringer Ingelheim, Novartis and Sanofi. SB has received advisory board and speaker fees from AstraZeneca, Bayer, Eli

Box 3
Treatment recommendations for patients with ASCVD.

- Consider initiating metformin + SGLT-2i/GLP-1RA rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT-2i or GLP-1RA with proven cardiovascular benefit as second-line therapy (A)
- Use basal insulin with caution when other options have failed, and glycaemic targets are not met (E)

Box 4
Treatment recommendations for patients with HF.

- Consider initiating metformin + SGLT-2i rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT-2i as second-line therapy (A)
- Avoid pioglitazone (A) and saxagliptin (A) and use basal insulin with caution (B)

Box 5
Treatment recommendations for patients with CKD.

- Consider initiating metformin + SGLT-2i rather than stepwise (E), according to the approved restrictions of dose and indications by eGFR
- Metformin as first-line therapy if eGFR $\geq$30 mL/min/1.73 m^2 (A)
- SGLT-2i as second-line therapy (eGFR range as determined per local label) (A), even when well-controlled on metformin alone (E)
- GLP-1RA as third-line therapy or if previous treatments are not tolerated (A), followed by DPP-4i (A)
- Reduce dose of glinides and reduce dose or discontinue SUs if eGFR $<$45 mL/min/1.73 m^2 to reduce the risk of hypoglycaemia (A)

Box 6
Treatment recommendations for patients at high cardiovascular risk.

- Consider initiating metformin + SGLT-2i/GLP-1RA/DPP-4i rather than stepwise (E)
- Metformin as first-line therapy (A)
- SGLT-2i or GLP-1RA or DPP-4i as second-line therapy where cost is not prohibitive (A). Of these, SGLT-2i or GLP-1RA with proven cardiovascular benefit is preferred (E)
- Newer-generation SUs or glinides when drug cost must be minimised (A)
- Pioglitazone in patients with NAFLD and where insulin resistance predominates (A)
- Basal insulin when other therapies have been explored and glycaemic targets are not met (E)
- Full basal-bolus insulin therapy only as a last resort (E)

Box 7
Treatment recommendations for patients with obesity.

- Consider initiating metformin + GLP-1RA/SGLT-2i rather than stepwise (E)
- Metformin as first-line therapy (A)
- GLP-1RA or SGLT-2i as second-line therapy (A)
- Where possible, avoid treatments that cause weight gain, including most SUs, glinides, pioglitazone and insulin (A)
- If basal insulin is required, consider fixed-ratio insulin/GLP-1RA combinations, if available (A)

Lilly and Novo Nordisk; advisory board fees from Abbott Laboratories, Novo Nordisk, Sanofi and Xeris Pharmaceuticals; and speaker fees from Eli Lilly. SBH has received advisory board and consultancy fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceutica, Merck, Novo Nordisk and Sanofi. SJ received speaker fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi. MM-C has received fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi; and grant funding from AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme and Sanofi. AMJN has received speaker fees from Becton Dickinson; and advisory board feed from Sanofi. PT has received advisory board,

Box 8
Treatment recommendations for elderly/frail patients.

- Avoid stringent glycaemic targets that increase risk of hypoglycaemia (E)
- Metformin as first-line therapy if tolerated and not contraindicated (A)
- DPP-4i is a safe and easy to use option (A)
- Assess adherence and avoid multiple daily injectable medications when possible (E)

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Data availability

Data will be made available on request.

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