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REVIEW ARTICLE

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Sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes: Barriers and solutions for improving uptake in routine clinical practice

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Abstract

Recent advances in type 2 diabetes (T2D) research have highlighted the benefits of sodium-glucose co-transporter-2 (SGLT-2) inhibitors, including cardiovascular and renal protection. However, uptake rates of these drugs remain low in patients with T2D, particularly in subpopulations most likely to benefit from them. This review considers the potential barriers to prescribing SGLT-2 inhibitors in T2D in clinical practice and outlines potential multidisciplinary recommendations to overcome these barriers. Safety concerns and a lack of clarity in and divergence of guidelines around the introduction of SGLT-2 inhibitors into treatment regimens may represent a barrier to uptake from the clinicians' perspective, including a general lack of understanding of the benefits associated with SGLT-2 inhibitors. Patient characteristics, such as socioeconomic status, may influence uptake because of the cost of SGLT-2 inhibitors, especially in the United States, where health insurance coverage could be a concern. SGLT-2 inhibitor prescription rates vary between clinical specialty (endocrinology, primary care, cardiology, and nephrology) and country, with cardiologists the lowest prescribers, and endocrinologists the highest. Primary care practitioners may experience more challenges in following SGLT-2 inhibitor-related guidelines than diabetes specialists as there may be fewer opportunities for education on how this drug class improves cardiovascular and

renal outcomes in patients with T2D. Uptake rates appear to vary between countries because of differences in guidelines and health insurance systems. The amendment of SGLT-2 inhibitor-related guidelines for more multidisciplinary use and the implementation of patient and clinician education may encourage uptake of these drugs, potentially improving long-term health outcomes among patients with T2D.

KEYWORDS
guidelines, sodium-glucose co-transporter-2 inhibitors, type 2 diabetes, uptake

1 | INTRODUCTION

Diabetes is a rising global healthcare burden associated with increased mortality and reduced life expectancy because of associated cardiovascular, kidney, and liver disease, and it represents one of the top 10 leading causes of death globally.[1] Approximately one in 11 adults worldwide now have diabetes, 90% of whom have type 2 diabetes (T2D).[2] Currently, most clinical practice guidelines and position statements recommend metformin as first-line therapy for individuals with T2D.[3–5]

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are a comparatively new class of medications indicated for the treatment of T2D because they decrease kidney glucose reabsorption, thus increasing urinary glucose excretion and lowering blood glucose levels.[6,7] In turn, SGLT-2 inhibitors reduce intraglomerular pressure, thereby preventing kidney disease and slowing its progression.[8] The renoprotective effects associated with SGLT-2 inhibitors are generally observed over a wide range of estimated glomerular filtration rate (eGFR) ranges and albuminuria categories.[9]

Results of large-scale randomised clinical trials of SGLT-2 inhibitors, such as dapagliflozin and empaglifozin, showed clear treatment benefits on cardiovascular and renal outcomes in patients with T2D.[10–14] In the CANVAS Program, patients with T2D treated with canagliflozin had a lower risk of composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke than those who received placebo (26.9 vs. 31.5 participants per 1000 patient-years, respectively; hazard ratio [HR] 0.86; 95% CI 0.75-0.97; $P < .001$ for non-inferiority).[10,11] Canagliflozin may also have a possible benefit with respect to the progression of albuminuria.[11] In the DECLARE-TIMI 58 trial, dapagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure by 17% (HR 0.83; 95% CI 0.73-0.95; $P = .005$) and the cardiorenal secondary composite outcome (≥ 40% decrease in eGFR to < 60 ml/min/1.73m^2, new end-stage renal disease, or death from renal or cardiovascular causes) was significantly reduced with dapagliflozin versus placebo (HR 0.76; 95% CI 0.67-0.87; $P < .0001$).[12,14,15] In the DAPA-CKD trial, the risk of a composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes, was significantly lower with dapagliflozin than with placebo in patients with chronic kidney disease (CKD) with and without T2D in the DAPA-CKD trial (9.2% [197/2152] vs. 14.5% [312/2152], respectively; $P < .001$). In the EMPA-REG OUTCOME trial, patients treated with empagliflozin had significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9% in the placebo group; 38% relative risk reduction).[13]

Despite recent recommendations from the American Diabetes Association (ADA), American College of Cardiology (ACC), Kidney Disease: Improving Global Outcomes (KDIGO), and European Society of Cardiology (ESC) in collaboration with European Association for the Study of Diabetes (EASD) on the use of SGLT-2 inhibitors in T2D management[16–19] (Figure 1), prescription rates in patients with T2D remain low in day-to-day clinical practice.[20,21] The aim of this review is to identify potential barriers to prescribing SGLT-2 inhibitors in patients with T2D, addressing viewpoints from endocrinology, cardiology, nephrology, and primary care, and to propose targeted solutions to overcome these barriers. Opinions for this review were gathered during an expert roundtable discussion involving all authors.

2 | COMPLEXITY AND DIVERGENCE OF GUIDELINES MAY REPRESENT A BARRIER TO THE INITIATION OF SGLT-2 INHIBITORS BY CLINICIANS

Several inconsistencies lie within the current clinical guidelines for second-line therapy in T2D. The 2019 ADA/EASD consensus report recommends SGLT-2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for: patients with CKD; those with established—or at high risk of developing—atherosclerotic cardiovascular disease; or heart failure.[23] For individuals without these conditions, five non-insulin second-line therapy options are listed, without a suggested hierarchy of use.[23] The American Association of Clinical Endocrinologists/American College of Endocrinology 2019 consensus statement suggests that SGLT-2 inhibitors and GLP-1 RAs may be preferred as first-line therapy in patients with recent-onset T2D.[23] Despite the shown cardioprotective benefits of GLP-1 RAs and SGLT-2 inhibitors, overall usage in UK clinical practice remains low in adults with T2D and slightly lower in those with pre-existing CVD history, based on data from the Clinical Practice Research Datalink.[25] Four oral

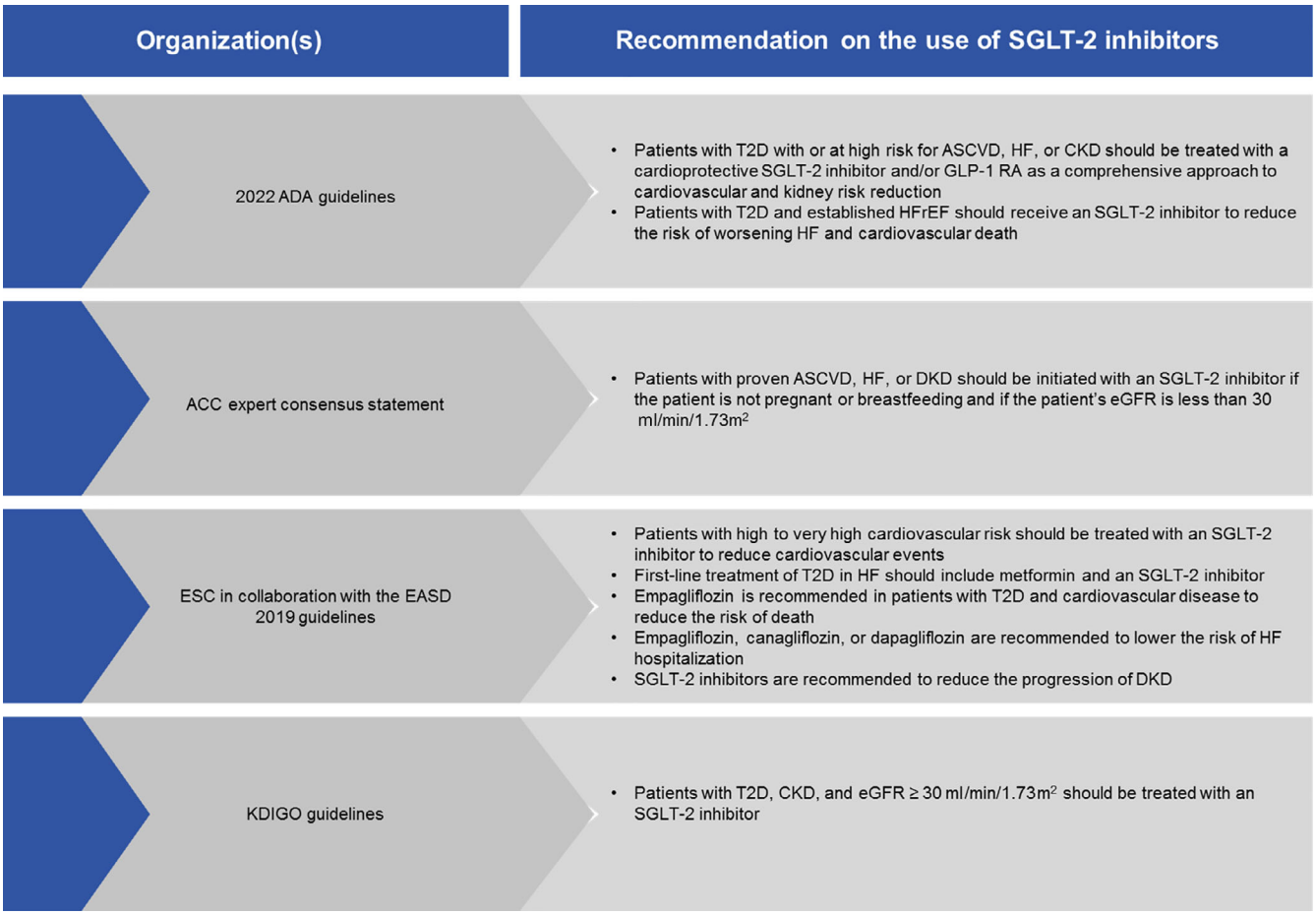

FIGURE 1 An overview of recommendations by the ADA, ACC, KDIGO, and the ESC in collaboration with EASD on the use of SGLT-2 inhibitors in patient populations.[16–18,86] ACC, American College of Cardiology; ADA, American Diabetes Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DKD, diabetic kidney disease; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; SGLT-2 inhibitor, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes

treatment options (sulphonylureas, thiazolidinediones, SGLT-2 inhibitors, or dipeptidyl peptidase-4 [DPP-4] inhibitors) are recommended by the American College of Physicians.[26]

Guidelines on when to initiate SGLT-2 inhibitors may benefit from further clarity.[17,27–30] The ADA guidelines suggest that SGLT-2 inhibitors and GLP-1 RAs should be considered for patients with T2D and CKD who require another agent in conjunction with metformin to target HbA1c levels or those who cannot tolerate or use metformin.[31] The lowering of HbA1c associated with SGLT-2 inhibitors has been shown to be limited in patients with T2D with an eGFR of less than 45 ml/min/1.73m^2.[3] However, emerging evidence from clinical trials suggests that SGLT-2 inhibitors have a cardioprotective and renal protective role not associated with glucose lowering in patients with an eGFR as low as 25-30 ml/min/1.73m^2.[8,27,32] Indeed, the cardiorenal benefits of SGLT-2 inhibitors are consistent across the eGFR range, including stage 4 CKD.[33] A reduction in heart failure hospitalization has also been observed across the different albuminuria subgroups in the CANVAS Program.[34]

Guidance on how to best address co-medications such as diuretics, renin-angiotensin system inhibitors, and blood pressure medications could be more extensive. In addition, advice on how to mitigate and manage DKA could be more prominent; research indicates that very-low-carbohydrate or ketogenic diets should be avoided by patients receiving SGLT-2 inhibitors,[35] however, many guidelines do not currently reflect this information in detail.

Some clinicians may express uncertainty as to how to define specific indications such as congestive heart failure and heart failure with reduced ejection fraction (HFrEF), as their definitions may differ across clinical trials, or may be challenging to diagnose in general practice.[36,37] Furthermore, clinicians working in areas such as primary care may not necessarily be exposed to guidelines tailored to diverging areas including nephrology, cardiology, and endocrinology. Therefore, consistency across specialty guidelines with regards to the use and approved indications for SGLT-2 inhibitors would aid ease of implementation. Suggestions on how to tailor current guidelines for multidisciplinary use are provided in Figure 2.

3 | CLINICIANS' CONCERNS AND PRESCRIBING TRENDS

Potential safety concerns associated with SGLT-2 inhibitors remain an issue for some clinicians, particularly in primary care, which may underlie a reluctance to prescribe these medications (Figure 3), despite the overall benefits in the mitigation of heart failure[38] and CKD[8] risks. For instance, acute, reversible eGFR decline may occur at around 4 weeks after SGLT-2 inhibitor initiation because of augmented distal nephron sodium delivery, ultimately leading to a reduction in glomerular hyperfusion and hyperfiltration.[39] This acute eGFR decline led to concerns around the safety of SGLT-2 inhibitors because of the perceived risk of acute kidney injury (AKI) with these therapies, but recent data confirm that this eGFR decline is not associated with AKI as these rare events mainly occur as a result of volume depletion.[39] Studies evaluating the eGFR slope suggest that a larger eGFR dip generally shows a stronger benefit of SGLT-2 inhibitors compared with placebo; sustained benefit in decreasing the eGFR slope has been shown for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin compared with placebo.[40,41] The cardiorenal benefits of SGLT-2 inhibitors were maintained regardless of this eGFR decline. Therefore, this initial eGFR decline should not lead to safety concerns or be a barrier to the uptake of SGLT-2 inhibitors.[39]

The permitted prescribing eGFR range for glycaemic control in patients with T2D can vary across SGLT-2 inhibitors.[42,43] Recommendations on the use of an SGLT-2 inhibitor to achieve renoprotection for patients with T2D and diabetic kidney disease (DKD) based on eGFR threshold can also vary across SGLT-2 inhibitors.[42,44] Differences in the prescribing information across SGLT-2 inhibitors thus may cause confusion among clinicians and potentially act as a barrier to their uptake.

An additional safety concern was highlighted in a Drug Safety Communication issued by the US Food and Drug Administration in 2015 warning of events adjudicated as DKA because of SGLT-2 inhibitor use in T2D.[45] The potential risk of DKA corresponded to a marked decline in overall SGLT-2 inhibitor use in the United States, despite events being rare in patients with T2D (~0.1%)[44] when SGLT-2 inhibitors are correctly prescribed,[35,45] even in severely ill, hospitalized patients.[46] A key clinical strategy should be that clinicians and patients with T2D are informed of the risks of SGLT-2 inhibitors and provided with support prior to initiation in order to mitigate DKA risk. Data from the recently published DARE-19 trial suggest that SGLT-2 inhibitors are well tolerated and associated with a low incidence of confirmed DKA events in patients who had T2D at baseline (0.3% [2/613] in the dapagliflozin group); these DKA events were non-severe and resolved after discontinuation.[46]

Other rare adverse events potentially related to empagliflozin, canagliflozin, and ertugliflozin use include urosepsis (0.4% [17/4687] in the EMPA-REG trial)[13] and pyelonephritis (0.3%; 13/4687).[47–49] The safety profile of SGLT-2 inhibitors is nevertheless well established[50] and many studies report benefits beyond glycaemic

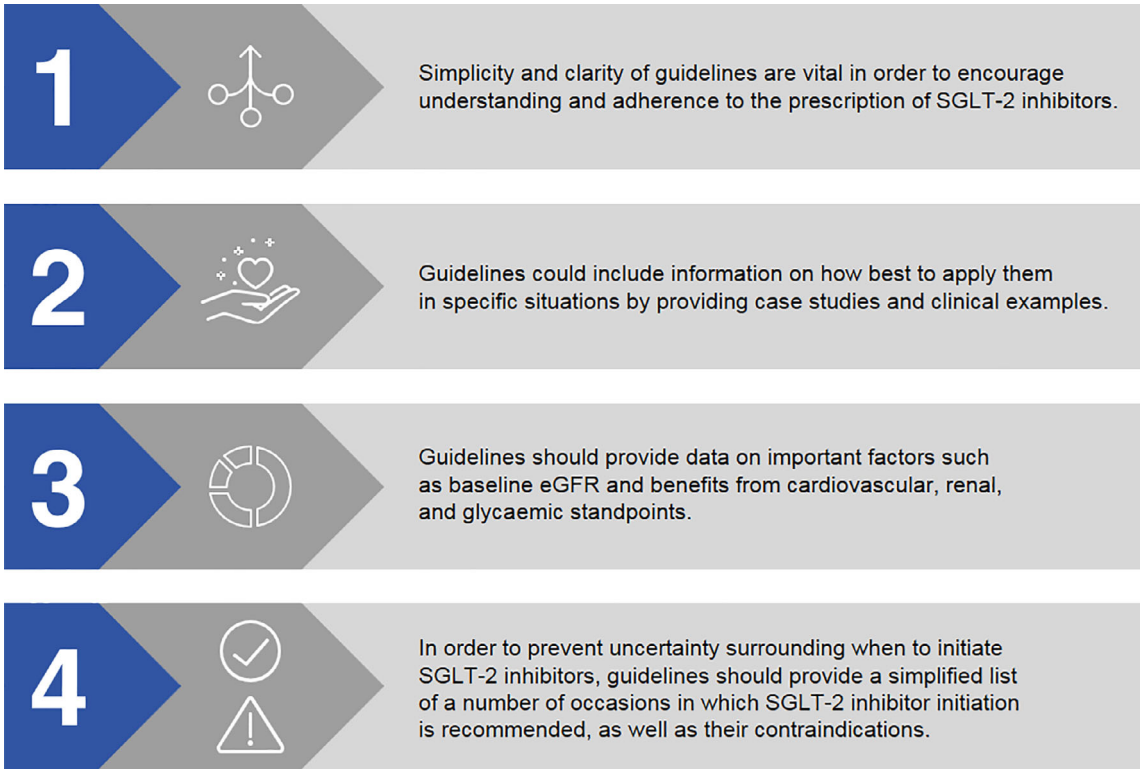

FIGURE 2 A summary of potential ways in which guidelines for type 2 diabetes management could be improved for multidisciplinary use. eGFR, estimated glomerular filtration rate; SGLT-2, sodium-glucose co-transporter-2

FIGURE 3 Benefits of sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes and potential adverse events. BP, blood pressure; DKA, diabetic ketoacidosis; HbA1c, glycated haemoglobin; HF, heart failure. [a]Hu M, et al.[88]; [b]Perkovic V, et al.[11]; [c]Pereira MJ and Eriksson JW[89]; [d]Lopaschuk GD and Verma S[90]; [e]Musso G, et al.[91]; [f]Vardeny O and Vaduganathan M[32]; [g]Williams SM and Ahmed SH[92]

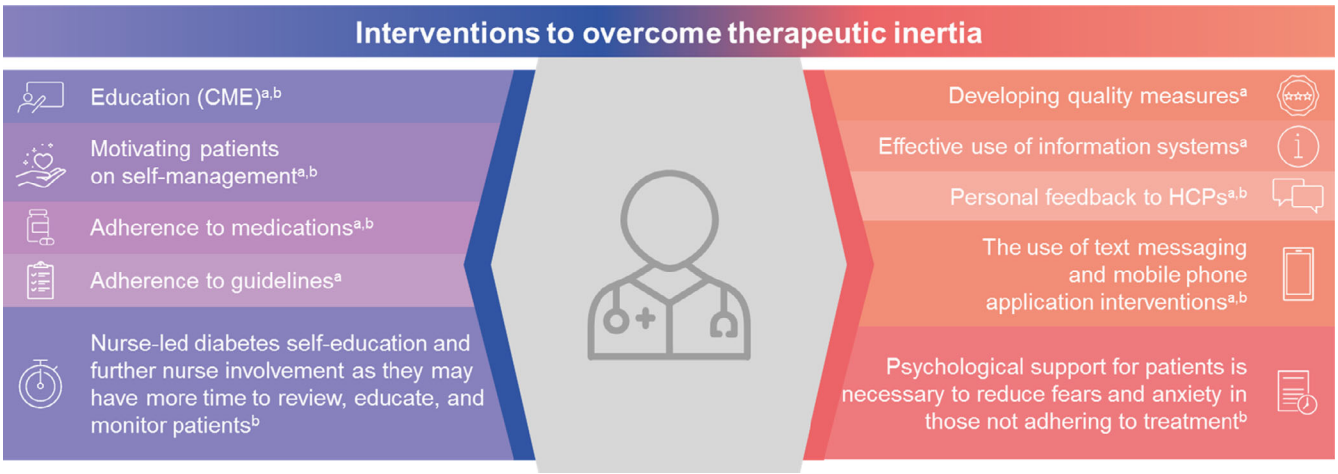

FIGURE 4 Potential interventions to overcome therapeutic inertia in patients with type 2 diabetes. CME, continuing medical education; HCPs, healthcare professionals. [a]Zafar A, et al.[54]; [b]Khunti S, et al.[53]

control, including cardiovascular and kidney protection.[11,38,51] Despite these benefits, therapeutic inertia among clinicians may play a role in the lack of uptake of this class of drugs, with many clinicians continuing to focus on glycaemic control as the primary outcome in the treatment of T2D.[21,52] There may be potential interventions to overcome therapeutic inertia[53,54] (Figure 4). The ADA have also recognized the potential impact of therapeutic inertia and have proposed a robust initiative to combat this, such as leveraging electronic health record and clinical-support tools, developing a registry of effective strategies, and targeting payer policies.[55]

A UK study of 81 532 patients with T2D conducted in 2017 indicated that DPP-4 and SGLT-2 inhibitors represented the most common second- and fourth-line therapies in primary care, respectively. An observed rapid increase in the use of these two drugs from 2010 to 2017 correlated with overall improvements in weight gain and rates of hypoglycaemia, although a causal relationship cannot be inferred from these results.[56] Another study found that 19.1%-27.6% of 238 619 patients with diabetes in Australia, Canada, England, and Scotland were prescribed DPP-4 inhibitors, while only 10.1%-15.3% were prescribed SGLT-2 inhibitors.[4] A further study observed that only 5.2% of patients with T2D who met the major eligibility criteria for EMPA-REG OUTCOME in the United States were initiated on SGLT-2 inhibitors in clinical practice.[57] However, prescription rates of SGLT-2 inhibitors in the United States appear to have increased from 2013 to 2020 in patients with DKD, particularly those aged younger than 65 years.[58]

SGLT-2 inhibitor prescribing trends appear to vary between specialties and countries.[59] A 2021 study of 440 599 patients with T2D identified large global variations in SGLT-2 inhibitor prescribing trends across 13 countries, with Canada and Israel showing the steepest increases. With regard to trends between specialties, data suggest that endocrinologists are the most probable to initiate an SGLT-2 inhibitor (10%-15% higher initiation than for non-endocrine specialties; $P < .001$).[45] However, less than 10% and 20% of UK-[60] and United States-based[61] patients with diabetes, respectively, see an endocrinologist. Cardiologists are among the lowest prescribers of SGLT-2 inhibitors (< 1%-< 5%),[57,58,62] possibly because of their concerns regarding adverse effects such as lower limb amputations or drug interactions.[32] However, the recent additions to the ESC guidelines, which recommend dapagliflozin or empagliflozin for patients

with HFrEF regardless of diabetes status, may encourage the uptake of SGLT-2 inhibitors among cardiologists.[63] In addition, primary care physicians may not be fully aware of the cardiovascular and renal protective roles of SGLT-2 inhibitors in T2D because of fewer educational opportunities regarding cardiovascular and renal disease in relation to diabetes, potentially leading to therapeutic inertia.[64] Lack of communication between clinicians may act as a further barrier to prescribing SGLT-2 inhibitors, especially if clearance is believed to be required from the patient's general practitioner (GP) or endocrinologist.[65] Therefore, collaborative care models with joint visits with clinicians from different specialties including endocrinology, nephrology, primary care, and cardiology may streamline communication and optimize therapeutic outcomes.

4 | PATIENT CHARACTERISTICS MAY INFLUENCE SGLT-2 INHIBITOR UPTAKE

Concern regarding adverse effects including genital mycotic infections and polyuria may serve to inhibit some patients' willingness to commence taking SGLT-2 inhibitors.[45] Conversely, weight loss and HbA1c-lowering benefits appear to motivate patients to initiate SGLT-2 inhibitors, which may be attributed to the majority of patients with T2D being overweight or obese.[66] Reluctance to initiate SGLT-2 inhibitors may be curbed if the various benefits and side effects are thoroughly explained in a balanced manner, and if patients feel included in the decision-making process. The ADA and EASD guidelines provide an effective integration of patient-centred strategies to achieve optimal outcomes in those with T2D, but may lack in parallel guidance and more targeted education on antidiabetic drug options that could be fully understood on a patient level, therefore clinician–patient communication is paramount.[67] Patients with a more thorough understanding of antidiabetic medications have been reported to show better glycaemic control and this could improve adherence.[68] Diabetes self-management education is also encouraged to facilitate the skills and knowledge necessary for diabetes self-care, including understanding the prevalence of cardiovascular (> 30%)[69] and renal (> 20%)[70] complications of diabetes and how they can be prevented or delayed with the use of SGLT-2 inhibitors.[71]

In the United States, patients may be influenced by direct-to-consumer (DTC) advertising of drugs, with those marketed to induce weight loss selected preferentially by patients beyond medications that possess less visible benefits such as functional heart or kidney improvement. Such preferences could be—in part—attributed to a lack of information on the role of SGLT-2 inhibitors in preventing progression to heart and renal failure.[72]

Race/ethnicity, gender, age, and socioeconomic differences are evident in SGLT-2 inhibitor uptake rates because of poorer access to quality healthcare and possible biases in healthcare delivery. In the United States, Black adults are among those least likely to receive an SGLT-2 inhibitor, despite this patient subset experiencing a disproportionately higher burden of cardiovascular and kidney diseases[73] and being more likely to request a prescription drug in response to DTC advertising than other ethnic groups.[74] A large cohort study identified an independent association of Black race (adjusted odds ratio [aOR] 0.83; 95% CI 0.81-0.85; $P < .001$) and Asian race (aOR 0.94; 95% CI 0.90-0.98; $P < .001$) with lower rates of SGLT-2 inhibitor use compared with Caucasians.[73] Female patients (aOR 0.84; 95% CI 0.82-0.85; $P < .001$) were also less probable to receive an SGLT-2 inhibitor than male patients.[73] Paradoxically, young, low-risk, non-Black patients with commercial health insurance have been found to be the most probable to be treated with SGLT-2 inhibitors,[45] while patients with heart failure, kidney disease, prior hypoglycaemia, and myocardial infarction are less probable to be prescribed an SGLT-2 inhibitor, despite evidence supporting the benefits of their use in these patients.[45] Prescription rate disparities have also been reported in the UK, where Black and Asian patients with T2D may be less likely to be prescribed GLP-1 RAs and SGLT-2 inhibitors than other ethnic groups.[75]

5 | COST-EFFECTIVENESS OF SGLT-2 INHIBITORS REMAINS AN OBSTACLE

Affordability and access to SGLT-2 inhibitors represent significant barriers to their uptake in patients with T2D (including those with heart failure, CKD, and albuminuria), particularly in the United States, because of the heterogeneity in costs within the healthcare system.[32,76] A 2021 study provided data of US median monthly average wholesale prices (AWP) of SGLT-2 inhibitors; median monthly AWP were comparable across SGLT-2 inhibitors, costing US$621, US$627, and US$622 for dapagliflozin, empagliflozin, and canagliflozin, respectively, although out-of-pocket co-pay costs are often considerably lower.[27] Other non-insulin glucose-lowering agents were much more affordable, with the reported monthly AWP for sulphonylureas ranging from US$52 to US$93.[27] However, SGLT-2 inhibitors may be more cost-effective than insulin and sulphonylureas[77] and are associated with increased quality-adjusted life years because of weight loss and decreased prevalence of cardiovascular morbidities;[78] payers and formulary committees should be made aware of these key data.[79] The 2019 ADA/EASD consensus report further highlights that choosing an antidiabetic drug class with the lowest acquisition cost can be an issue when managing patients with T2D whose HbA1c levels are above target.[23]

Variations in US health insurance coverage are also a key factor in prescription rates in T2D, with some insurance companies covering only selected SGLT-2 inhibitors: for instance, ertugliflozin is offered by only 6% of coverage plans.[80] Cost and insurance coverage will therefore largely determine which SGLT-2 inhibitor is selected.[81] In the United States, patient insurance co-payment monthly costs can range from under US$10 to US$600 for SGLT-2 inhibitors;[82] patients from high-income households (aOR 1.08; 95% CI 1.05-1.10; $P < .001$) are thus more probable to receive SGLT-2 inhibitors for patients with a median annual income of at least US$100 000.[73] The co-payment system is therefore highly individual, and medication use is dictated

by what each patient is able to afford on a case-by-case basis, especially in those on multiple T2D, hypertension, and cholesterol medications.

In Europe, prescription rates are less affected by health insurance coverage, however, other factors appear to affect uptake. Reimbursement criteria may vary across countries, with diabetes-related performance indicators such as HbA1c levels being incorporated into payer performance measures.[79] For example, in Italy, reimbursement legislation prevents GPs from prescribing SGLT-2 inhibitors without specialist approval, representing a large barrier to SGLT-2 initiation. As a result, the most common initial treatment for T2D is metformin in both monotherapy and combination therapy with sulphonylureas.[83] Primary care practitioners are able to prescribe SGLT-2 inhibitors in Spain with no major reimbursement limitations.[84] However, primary care practitioners are alerted when exceeding the estimated prescription rate threshold. This acts as an indicator rather than as a strict barrier, but may discourage some clinicians from prescribing SGLT-2 inhibitors. No such SGLT-2 inhibitor prescription restrictions exist in the UK, yet 2017 data highlighted low prescribing trends nonetheless, with DPP-4 inhibitors initiated most frequently (57%), followed by SGLT-2 inhibitors (18%).[85] These data are consistent with the NICE guidelines, which recommend DPP-4 and SGLT-2 inhibitors for first and second optimization of treatment, respectively.[86] The multiple barriers to SGLT-2 inhibitor uptake in current clinical practice and proposed solutions are provided in Figure 5.

6. CONCLUSIONS

The decision to initiate SGLT-2 inhibitor therapy in T2D is probably impacted by multiple factors including inconsistencies in guideline recommendations, safety concerns, patient characteristics, cost considerations, and the specialty of the healthcare provider. In order to improve uptake, further education of both patients and providers regarding the benefits versus the risks of SGLT-2 inhibitors in patients with T2D is needed. Support, particularly early in the treatment course, and with standpoints from all relevant specialties, including cardiology, nephrology, endocrinology, and primary care, independent of glycaemic benefits, is needed.

With regard to guidelines, safety issues associated with SGLT-2 inhibitors must be clarified, with clear guidance on patient eligibility provided, and indications such as CKD, heart failure, and cardiovascular disease must be defined clearly to provide further clarity for prescribing clinicians. Formulary committees should consider the cost-effectiveness of SGLT-2 inhibitor medications and quality-adjusted life years. Ultimately, more uniform implementation of this therapy in

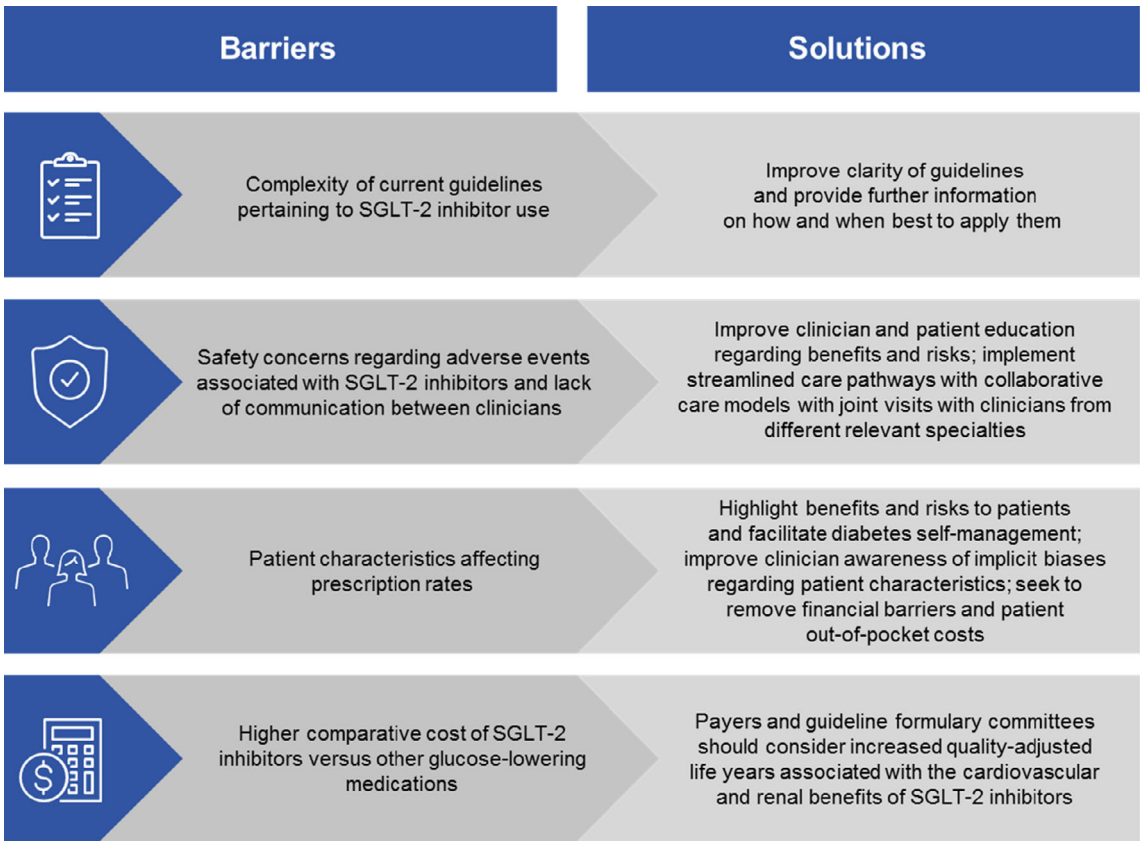

FIGURE 5 A summary of barriers to the uptake of sodium-glucose co-transporter-2 (SGLT-2) inhibitors in clinical practice and proposed solutions

line with trial findings and labelled indications could improve outcomes for patients with T2D.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors contributed to the roundtable discussion, the drafting of the manuscript, and critical revision for intellectual content.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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