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COMMENTARY

The Role of Real-World Evidence in Treatment Decision-Making, Regulatory Assessment, and Understanding the Perspectives of People with Type 2 Diabetes: Examples with Gliclazide MR

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ABSTRACT

Real-world evidence (RWE) plays an important role in the management of type 2 diabetes (T2D). It provides data about the effectiveness and safety of an intervention from outside the randomised controlled trial (RCT) setting and allows healthcare professionals (HCPs) to determine if RCT data are applicable to their patients in routine clinical practice. This review provides a discussion of the value of RWE in T2D management in day-to-day clinical practice, with a focus on RWE with sulfonylureas (SUs), and presents two examples of a new generation of international real-world studies in people with T2D managed in routine clinical practice. RWE plays a valuable role in advising HCPs in the day-to-day management of T2D, informing regulatory authorities with regard to pharmacovigilance and post-approval updates, and providing insights with regard to patients' treatment adherence and preference. RWE should be used alongside RCTs to increase HCP awareness and understanding of their patients' perspectives, potentially allowing for improvements in treatment adherence, glycaemic control and health-related quality of life (HRQoL). In addition, real-world studies must be conducted in a way that generates robust RWE by limiting the risks of bias and confounding as much as possible. A growing body of RWE is emerging from Asia. For example, in a preliminary HRQoL analysis of the Joint Asia Diabetes Evaluation (JADE) Register, Asian people with T2D had better HRQoL with gliclazide-based treatment than with other SU agents, despite being older and having more diabetes-related complications.

Keywords: Glycaemic control; Health-related quality of life; Real-world evidence; Sulfonylurea; Type 2 diabetes

Prior Presentation: This review article is based on the content of a symposium titled "When Practice Meets Evidence: New Data on Sulphonylureas from Real-World Evidence", which was presented at the International Diabetes Federation Congress 2022 held in Portugal on 6 December 2022.

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Key Summary Points

Real-world evidence (RWE) provides healthcare professionals (HCPs) with important information on the applicability of randomised controlled trial (RCT) data to their patients with type 2 diabetes (T2D) in routine clinical practice.

RWE has an important role in advising HCPs about optimal management of T2D and providing insights on patients' preference and adherence; these data complement RCT data in informing regulatory authorities on pharmacovigilance, drug approval and post-approval updates.

International real-world studies with sulfonylureas (SUs) include the JADE Register, which showed that gliclazide-based treatment was associated with improved health-related quality of life compared with other SU agents in Asian people with T2D.

INTRODUCTION

Clinical evidence for disease management can be generated by different types of studies, including randomised controlled trials (RCTs) and, in the case of type 2 diabetes (T2D), cardiovascular outcome trials (CVOTs) [1]. Recently, there has been growing recognition of the value of real-world evidence (RWE), derived from analysis of data gathered from real-world studies, such as observational retrospective and prospective studies and pragmatic randomised trials [2]. The main difference between RCTs and RWE is that an RCT asks, "can it work?", whereas a real-world study asks, "does it work?" [1].

RCTs evaluate drug efficacy under carefully controlled conditions in highly selected populations to maximise internal validity, but at the expense of limited external validity (i.e. information generalisable to a broad patient group). These RCTs often exclude people of advanced age and those with multiple comorbidities receiving concomitant medications [3]. As a result of the low background rate of cardiovascular events, populations in CVOTs are enriched by high-risk individuals. In addition to people without diabetic complications, who form the vast majority of those with T2D, young people with T2D are often excluded from CVOTs despite their high lifetime risk for premature mortality and morbidity due to long disease duration [4]. In routine clinical practice, there is considerable heterogeneity in terms of phenotype, trajectory and treatment response. This is further influenced by individuals' access to care, medications and support, as well as adherence, values and preferences [5]. Real-world studies collect data from outside the RCT setting, providing information about the effectiveness and safety of a treatment, as well as its value and cost-effectiveness, in clinical practice [6]. In prospective cohort studies that collect detailed participant data, RWE might allow the comparison of two treatments using propensity score matching [7], which can complement results from RCTs or reveal differences in safety or effectiveness of various drugs within the same class [8].

Apart from clinical events, real-world studies may provide data on patient-reported outcomes (PROs; e.g. treatment adherence, health-related quality of life [HRQoL] and psychosocial factors), financial burden of disease, healthcare resource utilisation and treatment cost-effectiveness. Thus, RWE allows healthcare professionals (HCPs) to assess if RCT data are applicable to their patients and whether the treatment works in routine clinical practice [9], considering the totality of the evidence from all sources.

This review article provides a discussion of the complementary value of real-world data in guiding routine clinical practice and informing regulatory decisions, focusing on RWE with sulfonylureas (SUs), and presents two examples of a new generation of RWE of SU therapy in people with T2D. This article is based on the content of a symposium titled "When Practice

Meets Evidence: New Data on Sulphonylureas from Real-World Evidence", which was presented at the International Diabetes Federation (IDF) World Diabetes Congress on 6 December 2022 in Lisbon, Portugal. The symposium was based on previously conducted studies and did not contain any new studies with human participants or animals performed by any of the authors.

WHAT IS RWE?

There are several types of real-world studies, including pragmatic research and prospective or retrospective observational studies (Table 1; Fig. 1) [10–12]. Pragmatic clinical trials offer an intermediate design between the strict control of an RCT and uncontrolled observational research. In these real-world studies, enrolled participants are prescribed treatment per guidelines or protocol, or per preference of prescribers or participants, but the follow-up schedules more closely resemble clinical practice than in an RCT (Table 1) [12, 13]. An example of this type of research is the TOSCA.IT study, which showed that SU therapy and pioglitazone were associated with a similar incidence of cardiovascular events when added to metformin in people with T2D [14].

As digital technology becomes standard in medical practice, there is an increasing opportunity to source real-world data from electronic health records, health insurance claims databases, regional or national registers, census data and the individual's own digital health devices [15]. Such data may be utilised in a range of different studies (Fig. 1), providing valuable RWE at a lower cost than RCTs. However, real-world studies may be subject to selection bias, data quality issues (e.g. unstructured or incomplete data collection), differences in outcome

Table 1 Comparison of the features of randomised controlled trials (RCTs), pragmatic trials and observational studies. Adapted from Fig. 1 in Anzueto and Kaplan [12], under a CC-BY 4.0 license (https://creativecommons.org/licenses/by/4.0/)

Parameter	RCT	Pragmatic trial	Real-world observational study
Participant selection criteria	Predefined inclusion and exclusion criteria	Minimal: real-world patient population(s)	Minimal: real-world patient population(s)
Data collection method	Rigorous process	Real world + additional sources	Real world
Monitoring	Strict	Routine clinical care	Routine clinical care
Follow-up	Usually shorter follow-up and frequent visits	Longer follow-up with few mandatory visits	Longer follow-up with no mandatory visits
Treatment adherence	High	Low	Low
Outcomes	Usually hard or objective endpoints; some may be PROs	May be entirely subjective or PROs; some objective	Dependent on data captured at patient–clinician interaction
Data quality and internal validity	Excellent	Intermediate	Variable
Cost per patient	High	Intermediate	Low
Stakeholder audience	Regulatory authorities and clinicians	Regulatory authorities, payers and clinicians	Traditionally payers and clinicians; increasingly regulatory authorities

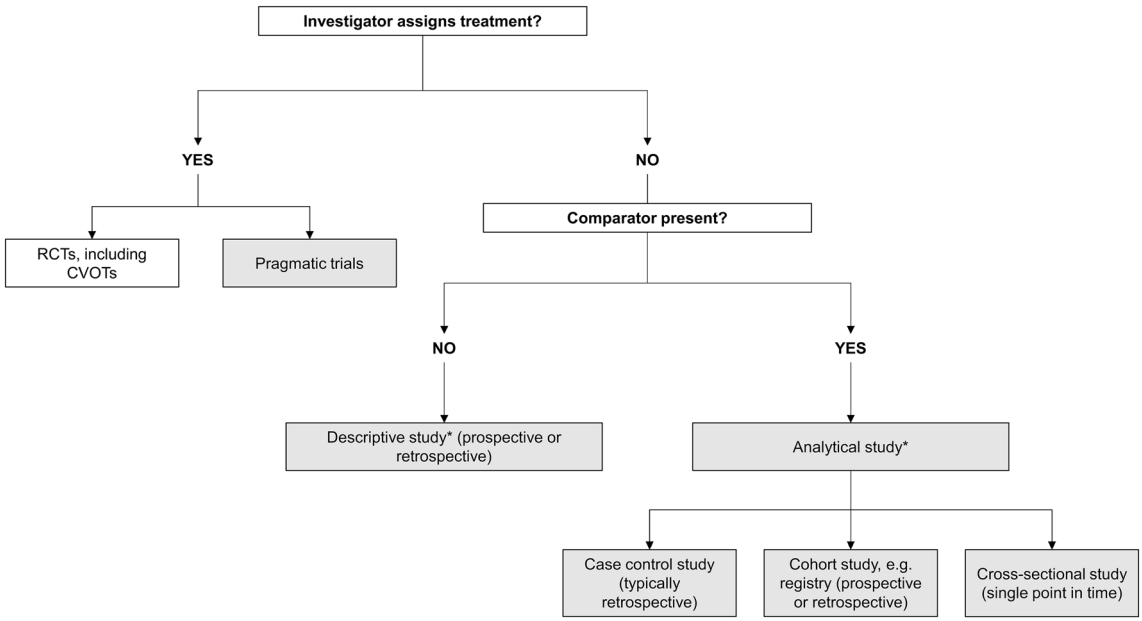

Fig. 1 Adapted with permission from Wolters Kluwer Health Inc and the author of Taur SR. Observational designs for real-world evidence studies. Perspect Clin Res. 2022;13(1):12–6 [10], available at https://journals.lww.com/picp/Fulltext/2022/13010/Observational_designs_for_real_world_evidence.3.aspx, accessed 24 July 2023, released under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International license (CC BY-NC-SA 4.0). Real-world studies are shaded in grey. *Sources of data for these studies include registries, electronic health records, health insurance claims databases, census data and patient monitoring devices (e.g. fitness monitors and glucose monitors) [15]. *CVOT* cardiovascular outcomes trial

definitions, confounding factors and interpretability [10, 11].

Data collected after completion of RCTs can also be a source of real-world data. For example, the United Kingdom Prospective Diabetes Study (UKPDS) continues to report ongoing evidence regarding the benefits of early and intensive glycaemic control on major diabetes and cardiovascular events and death rates after 10 years of post-RCT real-world follow-up in people with T2D [16]. As reported in a symposium at the European Association for the Study of Diabetes (EASD) 2022 Annual Meeting [17], the legacy effects of early intensive glycaemic control (with SUs, insulin or metformin) persist after 44 years of follow-up, demonstrating the importance of effective glycaemic control from immediately after T2D diagnosis to reduce the risk of micro- and macrovascular complications.

THE VALUE OF RWE IN TYPE 2 DIABETES MANAGEMENT

The value of RWE in managing people with T2D can be classified into three main categories. Firstly, RWE provides HCPs with information and meaningful insights into the epidemiology, natural history and prevention of the disease, as well as the effectiveness and safety of an intervention. Secondly, data from RWE inform regulatory authorities on long-term drug safety, and increasingly it also informs the clinical decision-making process over the life cycle of the drug. Lastly, RWE can provide insights on patients' perspectives that are not routinely captured in RCTs and might be subject to selection and volunteer bias in an RCT setting.

Informing HCP Decision-Making in Managing People with Type 2 Diabetes

RWE can provide HCPs with information regarding the applicability of RCT data in the day-to-day management of people with T2D. The current American Diabetes Association (ADA) and EASD guidelines for T2D largely focus on the identification of individuals with comorbid atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) or chronic kidney disease (CKD), and recommend treatment with sodium–glucose cotransporter 2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) in these high-risk patients [18, 19]. In these guidelines, SUs are listed as high-efficacy agents that can be incorporated into combination glucose-lowering drug (GLD) regimens, taking into account the patient's cardiovascular risk, the likelihood and impact of hypoglycaemia and weight gain, and the patient's ability to pay (since they are inexpensive compared with SGLT2is or GLP-1RAs) [18, 19].

The guideline recommendations for first-line use of SGLT2is and GLP-1RAs are based on data obtained from CVOTs [18, 19]. In most RCTs, investigators must follow the study protocol when managing their patients, whereas in clinical practice, HCPs can personalise treatment for each individual. Real-world studies indicate that many people with T2D treated in routine clinical practice would not be eligible for inclusion in the SGLT2i and GLP-1RA CVOTs [20, 21]. In the real-world, international DISCOVER study [20], which included 11,385 people with T2D who were initiated on second-line GLD therapy, the proportion who were eligible for inclusion in the SGLT2i CVOTs ranged from 7% for the EMPA-REG OUTCOME [22] and VERTIS-CV [23] studies to 20% for the CANVAS study [24] and 41% for the DECLARE TIMI-58 study [25]. In a real-world National Health and Nutrition Examination Survey (NHANES) database analysis of 20,142 people with T2D in the USA [21], 53–94% did not meet the inclusion criteria for the GLP-1RA CVOTs (i.e. the EXSCEL, SUSTAIN-6, LEADER, HARMONY OUTCOMES, REWIND and ELIXA studies [26–31]).

RWE also indicates that the clinical guideline algorithms do not address the treatment needs of many people with T2D. In a cohort study of 13,350 adults with T2D in primary care, 63% did not meet ADA 2021 criteria for treatment with SGLT2is or GLP-1RAs [32]. For these people with T2D who do not qualify for SGLT2i or GLP-1RA therapy, individual phenotypes derived from RWE may help personalise treatment, and assist in the move towards precision medicine in T2D management [33].

Real-world studies, when combined with data from RCTs and pragmatic clinical studies, can also inform HCPs on the comparative safety and effectiveness of commonly used second-line GLDs (e.g. SUs and dipeptidyl peptidase 4 inhibitors [DPP4is]), particularly among people with T2D who do not have ASCVD, HF or CKD. For example, the CAROLINA RCT compared the efficacy and safety of glimepiride (an SU) and linagliptin (a DPP4i) in people with T2D and ASCVD or high cardiovascular risk [34]. This study demonstrated equivalent glycaemic control and no difference in major adverse cardiovascular events between the two drugs, although the rates of hypoglycaemia (including severe hypoglycaemia) were higher with glimepiride [34].

The randomised, pragmatic GRADE study compared the effectiveness of four commonly used GLDs (i.e. insulin glargine, glimepiride, liraglutide and sitagliptin) when added to background metformin therapy in 5047 people with T2D [35]. In this study, participants who received glimepiride were 21% less likely to have a glycated haemoglobin (HbA1c) of $\geq$ 7% ($>$ 53.0 mmol/mol; $p \leq 0.001$) and 16% less likely to have an HbA1c of $\geq$ 7.5% ($\geq$ 58 mmol/mol) over 5 years compared with those who received sitagliptin [35]. The rate of severe hypoglycaemia was low with both drugs, with higher rates observed with glimepiride versus sitagliptin (2.2% vs 0.7%; $p \leq 0.001$) [35].

In a real-world UK Clinical Practice Research Datalink (CPRD) database study of people with T2D initiated on second-line GLD therapy with either gliclazide modified-release (MR) or sitagliptin, gliclazide MR-treated participants were more likely to achieve an HbA1c of $<$ 7% ($<$ 53.0 mol/mol) than sitagliptin-treated

participants, although the rates of hypoglycaemia, including severe hypoglycaemia, were similarly low in both treatment groups [7]. This difference between the RCT and real-world study may be due to residual confounders not captured in these studies or molecular differences between the two SU (glimepiride and gliclazide MR) or DPP4i (linagliptin and sitagliptin) agents. In addition, there are differences in the definition of hypoglycaemia between RCTs and real-world studies, with many RCTs requiring a measured blood glucose level, and real-world studies defining hypoglycaemia as self-reported events requiring self-treatment, with or without confirmation of blood glucose levels [36, 37]. The CAROLINA study, which enrolled a large proportion of people aged > 70 years with CKD, used force-titration of glimepiride treatment [34]. These characteristics and treatment strategies might have exaggerated the rate of hypoglycaemia with glimepiride when used in real-world practice, as many HCPs would not have used glimepiride at these high doses in elderly people with CKD.

The real-world DIA-RAMADAN study provides more information about the safety of gliclazide MR in people with T2D at particularly high risk of hypoglycaemia during the Ramadan period [38]. The ADA/EASD guidelines state that use of SU is associated with an increased risk for hypoglycaemia [18], but these guidelines were based on data from all SUs, including first-generation agents. In the DIA-RAMADAN study of 1214 people who practised prolonged fasting during Ramadan, gliclazide MR (a second-generation SU) was associated with a low rate of confirmed hypoglycaemia (1.6%), with no reports of severe hypoglycaemia, as well as improved glycaemic control and reduced body weight gain after 4–6 weeks compared with baseline [38]. These findings have important implications for a large global population of people with T2D who undergo periodic fasting during Ramadan.

Informing Regulatory Authorities

Historically, regulatory authorities have relied on RWE for pharmacovigilance (i.e. monitoring long-term safety after drug approval), but RWE is increasingly used to inform practice and policies. One example of the role of real-world pharmacovigilance data is to untangle the relationship between cancer risk and GLDs. For example, RCTs and a meta-analysis of RCT data found no increased risk of cancer with DPP4is [39–42]. In addition, a 2020 analysis using RWE with systematically collected data showed that DPP4i therapy was not associated with an increased risk of cancer compared with thiazolidinediones [43]. However, a population-based study in France demonstrated that the risk of thyroid cancer (including medullary thyroid carcinoma) was increased among participants who received GLP-1RAs for more than 1 year or DDP4is for more than 3 years [44]. These latter data were consistent with reports from the EudraVigilance database [45] and the World Health Organization (WHO) VigiBase [44]. An increased risk of bladder cancer has also been reported with pioglitazone in various meta-analyses [46–48], although careful analysis of RCT data with adjustment for baseline characteristics did not confirm these findings [49].

The risk association between diabetes, GLDs and cancer is a source of continuing controversy, as chronic hyperglycaemia affects multiple biological pathways that might lead to dysregulation of cellular growth [50]. RWE from registers with comprehensive documentation of confounders at baseline and follow-up has revealed an independent association between glycaemic variability and an increased cancer risk, especially in the presence of obesity [51]. Given that many new GLDs are added as third- or fourth-line treatment in people with long disease duration and poor glycaemic control, insufficient documentation of confounders might lead to erroneous conclusions regarding the risk of cancer. Indeed, using RWE, drugs such as metformin and renin–angiotensin–aldosterone system inhibitors have been shown to be associated with a reduced risk of all-site cancer with biological plausibility [52, 53]. This reinforces the importance of establishing patient registers with structured collection of confounders (e.g. disease duration, obesity and control of cardiometabolic risk factors) to enable more effective matching (e.g. by

propensity scores), particularly during the evaluation of clinical outcomes in people with multiple comorbidities treated with concomitant medications, such as those with T2D. Such registers are particularly important for evaluating outcomes like cancer that emerge only after long disease duration. Indeed, cancer is now a leading cause of death among people with T2D [5].

Beyond pharmacovigilance, regulatory authorities worldwide are moving towards using RWE to support drug registration. In Europe, Bakker and colleagues examined the use of RWE in regulatory applications submitted in 2018–2019 to support European Medicines Agency (EMA) new marketing authorisation and extension of indication applications [54]. Of the 46 applications to the EMA accompanied by RWE, 26 applications included this information in the preauthorisation package and RWE was considered to have supported the regulatory decision for 10 applications [54].

In 2016, the US government passed the "21st Century Cures Act", which compels the US Food and Drug Administration (FDA) to use RWE to speed up the process of approving new drug applications and extending the indications of existing products [55]. Within the FDA's new regulatory framework, RCT data remain the benchmark for new drug approvals, but after approval, RWE inform regulatory decisions regarding the extension of indication to additional populations of patients who may benefit from treatment, and the addition or modification of dosage recommendations. Comparative effectiveness or longer-term safety data based on RWE might also be included in the product packaging information [56].

Providing Insights on Patients' Perspectives

RCTs cannot provide unbiased data regarding adherence to treatment, as RCT participants are more likely to adhere to treatment than those treated in clinical practice. This is the so-called Hawthorne effect, whereby the individual's behaviour changes once they are enrolled in a clinical trial [57]. Adherence rates in RCTs typically exceed 80%, although RWE suggests that treatment adherence is considerably lower in clinical practice. In a meta-analysis of RWE, only 22% of studies had adherence rates of 80% or higher [58]. In the observational, retrospective STAY Study, people with T2D treated with once-weekly or daily GLP-1RAs had 1-year adherence rates between 31% and 43% [59]. A subsequent meta-analysis of RCT data and RWE similarly reported a mean rate of poor adherence of 38% among people with T2D [60]. These low rates of treatment adherence would negatively impact HbA1c levels and contribute to the poor glycaemic control, despite the prescription of GLDs confirmed to be efficacious in closely supervised settings.

Patient preference is an important consideration in T2D management, yet there is often discordance between what HCPs and their patients want from treatment. In a mixed-methods study comprising interviews of HCPs and their patients with T2D, the patients preferred oral GLDs (rather than injectable therapy), ideally administered once daily, and were less concerned about the cost of medications compared with HCPs [61]. With regard to outcomes, the patients were more likely than HCPs to rate blood pressure reduction and lower risk for amputation, diabetic retinopathy, stroke or sexual dysfunction as being important. In contrast, the HCPs were more likely to rate lower risks of hypoglycaemia and mortality and reductions in HbA1c and body weight as being important [61]. These findings illustrate the need for more alignment between HCPs and their patients on important outcomes for T2D management. Better understanding by HCPs of their patients' values, preferences and perspectives will likely improve patient adherence and treatment decision-making.

HRQoL is an important element of holistic disease management advocated by the latest ADA/EASD guidelines [18]. Given its importance in people with T2D, HRQoL should be an essential measurement in RCTs and real-world studies. However, there are very few real-world databases that routinely collect HRQoL information. A few studies have reported suboptimal HRQoL in people with T2D [62, 63] and prediabetes [64], with further decrement in the

presence of multiple comorbidities [65]. To date, there have been few large-scale real-world studies on treatment-related HRQoL, so the preliminary results from the Joint Asia Diabetes Evaluation (JADE) Register (discussed below) will provide important information to help HCPs make better decisions in the management of their patients.

THE NEED FOR INTERNATIONAL RWE IN TYPE 2 DIABETES

Diabetes is a global burden affecting an estimated 537 million adults worldwide in 2021, with this number projected to increase to 784 million by 2045 [66]. According to the IDF, 6.7 million premature deaths in 2021 were attributed to diabetes or its related complications [66].

RWE indicates that many people with T2D have suboptimal glycaemic control due to delayed intensification of glucose-lowering treatment. For example, in the real-world, prospective DISCOVER study in people with T2D initiated on second-line treatment, 80% of participants had an HbA1c of > 7.0% (> 53.0 mmol/mol), with a mean level of 8.3% (67.7 mmol/mol). The mean time from diagnosis to second-line GLD therapy intensification ranged from 4.6 years in Southeast Asia to 6.9 years in Africa (overall mean of 5.6 years) [67]. At the time of treatment escalation, mean HbA1c levels were > 8.0% (> 64.0 mmol/mol) in all regions and macrovascular or microvascular complications were present in 12.7% and 18.9% of participants, respectively [67]. This therapeutic inertia might explain why people with T2D often have inadequate glycaemic control, despite the availability of effective GLDs, and calls for more effective strategies to reduce clinical inertia and improve glycaemic control early [68].

As described above, real-world studies can address gaps in knowledge related to real-world treatment patterns and the effectiveness of T2D treatment. That being said, these studies must be conducted in a way that limits confounding factors, while reflecting clinical practice conditions, to minimise the risk of bias [10, 11]. A 2020 review of real-world studies in diabetes from around the world indicated that 71% of studies included at most 500 participants, and only 25% were conducted in primary care [69].

The two real-world studies described below provide examples of research conducted outside North America and Europe, demonstrating how well-conducted real-world studies can complement RCT research to answer specific questions related to the role of SU in the management of T2D.

THE REAL-WORLD ADD2DIA STUDY: GLICLAZIDE MR PLUS SGLT2I IN TYPE 2 DIABETES

Rationale

As a result of the progressive nature of T2D, single-agent GLD therapy often cannot provide adequate glycaemic control. As such, clinical practice guidelines recommend initiating treatment with combination therapy to attain early glycaemic control, improve glycaemic durability and delay treatment escalation [18, 19]. GLDs with complementary mechanisms of actions may act synergistically to address different biological defects in T2D. One example is the combined use of gliclazide, an SU [70], and an SGLT2i, which increases urinary elimination of glucose [71].

The hypothesis of the ADD2DIA study was based on the benefits of adding an SGLT2i to background SU therapy. The efficacy of this combination was supported by a meta-analysis of 24 RCTs in people with T2D [72]. In this meta-analysis, all GLDs improved glycaemic control when added to SU therapy, albeit with an increased risk of hypoglycaemia for most combinations except for SU + SGLT2i and SU + alpha-glucosidase inhibitor therapy. Further, in people treated with an SU, the addition of an SGLT2i or GLP-1RA reduced body weight compared with placebo, an effect that was not observed with other GLDs [72].

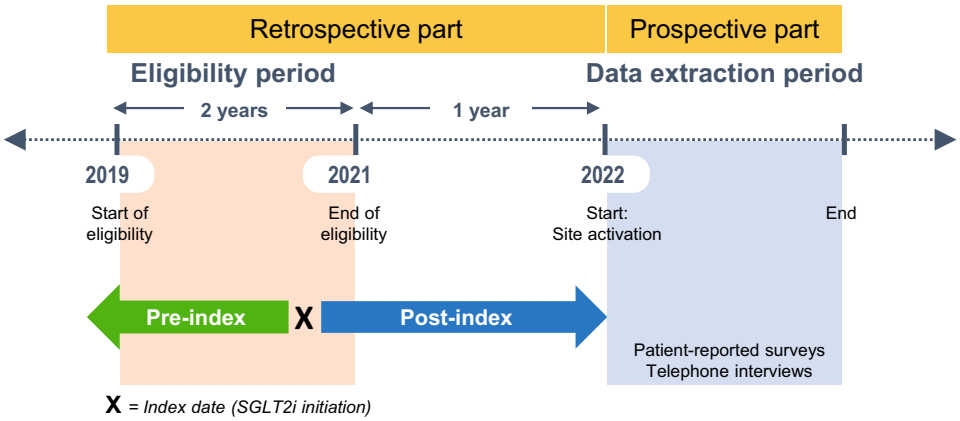

Fig. 2 Design of the ADD2DIA study [73]. *SGLT2i* sodium–glucose cotransporter 2 inhibitor

Study Design and Objectives

The ongoing international ADD2DIA study is being conducted in 25 centres across six countries (Brazil, China, Philippines, Russia, Saudi Arabia and Turkey), with a planned enrolment of 750 people with T2D (full details presented as a poster at the IDF World Diabetes Congress, 2022) [73]. The objective of the ADD2DIA study is to describe the effectiveness of adding an SGLT2i to gliclazide-based therapy (± metformin) in people with T2D, as measured by changes in HbA1c from baseline to the end of the study. The study is collecting data from adults diagnosed with T2D for at least 2 years and treated with gliclazide MR (≥ 60 mg/day) and an SGLT2i for at least 60 days. Other outcomes include adverse events of special interest, including hypoglycaemia, diabetic ketoacidosis and urinary tract infections. The relationship between combination therapy and the incidence of major cardiac events (including HF) and progression of kidney disease will also be explored [73].

The study design includes two components: a retrospective part (i.e. clinical outcomes) and a prospective part (i.e. patient survey and interview; Fig. 2). Retrospective data are collected from the index date (i.e. initiation of SGLT2i therapy) and included participants' disease history, comorbidities and concomitant medications before and after starting SGLT2i therapy. The prospective part of the study collects participants' experience and satisfaction with gliclazide MR plus SGLT2i combination therapy [73].

Preliminary Results

To date, no data from the ADD2DIA study have been published. However, preliminary results of an interim analysis of the Saudi cohort suggest that the combination of gliclazide MR plus SGLT2i is effective and safe over 2 years in patients with long-standing poorly controlled T2D and multiple cardiovascular risk factors (personal communication). Further results are awaited with interest.

THE REAL-WORLD JADE REGISTER: SU AND HRQOL IN ASIAN PEOPLE WITH TYPE 2 DIABETES

According to the IDF, nearly 50% of people with diabetes come from Asia [66], although there is a paucity of data on disease and treatment patterns, as well as treatment responses, in this large population. The JADE Register is an investigator-initiated regional program that commenced in 2007 with an aim to promote quality improvement and provide data-driven patient-centred care supported by more than 300 HCPs [8]. It uses a web-based platform that includes a structured protocol to allow for assessment of risk factors and complications (i.e. related to the eyes, feet, blood and urine),

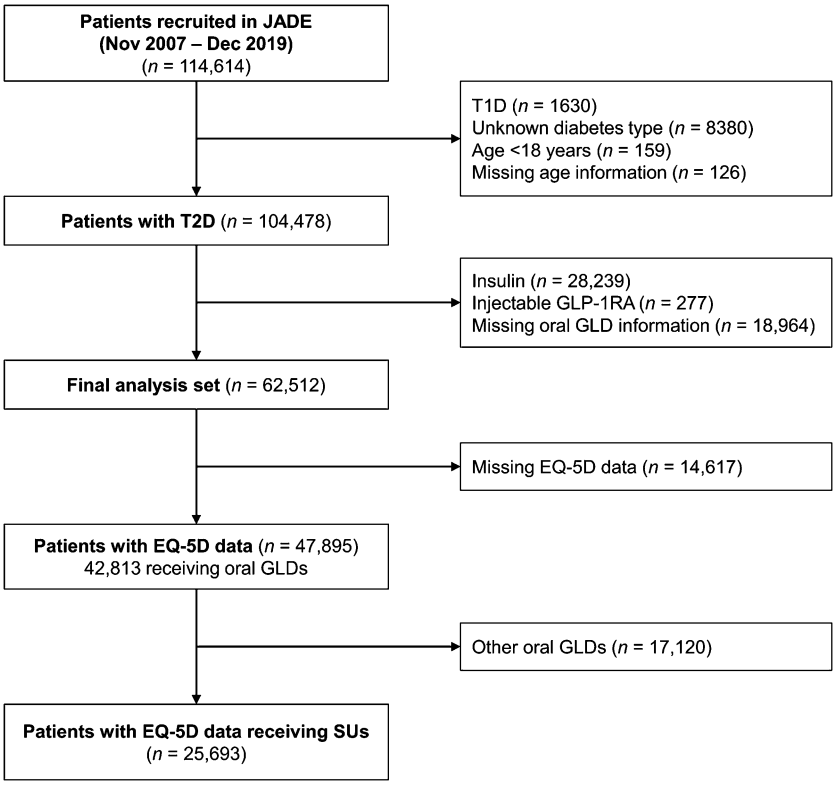

Fig. 3 Participant flow in the JADE Register [79]. *EQ-5D* EuroQol-5 Dimensions, *GLD* glucose-lowering drug, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *JADE* Joint Asia Diabetes Evaluation, *SU* sulfonylurea, *T1D* type 1 diabetes, *T2D* type 2 diabetes. Adapted from reference [79] Lim LL, Lau ESH, Pheng Chan S, et al. Real-world evidence on health-related quality of life in patients with type 2 diabetes mellitus using sulphonylureas: An analysis of the Joint Asia Diabetes Evaluation (JADE) Register. *Diabetes Research and Clinical Practice*. 2023. Published by Elsevier under a Creative Commons CC-BY license

in accordance with international guidelines. This allows for stratification of patient risk and the creation of personalised reports to empower self-management, early intervention and shared decision-making between HCPs and their patients [8]. Data are automatically de-identified upon participant enrolment to benchmark performance and generate RWE regarding treatment effectiveness and unmet needs in Asian people with T2D. To date, the JADE Register has recruited more than 100,000 Asian people with T2D from 11 countries [8, 74].

A recent analysis of the JADE Register included a report of the pattern of use of oral GLDs, as well as the effectiveness and safety of SU-based treatment in Asian adults with T2D (N = 62,512; Fig. 3) [8]. Among participants treated with oral GLDs (n = 54,783), 59.4% were treated with SU-based treatment; of those receiving an SU (n = 32,558), 46.7% were treated with gliclazide, with some variability amongst countries [8].

In the SU-treated group, gliclazide-treated participants (n = 12,078) were older and had a longer disease duration, lower HbA1c and lower body mass index (BMI) than participants treated with other SUs (n = 13,615) [8]. Apart from having a lower HbA1c, gliclazide-treated participants had lower rates of hypertension, dyslipidaemia and peripheral sensory neuropathy than those receiving other SUs. As a result of their older age and longer disease duration, gliclazide-treated participants were more likely to have diabetes-related complications (i.e.

diabetic retinopathy, CKD and coronary artery disease) [8]. In the SU-treated group, logistic regression analysis showed that gliclazide-treated participants had a higher likelihood of achieving an HbA1c of < 7% (< 53.0 mmol/mol; adjusted odds ratio [aOR] 1.09; 95% confidence interval [CI] 1.02–1.17; $p = 0.014$) and a lower likelihood of self-reported hypoglycaemia in the prior 3 months (aOR 0.81; 95% CI 0.72–0.92; $p = 0.001$) compared with those receiving other SU drugs [8].

These results differ from the results of RCTs and meta-analyses, which show similar HbA1c-lowering with gliclazide and other SUs [75–77]. The JADE authors speculated that ethnicity-related pharmacogenetic factors and the risk profile of the gliclazide-treated participants were the reasons for the superior effectiveness of gliclazide in the register [8].

HRQoL in the JADE Register

The JADE Register, designed to improve quality of care, is one of the few real-world studies to assess HRQoL in people with T2D. This is in contrast to other real-world studies, which are often based on administrative databases, that do not have a prespecified structure for data collection. In the JADE Register, HRQoL was assessed using the EuroQoL-5 Dimensions-3 Levels (EQ-5D-3L), a validated and widely used tool that provides a standardised measure of HRQoL [78]. The EQ-5D-3L includes five domains (i.e. mobility, self-care, usual activities,

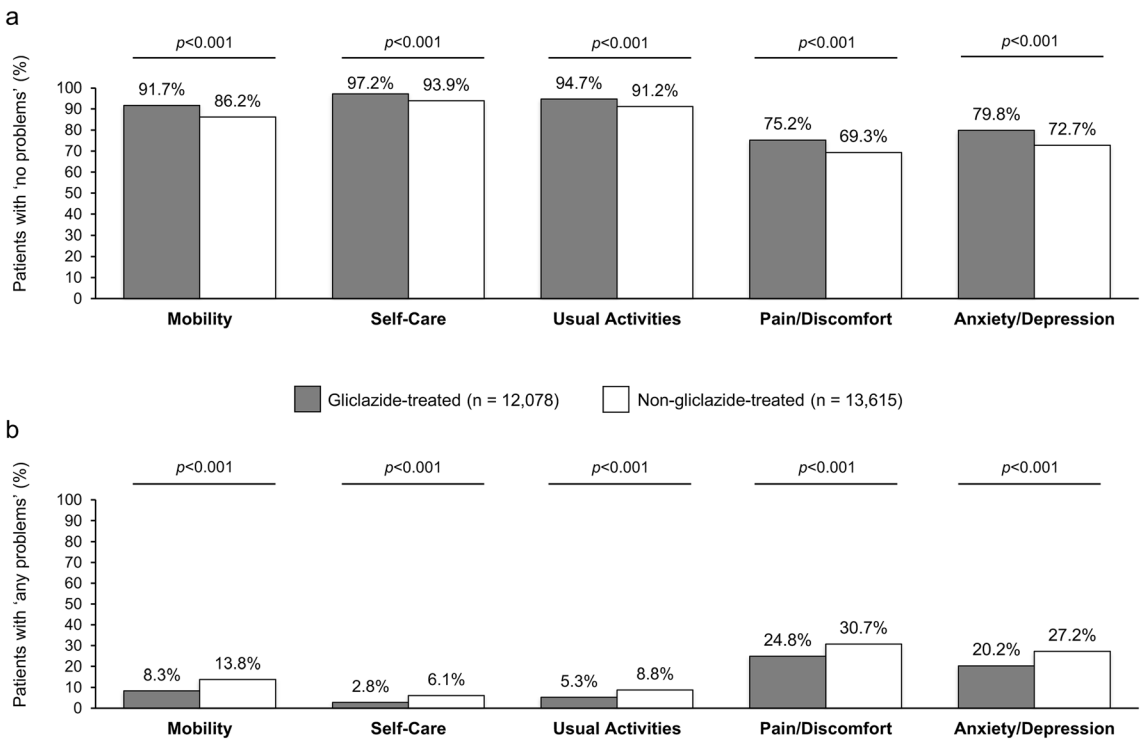

Fig. 4 Health-related quality of life with gliclazide versus other sulfonylureas among Asian people with type 2 diabetes in the JADE Register. The graphs show the proportion of participants with **a** 'no problems' and **b** 'any problems' (i.e. 'some problems' or 'extreme problems') for each EQ-5D-3L domain [79]. *EQ-5D-3L* EuroQol-5 Dimensions-3 Levels, *JADE* Joint Asia Diabetes Evaluation. Figure 4A was adapted from reference [79] Lim LL, Lau ESH, Pheng Chan S, et al. Real-world evidence on health-related quality of life in patients with type 2 diabetes mellitus using sulphonylureas: An analysis of the Joint Asia Diabetes Evaluation (JADE) Register. *Diabetes Research and Clinical Practice*. 2023. Published by Elsevier under a Creative Commons CC-BY license

pain/discomfort and anxiety/depression), each of which has three levels (i.e. 'no problems', 'some problems' or 'extreme problems'). The HRQoL analysis (full details presented as a poster at the IDF World Diabetes Congress, 2022) included 47,895 people with T2D who completed the EQ-5D-3L questionnaire, of whom 25,693 were receiving SU therapy (Fig. 3) [79].

In the preliminary HRQoL analysis, gliclazide-treated participants were more likely to report 'no problems' for the mobility, self-care, usual activities, pain/discomfort and anxiety/depression EQ-5D-3L domains than those receiving other SU agents (Fig. 4a) [79]. Similarly, gliclazide-treated participants were less likely to report any problems (i.e. 'some problems' or 'extreme problems') than non-gliclazide-treated participants across all five EQ-5D-3L domains (Fig. 4b). Amongst all SU-treated participants, the most frequently reported problems were related to the pain/discomfort and anxiety/depression domains [79]. These two negatively affected domains were also reported among people with T2D in a previous study [62].

In summary, in the preliminary analysis of the JADE Register, Asian people with T2D who received gliclazide-based regimens had better HRQoL than those receiving other SU agents, despite being older and having more diabetes-related complications. This might be due to the lower HbA1c levels, reduced risk of hypoglycaemia and lower rates of hypertension, dyslipidaemia and peripheral sensory neuropathy in the gliclazide group versus other SU-treated participants, in addition to the known differences in molecular structure and pharmacokinetic or pharmacodynamic properties amongst different SU agents [80–82].

CONCLUSIONS

Current ADA/EASD guidelines are based on the results of RCTs, but many real-world patients do not meet eligibility criteria for these studies. RWE plays an important role in the management of T2D by helping HCPs assess the effectiveness and applicability of GLDs use in routine clinical practice, and providing insights into patients' adherence, HRQoL and preferences. From a regulatory perspective, RWE continues to play an important role in monitoring longer-term safety but is starting to play a larger role in the approval and extension of indications for GLDs. However, the quality and integrity of the source data, study design and data analysis are of paramount importance if RWE is to have clinical utility and trustworthiness going forward. The two examples of real-world studies described here show how both retrospective and prospective data, including HRQoL data, can be collected across different countries to answer specific questions in T2D management, in this case the safety and effectiveness of SUs (particularly gliclazide) in T2D management. We encourage physicians to consider both RCT data and RWE when making treatment decisions for patients with T2D, since these two types of evidence provide complementary information about the likely effects of treatment in clinical practice.

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