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ORIGINAL RESEARCH

ADD2Dia: Real-World Clinical Effectiveness of Adding a Sodium-Glucose Cotransporter 2 Inhibitor to Gliclazide-Based Therapy in Type 2 Diabetes

Rodrigo O. Moreira · Nemencio A. Nicodemus Jr. · Abdurrahman Comlekci · Miao Yu · Mussa H. Almalki

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ABSTRACT

Introduction: This study investigated the real-world clinical effectiveness and tolerability of adding a sodium-glucose cotransporter 2 inhibitor (SGLT2i) to gliclazide modified release (MR)-based therapy in a sample of patients with type 2 diabetes (T2D) across five countries, and its value as an effective and well-tolerated strategy in T2D management in a diverse patient population, including those at high risk.

Methods: This non-interventional, retrospective chart review study included patients with T2D treated with gliclazide MR-based therapy and an SGLT2i for at least 60 days. The primary outcome was change in glycated hemoglobin (HbA1c) levels. Secondary outcomes included treatment patterns, proportion of patients achieving an HbA1c target < 7%, changes in lipid profile, blood pressure, weight, new-onset comorbidities, and adverse events of special interest (AESI).

Results: A total of 537 patients (47.7% female, mean age of 59.2 years, mean disease duration 10.0 years) were included, of whom 75.4% were obese/overweight and 15.1% had atherosclerotic cardiovascular disease (ASCVD). At baseline, HbA1c was uncontrolled (≥ 7%) in 87.2% of patients (mean HbA1c of 8.7% [SD 1.7]). Mean HbA1c reductions were – 1.1% (SD 1.8) at 6 months, – 0.7% (SD 1.9) at 2.4 years, and – 0.6% (SD 1.7) at 3 years. The proportion of

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R. O. Moreira (✉)
Instituto Estadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE), Rua Moncorvo Filho 90, Rio de Janeiro CEP 20211-340, Brazil
e-mail: rodrigomoreira@unipac.br

R. O. Moreira
Centro Universitário Presidente Antônio Carlos-Campus JF (UNIPAC/JF), Juiz de Fora, Brazil

N. A. Nicodemus Jr.
University of the Philippines-College of Medicine, Manila, Philippines

A. Comlekci
Dokuz Eylul University Medical School, Izmir, Turkey

M. Yu
Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

M. H. Almalki
Obesity, Endocrine, and Metabolism Centre, King Fahad Medical City, Second Cluster, Riyadh, Saudi Arabia

M. H. Almalki
College of Medicine, Alfaisal University, Riyadh, Saudi Arabia

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patients with HbA1c < 7% increased from 12.8% at baseline to 29.3% at least once during follow-up. Mean body weight decreased by 1.7 kg (95% CI – 2.2, – 1.3). AESIs were reported in 40 patients (7.4%) with urinary tract infections being the most common (6.8%).

***Conclusion*:** The first real-world study of the long-term combination of gliclazide MR and SGLT2i demonstrated its value as an effective and well-tolerated strategy in T2D management, particularly in high-risk populations. This combination provided clinically meaningful and sustained HbA1c reductions and improved cardiometabolic parameters in a diverse T2D population, with very few adverse events. These results align with current guidelines emphasizing the importance of early combination treatment and multifactorial risk management in T2D and highlight the need to address late treatment intensification indicative of clinical inertia.

***Trial Registration*:** ClinicalTrials.gov Identifier NCT06708091.

PLAIN LANGUAGE SUMMARY

A significant proportion of people with type 2 diabetes do not control their blood glucose (sugar) level despite taking medicines to reduce it. Poor glucose control increases the risk of heart, circulatory and kidney problems, and death. The ADD2Dia study investigated whether combining two diabetes medicines with different mechanisms would improve a key measure of glucose control called HbA1c in people with long-term, poorly controlled type 2 diabetes. The study was carried out in routine practice at 25 sites in five countries, so patients were typical of those doctors treat in their clinics. When patients added a sodium-glucose cotransporter inhibitor to the gliclazide modified release-based therapy they were already taking, there was a meaningful, early and long-term improvement in their glucose control, especially in those with highest HbA1c levels. The proportion of people who achieved the desired HbA1c target of less than 7% doubled from 12.8% at the start of the study to 29.3% at the end. There were also improvements in body weight, cholesterol, and blood pressure. Few adverse effects were reported, and rates of hypoglycemia (a potentially dangerous fall in glucose level) were low. The results are in line with current guidelines for doctors that stress the importance of early combination treatment for people with type 2 diabetes and the management of other risk factors for heart and circulatory diseases. They support the effectiveness and tolerability of gliclazide modified release and sodium-glucose cotransporter inhibitor in a wide range of people with poorly controlled type 2 diabetes.

Keywords: Combination treatment; Gliclazide MR; HbA1c; Real-world; SGLT2i; Type 2 diabetes

Key Summary points

Why carry out this study?
ADD2Dia is the first real-world study of the long-term combination of gliclazide MR and SGLT2i in a diverse T2D population, addressing existing real-world needs.
Despite existing therapies, a significant and worrisome number of patients remained uncontrolled 10 years after diagnosis, demonstrating an urgent need for practical, effective solutions.
What was learned from this study?
Gliclazide MR and SGLT2i combination provided clinically meaningful, early, and sustained HbA1c reductions and improved cardiometabolic parameters.
The results align with current guidelines emphasizing the importance of early combination treatment and multifactorial cardiovascular and renal risk management in T2D.
The good tolerability, with very few adverse events (including low levels of hypoglycemia) and strong persistence with the prescribed treatment, up to 3 years, support this combination as a practical, highly efficient, sustainable solution to tackle critical challenges being faced in diabetes care today.

INTRODUCTION

Diabetes is a major global health challenge, with type 2 diabetes (T2D) being the most prevalent form. In 2024, the International Diabetes Federation (IDF) estimated that diabetes affected 589 million adults, resulting in over 3.4 million deaths (9.3% of global deaths from any cause) [1]. The prevalence, currently 11.1%, is predicted to increase to 13% by 2050 [1]. Projections indicate a substantial increase in the number of people with diabetes in the coming years: 853 million by 2050 (13% of all cause global deaths), particularly in low- and middle-income countries.

Despite the availability of glucose-lowering drugs (GLDs), a significant proportion of patients with T2D exhibit suboptimal glycemic control. Achieving optimal glycemic control is paramount in T2D management to reduce the risk of micro- and macrovascular complications, including cardiovascular (CV) and kidney disease events, as well as all-cause mortality [2, 3].

Data from the UK Prospective Diabetes Study (UKPDS) and other trials of GLDs have consistently supported early and optimal control of both blood glucose and cardiometabolic risk factors to reduce CV and kidney disease events and all-cause mortality, with legacy effects lasting at least 20 years [4–9]. However, clinical inertia often prevents patients with poor control from moving to more intensive therapy [10–12]. Recent data from the US National Health and Nutrition Examination Survey (NHANES) suggest that, even with the new medications available, the number of patients with T2D achieving an HbA1c < 7% has decreased from 54.3% in 2017–2020 to only 43.5% in 2021–2023 [13].

Current international guidelines emphasize the importance of both glucocentric and cardiorenal approaches to T2D management [3, 14, 15]. The latest 2025 IDF guidelines support early combination treatment based on the need for additional glycemic efficacy and cardiorenal protection at treatment initiation to extend the time to treatment failure, along with multifactorial risk management (e.g., weight, lipid profile, and blood pressure control) [3]. They strongly recommend the addition of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) for individuals with T2D not at glycemic target, irrespective of cardiorenal risk.

GLDs with complementary mechanisms of action have the potential to provide both glycemic control and cardiorenal protection in T2D [16–19]. Sulfonylureas (SU) stimulate insulin secretion, addressing a key underlying defect in T2D, while SGLT2i lower hyperglycemia via an insulin-independent mechanism (by promoting renal glucose excretion), allowing combination with other antidiabetic drugs with minimal risk of hypoglycemia. Gliclazide modified release (MR) is a once-daily SU with a lower incidence of severe hypoglycemia than other SUs. The combination of SGLT2i and SU, with or without metformin, is expected to provide holistic care to patients with T2D, offering complementary mechanisms of action and clinical benefits, including glycemic control, weight management, and cardiorenal protection.

Recent evidence supports an expanding role for SGLT2i in heart and kidney health [14, 20–26]. SGLT2i have demonstrated benefits across a broad range of cardiometabolic disease, reducing in patients with T2D the risk of hospitalization for heart failure (HF) by 28%, CV death by 15%, as well as all-cause mortality by 13% [22]. The recent SMART study showed an important reduction in the risk of major adverse cardiovascular events (MACE) irrespective of atherosclerotic cardiovascular disease (ASCVD), diabetes, or kidney function [26]. Among available SGLT2i, dapaglifozin showed benefits in different patient profiles [27–39]. The post hoc analyses of the DECLARE-TIMI 58 trial showed that dapagliflozin reduced the risk of first and subsequent hospitalizations in patients with T2D at high CV risk, including those without evidence of CV disease [40].

While all classes of antidiabetic drugs have been shown to improve glycemic control when added to an SU, the addition of an SGLT2i has resulted in superior effects in terms of weight loss, with no increased risk of hypoglycemia [41].

In the DECLARE-TIMI 58 trial of dapagliflozin and the EMPA-REG Outcome trial of empagliflozin, approximately 43% of patients were

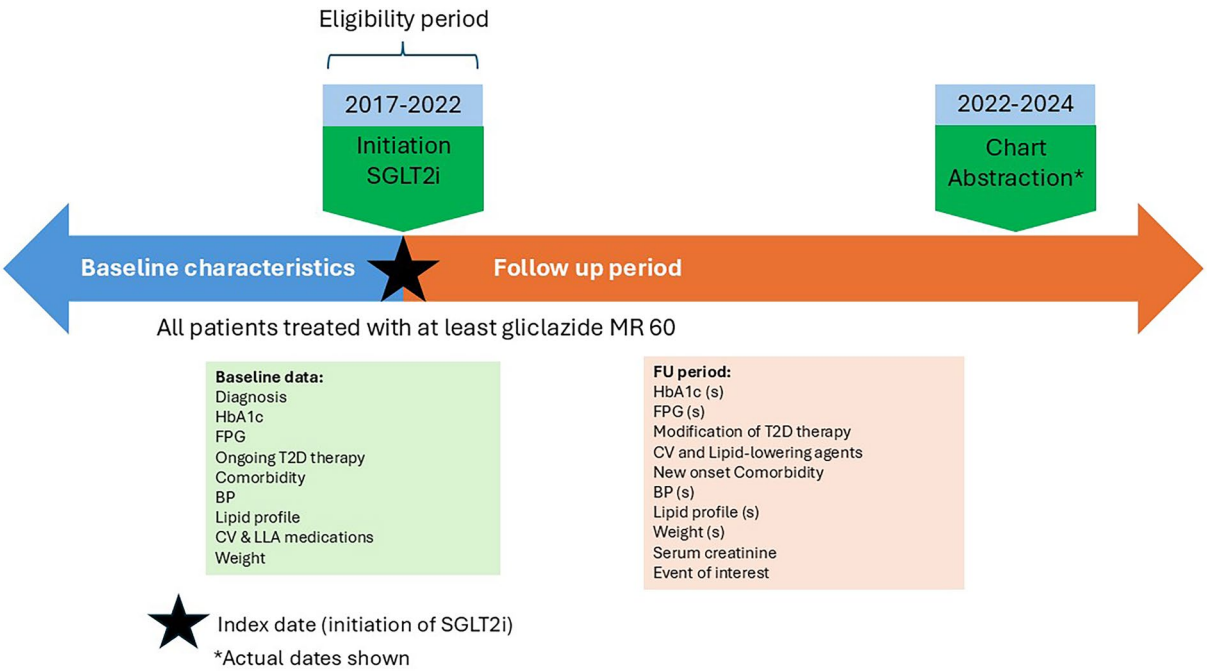


Fig. 1 Study design. SGLT2i, sodium-glucose cotransporter 2 inhibitor; MR, modified release; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; T2D, type 2 diabetes; BP, blood pressure; CV, cardiovascular; LLA, lipid-lowering agents

taking an SU [37, 42], but few studies have assessed the effectiveness of SUs combined with an SGLT2i in a real-world setting, and none have specifically assessed gliclazide MR in combination with an SGLT2i. To better understand the benefits of combination treatment in a diverse population of patients with T2D treated in a range of different healthcare systems, the retrospective international ADD2Dia study evaluated the real-world effectiveness and tolerability of combining gliclazide MR with an SGLT2i.

METHODS

This non-interventional, retrospective chart review study aimed to evaluate the effectiveness of combining an SGLT2i with gliclazide MR in patients with T2D. The study included adult patients (≥ 18 years) diagnosed with T2D at least 2 years prior to SGLT2i initiation. All patients were on gliclazide MR at a minimum dose of 60 mg/day at the index date, defined as the date when SGLT2i was added to gliclazide MR, also referred to as baseline (Fig. 1). SGLT2i were introduced at the index date (baseline) when a physician prescribed add-on therapy with SGLT2i to gliclazide MR. Treatment continued up to discontinuation of the combination therapy, date of data collection initiation, loss to follow-up, or death, whichever occurred first. This study was non-interventional and the protocol did not interfere with standard medical care. No specific recommendations concerning dose escalation were provided.

Permitted background therapies alongside gliclazide MR at index date included metformin, dipeptidyl peptidase 4 inhibitors (DPP4i), and low dose insulin (up to 20 units/day). This low dose needed to be stable for a minimum of 3 months prior to the index date. High doses of insulin can mask the effects of oral GLDs and, by limiting the insulin dose, a controlled and standardized environment was created for evaluating the efficacy of the tested drugs without the confounding influence of high insulin

levels. The approach minimized variability and allowed a clearer comparison of the effects of the oral GLDs, ensuring consistency/accuracy of the trial results.

Exclusion criteria included diagnosis of type 1 diabetes (T1D), use of non-permitted GLD at baseline, having a life-threatening cancer with life expectancy of less than 1 year at index date or treatment with chemotherapy, oral or intravenous steroids at that date, or enrollment in a therapeutic investigational drug or device trial during the post-index period. Informed consent for medical record review and the use of research-related health information was obtained in accordance with local regulations.

Between January 2017 and June 2022, patients were initiated on an SGLT2i and the combination continued for a minimum of 60 days. Data collection was completed by May 2024. Patients were enrolled in the study across 25 sites: in Brazil (7), China (2), the Philippines (7), Saudi Arabia (4), and Turkey (5).

The primary objective of the study was to evaluate the effectiveness of gliclazide MR and SGLT2i combination therapy in patients with T2D, as measured by changes in glycated hemoglobin (HbA1c) levels from baseline to end of follow-up. For the primary analysis, the global population included participants with at least two HbA1c measurements: one at baseline and another ≥ 60 days after SGLT2i initiation. As HbA1c reductions can be influenced by different factors, an additional confirmatory analysis was performed. Taking into account these parameters (baseline HbA1c, age, disease duration, baseline glomerular filtration rate [eGFR], gliclazide MR dose level, gender, prior CV disease, body mass index [BMI], baseline fasting blood glucose [FBG], metformin at baseline, DPP4i at baseline, insulin at baseline, summary renal disease at baseline, summary hypertension at baseline, baseline total cholesterol, baseline high density lipoprotein-cholesterol (HDL-c), baseline low density lipoprotein LDL-cholesterol (LDL-c), and baseline triglyceride [TG]), in those patients with available values, the mixed-effects model for repeated measures (MMRM) statistical test was used (see Statistical Analysis). Secondary objectives included assessment of treatment patterns of SGLT2i–gliclazide MR combination therapy and the proportion of patients reaching HbA1c targets. Additionally, changes in lipid profile, blood pressure, weight, and the onset of new comorbidities were evaluated. Only adverse events of special interest (AESI) were evaluated in the context of this retrospective analysis.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were reported as frequency and percentages (*n*, %), and two-sided 95% confidence intervals (CIs) were applied.

The HbA1c change from baseline to each month post-index of gliclazide MR–SGLT2i combined treatment was estimated by MMRM in a two-step approach. As the first step, a MMRM including the month (time) and the HbA1c baseline value as fixed effects was used to select the best variance–covariance structure matrix based on the overall sample of patients and was maintained for any subgroup analyses performed (e.g., for the subgroup of patients with a baseline HbA1c value ≥ 7). As the second step, a *K*-fold cross-validation was used to select the baseline demographics and clinical characteristics as covariate for adjustment. The data were partitioned between the training set (4/5) and the test set (1/5). Model performance was assessed using average squared error (ASE). Age, disease duration, and time-varying gliclazide MR dose level were forced in every model as key variable. BMI, baseline eGFR, FPG, total cholesterol, HDL, and LDL were selected by the cross-validation model as covariates. Final analyses were performed after database lock, according to the SAP (version 2.0, 06 March 2024) using SAS Enterprise Guide Version 8.3 (SAS Institute, Cary, NC).

Ethical Approval

The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Ethics approval was received from appropriate committees in each of the countries where the study was conducted, representing all the sites that were included (Supplementary

Table 1). Informed consent for medical record review and the use of research-related health information was obtained in accordance with local regulations.

RESULTS

From 575 patients with T2D enrolled in the study, 537 were included in the analysis, while 38 were withdrawn as a result of not meeting one or more eligibility criteria. At baseline, 87.2% of the population had uncontrolled HbA1c (≥ 7%), predominantly in the primary prevention group. The mean baseline HbA1c in this population was 9.0%, the median value was 8.7%, and the min/max values were distributed between 7% and 14.2%. At baseline more than 75% of patients were overweight/obese, and presented comorbidities (mostly hypertension and dyslipidemia) (Table 1). Medication use at baseline is summarized in Table 2.

Patients had been diagnosed with T2D for an average of 10.0 years, and an SGLT2i was added at an average of 37.3 months after starting gliclazide MR. Dapagliflozin was initiated in 273 patients (50.8%), empagliflozin in 249 (46.4%), and canagliflozin in the remaining 15 (2.8%) of patients. Mean (SD) daily doses of dapagliflozin, empagliflozin, and canagliflozin were 9.7 mg (1.2), 15.6 mg (7.4), and 100 mg (0.0), respectively.

SGLT2i was initiated mostly for glucose control alone (57.4%), but also for glucose control combined with other benefits: CV (29.8%), renal (20.1%), weight management (21.4%), or lower risk of hypoglycemia (19.2%). The median duration of treatment with both gliclazide MR and SGLT2i was 29.7 months.

HbA1c reduction was observed at 6 months, and was maintained for up to 3 years (Table 3). The proportion of patients achieving target HbA1c levels (< 7%) increased from 12.8% at baseline to 29.3% at least once during follow-up. These descriptive results were confirmed in patients eligible for the MMRM statistical tests (Fig. 2).

Sixty percent of patients remained on the combination of gliclazide MR + SGLT2i for more than 2 years, with a median time to the first gliclazide MR dose modification of 13 months (range 0–76.5 months) and a median time to first SGLT2i dose modification of 18.9 months (range 0.2–54.2). Thirty percent of patients remained on the combination therapy gliclazide MR + SGLT2i for more than 3 years. The combination was discontinued in 2.2% of patients compared to 6.9% with gliclazide MR alone and 7.6% with SGLT2i alone. A total of 78 patients (14.5%) and 26 patients (4.8%) had a post-baseline dose modification of gliclazide MR, and SGL2i respectively. Intensification of CV and lipid-lowering medications was observed in 13.4% and 18.1% of patients, respectively, mostly involving antihypertensives and statins.

Patients treated with combination therapy presented additional improvements in body weight, lipid profile (except LDL-c), and systolic/diastolic blood pressure (Table 4). With regard to BP, SBP/DBP values were within normal range at the end of follow-up (mean SBP 129.6 mmHg; DBP 75.3 mmHg).

AESIs were reported by 40 out of 537 patients (7.4%). Overall, urinary tract infections were reported in 26 patients (4.8%), genital mycosis in six (1.1%), and hypoglycemia in five (0.9%), none of which were severe. Additionally, bone fractures were reported in two patients (0.4%), amputation in one (0.2%), and one (0.2%) case of mild diabetic ketoacidosis. New-onset CV disease (including hypertension), dyslipidemia, neuropathy, and psychiatric disease occurred in 5.0% (1.7%), 4.1%, 2.4%, and 0.9%, respectively. New-onset renal disease occurred in four (0.7%) patients.

Seven patients experienced chronic kidney disease (CKD)-related events during follow-up: six patients showed doubling of serum creatinine (with one case attributed to data entry error, two to dehydration, and three to actual renal function decline) and one patient, with an eGFR of 15.1 mL/min/1.73 m^2 at baseline, had a reduction of eGFR to less than 15 mL/min/1.73 m^2.

CV events included three MACE, two new-onset HF cases, and three hospitalizations among patients with pre-existing HF. No mortality occurred.

Table 1 Baseline characteristics of patients ($N = 537$)

Characteristic	Value
Mean age (years)	59.2
Range 18–64 years	373 (69.5%)
Sex	
Male	281 (52.3%)
Female	256 (47.7%)
Mean weight kg (SD)	76.7 (16.9)
Mean BMI kg/m^2 (SD)	29.0 (5.4)
BMI > 30 kg/m^2	134 (38.4%)
BMI 25–30 kg/m^2	129 (37.0%)
Duration of T2D at baseline (years)	
Mean (SD)	10.0 (6.8)
Median (range), years	8.7 (1.9–42.0)
Mean HbA1c (SD)	8.7% (1.7)
HbA1c < 7%	69 (12.8%)
HbA1c ≥ 7%	468 (87.2%)
HbA1c > 8%	336 (63.0%)
HbA1c > 9% (%)	197 (36.7%)
Mean fasting blood glucose mg/dL (SD)	180.9 (61.8)
Mean blood pressure (SBP/DBP) mmHg (SD)	131.6/77.4 (16.7/9.9)
Mean total cholesterol (mg/dL) (SD)	181.4 (47.3)
Mean LDL-C (mg/dL) (SD)	102.7 (39.9)
Mean HDL-C mg/dL (SD)	44.7 (13.2)
Mean TG (mg/dL) (SD)	174.4 (94.9)
Mean serum creatinine (mg/dL) (SD)	0.9 (0.3)
Comorbidities[a]	
CV Comorbidities	361 (67.2%)
eASCVD	100 (15.1%)
Atrial fibrillation	2 (0.4%)
Heart failure	8 (1.5%)
Hypertension	341 (63.5%)
Dyslipidemia	321 (59.8%)
Neuropathy	66 (12.3%)
Renal disease	37 (6.9%)
Psychiatric disorders	22 (4.1%)

BMI body mass index, *T2D* type 2 diabetes, *SD* standard deviation, *HbA1c* glycated hemoglobin, *SBP* systolic blood pressure, *DP* diastolic blood pressure, *LDL-c* low density lipoprotein cholesterol, *HDL-c* high density lipoprotein cholesterol, *TG* triglyceride, *CV* cardiovascular, *eASCVD* established atherosclerotic cardiovascular disease

[a]Based on investigator's diagnosis

DISCUSSION

The ADD2Dia study results hold particular clinical relevance, indicating that therapy with gliclazide MR and an SGLT2 inhibitor remains effective even in challenging, difficult-to-treat populations, characterized by long-standing, poorly controlled diabetes (HbA1c > 8% in 63% of patients, with fewer than 15% achieving target glycemic levels), where treatment intensification has been delayed. In ADD2Dia, the combination of gliclazide MR and an SGLT2i produced rapid glycemic improvements following initiation, before any dose or treatment modifications were made. This early improvement was sustained over the long term, with a 0.6% reduction in HbA1c observed up to 3 years, underscoring the benefits of this combination therapy in real-world practice. As expected, the HbA1c change was linearly related to the baseline HbA1c level. A significant reduction of 1.9% was observed in more complicated patients having HbA1c > 9%. This finding has important implications for clinicians, as it suggests that this combination therapy may delay the need for insulin in such patients [43].

Table 2 Baseline medication of patients ($N = 537$)

Baseline medication	Value
Mean (SD) number of treatments	1.3 (0.7)
Gliclazide MR + other GLDs	461 (85.8%)
Gliclazide MR only	76 (14.2%)
Metformin	417 (77.7%)
DPP4i	267 (49.7%)
Low dose insulin	36 (6.7%)
Oral combination (SPC)	168 (31.3%)
CV medications	332 (61.8%)
ARBs	217 (65.4%)
ACEis	51 (15.4%)
CCBs	113 (34%)
Beta-blockers	92 (27.7%)
Salicylates	76 (22.9%)
Diuretics	65 (19.6%)
Antiplatelets	33 (9.9%)
Anticoagulant	6 (1.8%)
Others	14 (4.2%)
Lipid-lowering medications	364 (67.8%)
Statin	313 (86.0%)
Cholesterol absorption inhibitor	25 (6.9%)
Fibrate	34 (9.3%)
Other medication	89 (24.5%)

MR modified release, *GLD* glucose-lowering drug, *DPP4i* dipeptidyl peptidase 4 inhibitor, *SPC* single-pill combinations, *ARB* angiotensin receptor blocker, *ACEi* angiotensin-converting enzyme inhibitor, *CCB* calcium channel blocker

The effectiveness of this combination was further supported by the doubling of the proportion of patients achieving HbA1c < 7% during the follow-up period, increasing from 12.8% at baseline to 29.3%. The statistical MMRM approach in a subset of patients corroborated these results.

Moreover, treatment persistence in the ADD2Dia study was remarkably high, with 30% of patients remaining on the combination therapy, gliclazide MR + SGLT2i, for more than 3 years, compared to other real-world studies in which only 18% of DPP4i users remained persistent at 12 months [44].

The combination treatment was well tolerated with few adverse events including only mild hypoglycemic episodes, while simultaneously conferring benefits on body weight and cardiometabolic risk factor control.

In routine clinical practice, many patients with T2D experience challenges in achieving adequate glycemic control despite the availability of several medications. Research indicates that treatment intensification is often delayed, even though guidelines emphasize early intervention as vital for reducing complications. While randomized controlled trials (RCTs) offer robust evidence of a treatment's efficacy in controlled settings, real-world evidence (RWE) provides valuable insights into its effectiveness in routine clinical practice. RCTs typically demonstrate greater HbA1c reductions (ranging from 0.8% to 1% in RCTs with SU + SGLT2i) due to strict protocol adherence and optimized treatment conditions [19, 45–47]. In contrast, RWE

Table 3 HbA1c change according to time period

	6 months	End of follow-up (29.1 months)	Up to 3 years
Global population, $n = 537$	− 1.0% (SD 1.7)	− 0.7% (SD 1.9)	− 0.6% (SD 1.7)
Uncontrolled population at baseline (patients with HbA1c ≥ 7%), $n = 468$	− 1.1% (SD 1.8)	− 0.9% (SD 1.9)	− 0.8% (SD 1.5)

HbA1c glycated hemoglobin, *SD* standard deviation

studies often report more modest glycemic improvement, reflecting the complexities of actual clinical practice, including variable medication adherence, lifestyle factors, and heterogenous patient populations. In ADD2Dia, the reduction observed in HbA1c was comparable to that observed in RCTs.

The baseline characteristics of the ADD2Dia study population demonstrated the late treatment intensification indicative of clinical

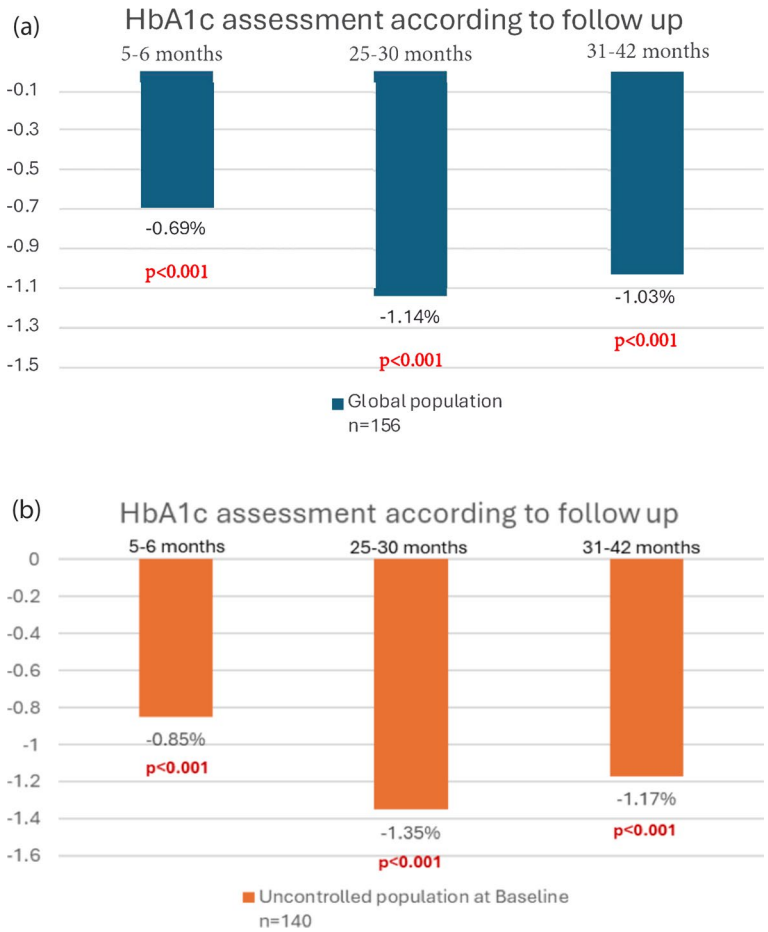


Fig. 2 HbA1c evolution during follow-up in **a** the global population and **b** the population with HbA1c ≥ 7% at baseline (MMRM test). HbA1c, glycated hemoglobin; MMRM, mixed-effects model for repeated measures

Table 4 Assessment of biological parameters during the follow-up period in the overall population ($n = 537$)

Parameter	Change from baseline to end of follow-up	
	Mean change (SD)	95% CI
Body weight (kg)	− 1.7 (4.4)	− 2.2, − 1.3
SBP (mmHg)	− 2.0 (17.8)	− 3.9, − 0.1
DBP (mmHg)	− 2.1 (10.7)	− 3.2, − 1.0
Total cholesterol (mg/dL)	− 11.4 (50.3)	− 16.7, − 6.1
LDL-c (mg/dL)	− 6.5 (44.4)	− 11.9, − 1.0
HDL-c (mg/dL)	+ 0.3 (12.5)	− 1.2, 1.7
Triglycerides (mg/dL)	− 17.5 (86.4)	− 27.0, − 8.0
Serum creatinine (mg/dL)	0.0 (0.3)	− 0.0, 0.0

SD standard deviation, *CI* confidence interval

inertia, an issue identified in previous T2D studies [12, 48–51]. This situation, observed in real-world clinical practice, contrasts with recently updated guideline recommendations, which support combination therapy at treatment initiation and early treatment intensification. Early and intensive glycemic control in T2D not only reduces micro- and macrovascular complications but also has a legacy effect in reducing the risk of complications [3, 14, 15, 20]. Guideline recommendations are based on landmark trials (VERIFY [52], UKPDS [5]), demonstrating greater and durable long-term benefits for patients. Long-term (44 years) follow-up data from UKPDS showed that early intensive glycemic control resulted in significant risk reductions in death from any cause, myocardial infarction, and microvascular complications (10%, 17%, and 26%, respectively) [5]. Additionally, new data from the ADVANCE study showed that intensive glucose lowering may be recommended irrespective of age at diagnosis or diabetes duration, with the combined micro- and macrovascular benefits maintained in patients with younger-onset (< 50 years of age) and longer duration of diabetes (> 10 years) [53]. Finally, a recently published expert position paper highlights the importance of early intensive glycemic control as key to T2D management [2].

Balancing the focus on glycemic control and organ protection, particularly for those at low risk of cardiorenal complications in both optimal and basic care, is now clearly recommended in the 2025 IDF guidelines [3], especially with SGLT2i, usually added to metformin (to mitigate the consequences of poor glycemic control and to improve cardiorenal outcomes), and with any oral GLD. In this context, the combination of new-generation SU (gliclazide MR) with SGLT2i can be beneficial. Supporting evidence comes from a clinical trial comparing glimepiride (SU) monotherapy versus glimepiride plus dapagliflozin (SGLT2i) in patients with inadequately controlled T2D on SU monotherapy [45]. The combination therapy demonstrated superior glycemic control, with significantly greater HbA1c reductions compared to SU alone [45].

In addition to this evidence, several clinical trials have demonstrated the beneficial effects of SGLT2i in reducing MACE, renal and HF events, and CV death in patients with T2D [22–26, 54–57]. The low incidence rates of major CV events (0.23 events per 100PYs) and kidney events (0.54 events per 100 PYs) observed in our study are consistent with results of the CANVAS trial [58] and aligned with results from CREDENCE, SUGAR-DM-HF, DAPA-CKD, and DAPA-HF trials [22–26, 54–57]. Recently, the SMART-C study showed that SGLT2i consistently reduced MACE across a broad range of patient profiles and all key subgroups, irrespective of ASCVD, diabetes, or kidney function [59].

There were limitations in the design of ADD2Dia, as is common with most observational cohort studies. As a retrospective chart review, this study is subject to limitations including potential selection bias, incomplete data capture, and lack of a control group. The ADD2Dia study was conducted in real-world clinical practice and was non-interventional. Randomization by sex was not specified in the study protocol, and both men and women were included without any specific restrictions. Almost all RCTs to date have failed to demonstrate a difference in glycemic control

between male and female participants. It seems that gender is not a variable that significantly impacts response to SGLT2 inhibitors. Therefore, we did not believe that analyzing data according to gender would lead to significant results.

Efforts were made to include physicians who varied by geographical location, specialty, and practice setting to increase the generalizability of the data. In real-world settings, the absence of standardized follow-up intervals may affect the precision of outcome measurement, though the case report form was developed with flexibility to allow diverse usual care patterns and outcome data to be collected.

Index treatment combinations may have contributed to efficacy, and patients may have been less inclined to report mild AESIs (e.g., mild UTI or hypoglycemic events) to their physicians, so these events may have been underrepresented in medical charts.

Enrolled patients already received gliclazide MR at a stable minimum dose of 60 mg at baseline, suggesting that gliclazide was well tolerated in these patients, and adherence to gliclazide MR or SGLT2i during the study was not assessed. The end of study period for each patient was defined as discontinuation of the combination therapy, date of data collection initiation, loss to follow-up, or death, whichever occurred first. Consequently, the documented duration of the index treatment may have been shorter than the actual duration, suggesting that patients could have been on the combination treatments for longer than reflected in the study data.

CONCLUSION

The first-real world study of the long-term combination of gliclazide MR and SGLT2i demonstrated its value as an effective and well-tolerated strategy in T2D management, particularly in high-risk populations. This combination provided early and sustained HbA1c reductions and improved cardiometabolic parameters with very few hypoglycemic events. The results align with current guidelines emphasizing early combination treatment and multifactorial risk management in T2D and provide evidence supporting the effectiveness and tolerability of gliclazide MR + SGLT2i for managing T2D in diverse populations.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Rodrigo Moreira: Fees as speaker from Servier, Novo Nordisk, AstraZeneca, Bayer, Eli Lilly. Nemencio A Nicodemus Jr.: Speaker honoraria from Servier, AstraZeneca, Boehringer Ingelheim and Taisho. Abdurrahman Comlekci: No conflict of interest. Miao Yu: Honoraria for speaker engagement from MSD, Novo Nordisk, Sanofi, Eli Lilly, Novartis, Servier and AstraZeneca; has served on Advisory boards for Novo Nordisk, Sanofi, MSD, Eli Lilly, Roche and AstraZeneca. Mussa H Almalki: No conflict of interest.

Ethical Approval. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Ethics approval was received from appropriate committees in each of the countries where the study was conducted, representing all the sites that were included (Supplementary Table 1). Informed consent for medical record review and the use of research-related health information was obtained in accordance with local regulations.

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