




REVIEW ARTICLE

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

Kamlesh Khunti MD, PhD^{1,2}  | Serge Jabbour MD³  | Xavier Cos MD, PhD^{4,5} |
Sunder Mudaliar MD^{6,7} | Christian Mende MD⁸ | Marc Bonaca MD⁹ |
Paola Fioretto MD, PhD¹⁰ 

¹Diabetes Research Centre, College of Medicine, Biological Sciences and Psychology, University of Leicester, Leicester, UK

²NIHR Applied Research Collaboration - East Midlands, Leicester, UK

³Thomas Jefferson University, Philadelphia, Pennsylvania, USA

⁴Sant Marti de Provençals Primary Care Centres, Barcelona, Spain

⁵Institut Català de la Salut. IDIAP Jordi Gol. DAP_Cat Study Group CIBERDEM, Universitat Autònoma de Barcelona, Barcelona, Spain

⁶Department of Medicine, University of California, San Diego School of Medicine, San Diego, California, USA

⁷Veterans Affairs Medical Center, San Diego, California, USA

⁸Department of Medicine, University of California San Diego, La Jolla, California, USA

⁹Department of Medicine, Division of Cardiology, University of Colorado School of Medicine, Aurora CO; CPC Clinical Research, Aurora, Colorado, USA

¹⁰Department of Medicine, University of Padua, Unite of Medical Clinic 3, Hospital of Padua, Padua, Italy

Correspondence

Kamlesh Khunti, FRCGP, FRCP, MD, PhD,
FMedSci, Diabetes Research Centre, College
of Medicine, Biological Sciences and
Psychology, University of Leicester,
Gwendolen Road, Leicester LE5 4PW, UK.
Email: kk22@leicester.ac.uk

Funding information

Funding was provided by AstraZeneca for the development of this manuscript and expert participation in the roundtable discussion that formed the basis of the content.

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

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

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 empagliflozin, 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 ($\geq 40\%$ decrease in eGFR to < 60 ml/min/1.73m², 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 management¹⁶⁻¹⁹ (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

Organization(s)	Recommendation on the use of SGLT-2 inhibitors
2022 ADA guidelines	<ul style="list-style-type: none"> • Patients with T2D with or at high risk for ASCVD, HF, or CKD should be treated with a cardioprotective SGLT-2 inhibitor and/or GLP-1 RA as a comprehensive approach to cardiovascular and kidney risk reduction • Patients with T2D and established HFrEF should receive an SGLT-2 inhibitor to reduce the risk of worsening HF and cardiovascular death
ACC expert consensus statement	<ul style="list-style-type: none"> • Patients with proven ASCVD, HF, or DKD should be initiated with an SGLT-2 inhibitor if the patient is not pregnant or breastfeeding and if the patient's eGFR is less than 30 ml/min/1.73m²
ESC in collaboration with the EASD 2019 guidelines	<ul style="list-style-type: none"> • Patients with high to very high cardiovascular risk should be treated with an SGLT-2 inhibitor to reduce cardiovascular events • First-line treatment of T2D in HF should include metformin and an SGLT-2 inhibitor • Empagliflozin is recommended in patients with T2D and cardiovascular disease to reduce the risk of death • Empagliflozin, canagliflozin, or dapagliflozin are recommended to lower the risk of HF hospitalization • SGLT-2 inhibitors are recommended to reduce the progression of DKD
KDIGO guidelines	<ul style="list-style-type: none"> • Patients with T2D, CKD, and eGFR \geq 30 ml/min/1.73m² should be treated with an SGLT-2 inhibitor

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/1.73m².³ 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/1.73m².^{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 multi-disciplinary 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 failure³⁸ and CKD⁸ 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 established⁵⁰ and many studies report benefits beyond glycaemic

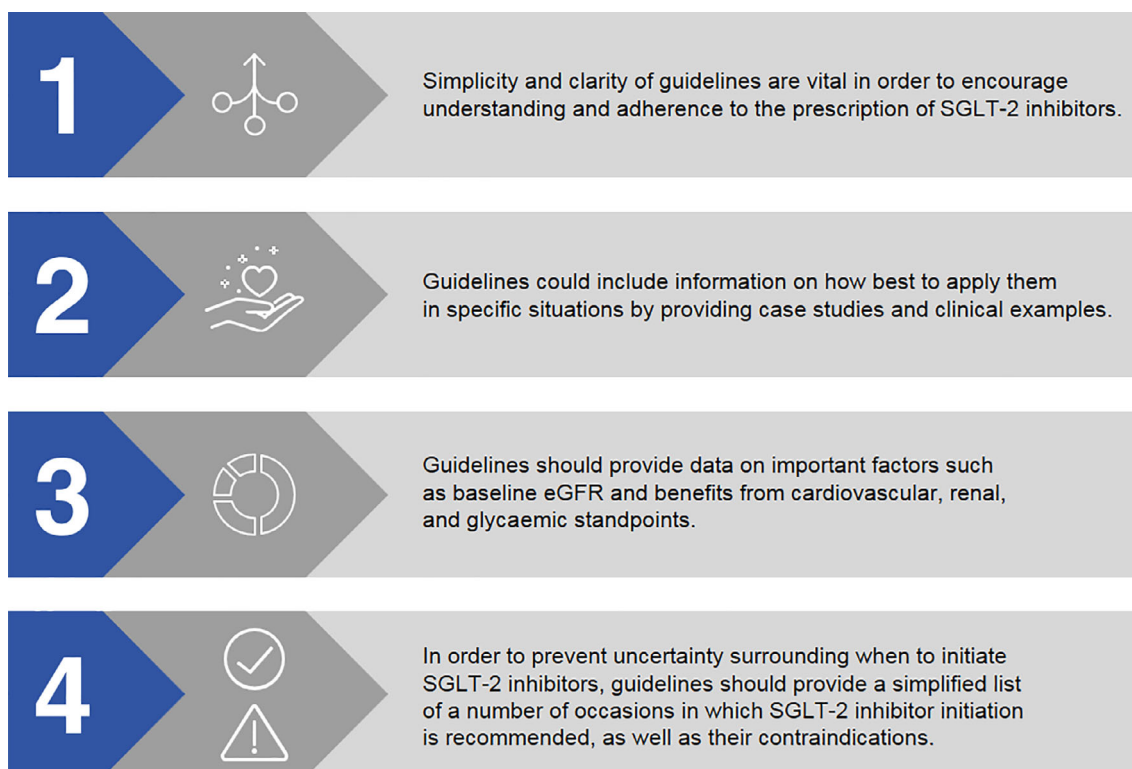


FIGURE 2 A summary of potential ways in which guidelines for type 2 diabetes management could be improved for multidisciplinary use. eGFR, estimated glomerular filtration rate; SGLT-2, sodium-glucose co-transporter-2



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. ^aHu M, et al. ⁸⁸; ^bPerkovic V, et al. ¹¹; ^cPereira MJ and Eriksson JW⁸⁹; ^dLopaschuk GD and Verma S⁹⁰; ^eMusso G, et al. ⁹¹; ^fVardeny O and Vaduganathan M³²; ^gWilliams SM and Ahmed SH⁹²

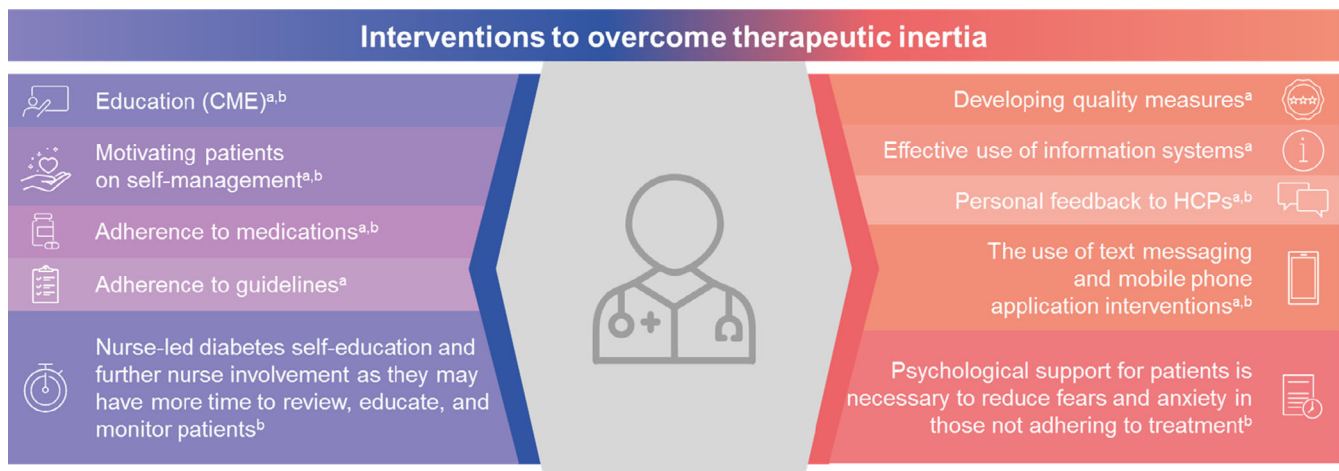


FIGURE 4 Potential interventions to overcome therapeutic inertia in patients with type 2 diabetes. CME, continuing medical education; HCPs, healthcare professionals. ^aZafar A, et al. ⁵⁴; ^bKhunti S, et al. ⁵³

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-based⁶¹ 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 diseases⁷³ 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 sulphonylureas⁷⁷ 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

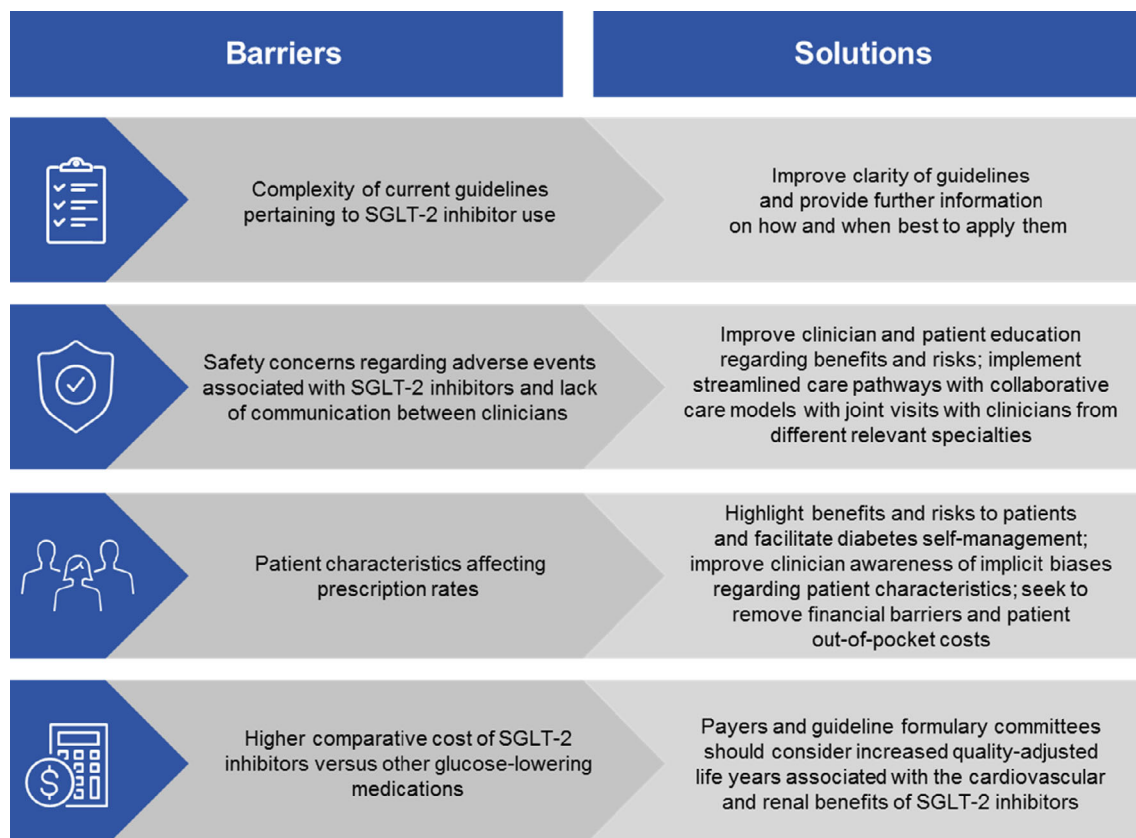


FIGURE 5 A summary of barriers to the uptake of sodium-glucose co-transporter-2 (SGLT-2) inhibitors in clinical practice and proposed solutions

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

ACKNOWLEDGEMENTS

Medical writing support was provided by Sally Sheldon and Jonathon Ackroyd, Springer Healthcare Ltd, and was funded by AstraZeneca.

CONFLICT OF INTEREST

KK has acted as a consultant, speaker or received grants for investigator-initiated studies for AstraZeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG/Menarini Group, Janssen, and Napp. He is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). CM received honoraria for speaking engagements and/or advisory board meetings for Boehringer Ingelheim, Lilly, Janssen, AstraZeneca, and Bayer. XC served as an advisor or consultant for: AstraZeneca, Boehringer Ingelheim, Esteve, Lilly, Novartis, Novo Nordisk, Sanofi Diabetes, and Sanofi Pasteur; served as a speaker or a member of a speakers' bureau for: AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Sanofi Diabetes, and Sanofi Pasteur; received grants for clinical research from: AstraZeneca, Boehringer Ingelheim, Novartis, and Sanofi. SJ works as a consultant for AstraZeneca and Eli Lilly. SM served as a member of a speakers' bureau for AstraZeneca. PF received speaker and advisory member fees from Astra Zeneca, Boehringer Ingelheim, Lilly, Mundipharma, and Bayer. MB had grant support provided to CPC Clinical Research by Agios Pharmaceuticals, Amgen, ARCA BioPharma, AstraZeneca, Bayer, Better Therapeutics, BMS, Cardiol Therapeutics, CellResearch, Heart Flow, HDL Therapeutics, Jansen, Merck, NovoNordisk, Regio, Virta, and Wraser, and to BWH from AstraZeneca for DECLARE-TIMI 58.

AUTHOR CONTRIBUTIONS

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

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14684>.

DATA AVAILABILITY STATEMENT

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

ORCID

Kamlesh Khunti  <https://orcid.org/0000-0003-2343-7099>

Serge Jabbour  <https://orcid.org/0000-0002-4080-0470>

Paola Fioretto  <https://orcid.org/0000-0003-3445-0387>

REFERENCES

- Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep*. 2020;10(1):14790.
- Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843.
- American Diabetes Association professional practice committee. 9. Pharmacologic approaches to glycemic treatment: standards of medical Care in Diabetes—2022. *Diabetes Care*. 2021;45(Supplement_1):S125-S143.
- Greiver M, Havard A, Bowles JK, et al. Trends in diabetes medication use in Australia, Canada, England, and Scotland: a repeated cross-sectional analysis in primary care. *Br J Gen Pract*. 2021;71(704):e209-e218.
- Seidu S, Cos X, Brunton S, et al. A disease state approach to the pharmacological management of type 2 diabetes in primary care: a position statement by primary care diabetes Europe. *Prim Care Diabetes*. 2021;15(1):31-51.
- Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res*. 2015;12(2):78-89.
- Scheen AJ. Sodium-glucose cotransporter type 2 inhibitors for the treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2020;16(10):556-577.
- Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
- Giorgino F, Vora J, Fenici P, Solini A. Renoprotection with SGLT2 inhibitors in type 2 diabetes over a spectrum of cardiovascular and renal risk. *Cardiovascular Diabetol*. 2020;19(1):196.
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306.
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
- Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139(22):2528-2536.
- Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617.
- Das SR, Everett BM, Birtcher KK, et al. 2020 expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes: a report of the American College of Cardiology Solution set Oversight Committee. *J Am Coll Cardiol*. 2020;76(9):1117-1145.
- Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of diabetes (EASD). *Eur Heart J*. 2019;41(2):255-323.
- Chaplin S. Primary care prescribing for diabetes: latest figures show upward trend in volume and cost. *Pract Diabetes*. 2019;36(1):30-32.
- de Boer IH, Caramori ML, Chan JCN, et al. Executive summary of the 2020 KDIGO diabetes management in CKD guideline: evidence-based advances in monitoring and treatment. *Kidney Int*. 2020;98(4):839-848.
- American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical Care in Diabetes—2022. *Diabetes Care*. 2021;45(Supplement_1):S144-S174.

21. Mata-Cases M, Franch-Nadal J, Real J, Vlachos B, Gómez-García A, Mauricio D. Evaluation of clinical and antidiabetic treatment characteristics of different sub-groups of patients with type 2 diabetes: data from a Mediterranean population database. *Prim Care Diabetes*. 2021; 15(3):588-595.
22. Kanumilli N, Brunton S, Cos X, et al. Global survey investigating causes of treatment inertia in type 2 diabetes cardiorenal risk management. *J Diabetes Complications*. 2021;35(3):107813.
23. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2020; 43(2):487-493.
24. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm. *Endocr Pract*. 2019;25(1):69-101.
25. Farmer RE, Beard I, Raza SI, et al. Prescribing in type 2 diabetes patients with and without cardiovascular disease history: a descriptive analysis in the UKPRD. *Clin Ther*. 2021;43(2):320-335.
26. Shin JI. Second-line glucose-lowering therapy in type 2 diabetes mellitus. *Curr Diab Rep*. 2019;19(8):54.
27. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical Care in Diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S111-s124.
28. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. *Endocr Pract*. 2020;26(1):107-139.
29. de Boer IH, Caramori ML, Chan JC, et al. Executive summary of the 2020 KDIGO diabetes management in CKD guideline: evidence-based advances in monitoring and treatment. *Kidney Int*. 2020; 2098(2024):2839-2848.
30. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021; 46:101102.
31. American Diabetes Association. Addendum. 11. Microvascular complications and foot care: standards of medical Care in Diabetes—2021: Diabetes Care 2021; 44 (Suppl. 1): S151–S167. *Diabetes Care*. 2021;44(9):2186-2187.
32. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *JACC Heart Fail*. 2019;7(2):169-172.
33. Chertow GM, Vart P, Jongs N, et al. Effects of dapagliflozin in stage 4 chronic kidney disease. *J Am Soc Nephrol*. 2021;32(9):2352-2361.
34. Fontes-Carvalho R, Santos-Ferreira D, Raz I, Marx N, Ruschitzka F, Cosentino F. Protective effects of SGLT-2 inhibitors across the cardiorenal continuum: two faces of the same coin. *Eur J Prev Cardiol*. 2021;zwab034.
35. Monami M, Nreu B, Zannoni S, Lualdi C, Mannucci E. Effects of SGLT-2 inhibitors on diabetic ketoacidosis: a meta-analysis of randomised controlled trials. *Diabetes Res Clin Pract*. 2017;130:53-60.
36. Bashier A, Bin Hussain A, Abdelgadir E, Alawadi F, Sabbour H, Chilton R. Consensus recommendations for management of patients with type 2 diabetes mellitus and cardiovascular diseases. *Diabetol Metab Syndr*. 2019;11:80.
37. Smeets M, De Witte P, Peters S, Aertgeerts B, Janssens S, Vaes B. Think-aloud study about the diagnosis of chronic heart failure in Belgian general practice. *BMJ Open*. 2019;9(3):e025922.
38. McMurray JJ, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; 381(21):1995-2008.
39. Heerspink HJL, Cherney DZI. Clinical implications of an acute dip in eGFR after SGLT2 inhibitor initiation. *Clin J Am Soc Nephrol*. 2021; 16(8):1278-1280.
40. Kraus BJ, Weir MR, Bakris GL, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int*. 2021;99(3):750-762.
41. Gregg LP, Navaneethan SD. Are all SGLT2 inhibitors created equal? *Clin J Am Soc Nephrol*. 2021;16(9):1309-1311.
42. Jeong SJ, Lee SE, Shin DH, Park IB, Lee HS, Kim K-A. Barriers to initiating SGLT2 inhibitors in diabetic kidney disease: a real-world study. *BMC Nephrol*. 2021;22(1):177.
43. NICE. SGLT-2 Inhibitors. 2021. <https://cks.nice.org.uk/topics/diabetes-type-2/prescribing-information/sglt-2-inhibitors/>. Accessed February 2022.
44. U.S. Food and Drug Administration. FDA Revises Labels of SGLT2 Inhibitors for Diabetes to Include Warnings about Too Much Acid in the Blood and Serious Urinary Tract Infections. 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious>. Accessed February 2022.
45. The Renal Association. *Clinical Practice Guidelines for Management of Hyperglycaemia in Adults with Diabetic Kidney Disease*. UK Kidney Association; 2021. https://ukkidney.org/sites/renal.org/files/Managing%20hyperglycaemia%20in%20people%20with%20DKD_final%20draft.pdf. Accessed February 2022.
46. Erond N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. *Diabetes Care*. 2015;38(9):1680-1686.
47. McCoy RG, Dykhoff HJ, Sangaralingham L, et al. Adoption of new glucose-lowering medications in the U.S.-the case of SGLT2 inhibitors: nationwide cohort study. *Diabetes Technol Ther*. 2019;21(12): 702-712.
48. Kosiborod MN, Esterline R, Furtado RHM, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diab Endocrinol*. 2021;2099(2029):2586-2594.
49. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol*. 2016;101(1):157-166.
50. Matthews DR, Li Q, Perkovic V, et al. Effects of canagliflozin on amputation risk in type 2 diabetes: the CANVAS program. *Diabetologia*. 2019;62(6):926-938.
51. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383(15): 1425-1435.
52. Scheen AJ. Efficacy and safety profile of SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease. *Expert Opin Drug Saf*. 2020;19(3):243-256.
53. Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. *Diabetologia*. 2018;61(10):2118-2125.
54. Scherthaner G, Shehadeh N, Ametov AS, et al. Worldwide inertia to the use of cardiorenal protective glucose-lowering drugs (SGLT2i and GLP-1 RA) in high-risk patients with type 2 diabetes. *Cardiovasc Diabetol*. 2020;19(1):185.
55. Khunti S, Khunti K, Seidu S. Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia. *Ther Adv Endocrinol Metab*. 2019;10:2042018819844694.
56. Zafar A, Davies M, Azhar A, Khunti K. Clinical inertia in management of T2DM. *Prim Care Diabetes*. 2010;4(4):203-207.
57. Gabbay RA, Kendall D, Beebe C, et al. Addressing therapeutic inertia in 2020 and beyond: a 3-year initiative of the American Diabetes Association. *Clin Diabetes*. 2020;38(4):371-381.
58. Dennis JM, Henley WE, McGovern AP, et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010-2017. *Diabetes Obes Metab*. 2019;21(7):1576-1584.

59. Arnold SV, Inzucchi SE, Tang F, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR[®] research to practice project. *Eur J Prev Cardiol.* 2017;24(15):1637-1645.
60. Harris ST, Patorno E, Zhuo M, Kim SC, Paik JM. Prescribing trends of Antidiabetes medications in patients with type 2 diabetes and diabetic kidney disease, a cohort study. *Diabetes Care.* 2021;44(10):2293-2301.
61. Khunti K, Kosiborod M, Kim DJ, et al. Cardiovascular outcomes with sodium-glucose cotransporter-2 inhibitors vs other glucose-lowering drugs in 13 countries across three continents: analysis of CVD-REAL data. *Cardiovasc Diabetol.* 2021;20(1):159.
62. Andrade LF, Rapp T, Sevilla-Dedieu C. Exploring the determinants of endocrinologist visits by patients with diabetes. *Eur J Health Econ.* 2016;17(9):1173-1184.
63. Saudek CD. The role of primary care professionals in managing diabetes. *Clin Diabetes.* 2002;20(2):65-66.
64. Dave CV, Schneeweiss S, Wexler DJ, Brill G, Patorno E. Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013-2018. *Diabetes Care.* 2020;43(4):921-924.
65. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2021;42(36):3599-3726.
66. Lavoie KL, Rash JA, Campbell TS. Changing provider behavior in the context of chronic disease management: focus on clinical inertia. *Ann Rev Pharmacol Toxicol.* 2017;57:263-283.
67. Rushforth B, McCrorie C, Glidewell L, Midgley E, Foy R. Barriers to effective management of type 2 diabetes in primary care: qualitative systematic review. *Br J Gen Pract.* 2016;66(643):e114-e127.
68. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. *Diabetes Metab Syndr Obes.* 2014;7:587.
69. Ha JF, Longnecker N. Doctor-patient communication: a review. *Ochsner J.* 2010;10(1):38-43.
70. McPherson ML, Smith SW, Powers A, Zuckerman IH. Association between diabetes patients' knowledge about medications and their blood glucose control. *Res Social Adm Pharm.* 2008;4(1):37-45.
71. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. *Cardiovasc Diabetol.* 2018;17(1):1-19.
72. Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: world wide difference of prevalence and risk factors. *J Nephropharmacol.* 2016;5(1):49.
73. de Boer IH, Caramori ML, Chan JC, et al. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int.* 2020;98(4):S1-S115.
74. Klara K, Kim J, Ross JS. Direct-to-consumer broadcast advertisements for pharmaceuticals: off-label promotion and adherence to FDA guidelines. *J Gen Intern Med.* 2018;33(5):651-658.
75. Eberly LA, Yang L, Eneanya ND, et al. Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US. *JAMA Netw Open.* 2021;4(4):e216139.
76. Datti B, Carter MW. The effect of direct-to-consumer advertising on prescription drug use by older adults. *Drugs Aging.* 2006;23(1):71-81.
77. Whyte MB, Hinton W, McGovern A, et al. Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: a retrospective cohort analysis. *PLoS Med.* 2019;16(10):e1002942.
78. McCoy IE, Han J, Montez-Rath ME, Chertow GM, Rhee JJ. Patient and provider characteristics associated with sodium-glucose cotransporter 2 inhibitor prescription in patients with diabetes and Proteinuric chronic kidney disease. *Clin Diabetes.* 2020;38(3):240-247.
79. Hong D, Si L, Jiang M, et al. Cost effectiveness of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors: a systematic review. *Pharmacoeconomics.* 2019;37(6):777-818.
80. McEwan P, Bennett H, Khunti K, et al. Assessing the cost-effectiveness of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus: a comprehensive economic evaluation using clinical trial and real-world evidence. *Diabetes Obes Metab.* 2020;22(12):2364-2374.
81. Lopez JM, Macomson B, Ektare V, Patel D, Botteman M. Evaluating drug cost per response with SGLT2 inhibitors in patients with type 2 diabetes mellitus. *Am Health Drug Benef.* 2015;8(6):309-318.
82. Luo J, Feldman R, Rothenberger SD, Hernandez I, Gellad WF. Coverage, formulary restrictions, and out-of-pocket costs for sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists in the Medicare part D program. *JAMA Netw Open.* 2020;3(10):e2020969.
83. Simes BC, MacGregor GG. Sodium-glucose cotransporter-2 (SGLT2) inhibitors: a clinician's guide. *Diabetes Metab Syndr Obes.* 2019;12:2125-2136.
84. Genuardi MV, Mather PJ. The dawn of the four-drug era? SGLT2 inhibition in heart failure with reduced ejection fraction. *Ther Adv Cardiovasc Dis.* 2021;15:17539447211002678.
85. Moreno Juste A, Menditto E, Orlando V, et al. Treatment patterns of diabetes in Italy: a population-based study. *Front Pharmacol.* 2019;10:870.
86. Fadini GP, Tentolouris N, Caballero Mateos I, Bellido Castañeda V, Morales PC. A multinational real-world study on the clinical characteristics of patients with type 2 diabetes initiating dapagliflozin in southern Europe. *Diabetes Ther.* 2020;11(2):423-436.
87. Excellence NifHaC. Managing blood glucose in adults with type 2 diabetes. <https://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults/managing-blood-glucose-in-adults-with-type-2-diabetes>. Accessed May 28, 2021.
88. Hu M, Cai X, Yang W, Zhang S, Nie L, Ji L. Effect of hemoglobin A1c reduction or weight reduction on blood pressure in glucagon-like peptide-1 receptor agonist and sodium-glucose cotransporter-2 inhibitor treatment in type 2 diabetes mellitus: a meta-analysis. *J Am Heart Assoc.* 2020;9(7):e015323.
89. Pereira MJ, Eriksson JW. Emerging role of SGLT-2 inhibitors for the treatment of obesity. *Drugs.* 2019;79(3):219-230.
90. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *J Am Coll Cardiol Basic Trans Sci.* 2020;5(6):632-644.
91. Musso G, Saba F, Cassader M, Gambino R. Diabetic ketoacidosis with SGLT2 inhibitors. *BMJ.* 2020;371:m4147.
92. Williams SM, Ahmed SH. 1224-P: Improving compliance with SGLT2 inhibitors by reducing the risk of genital mycotic infections: the outcomes of personal hygiene advice. *Diabetes.* 2019;68(Supplement_1):1224.

How to cite this article: Khunti K, Jabbour S, Cos X, et al. Sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes: Barriers and solutions for improving uptake in routine clinical practice. *Diabetes Obes Metab.* 2022;24(7):1187-1196. doi:10.1111/dom.14684