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Comparative effectiveness of gliclazide modified release versus sitagliptin as second-line treatment after metformin monotherapy in patients with uncontrolled type 2 diabetes

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Abstract

Aims: To compare the effectiveness and safety of gliclazide modified release (MR) to sitagliptin as type 2 diabetes mellitus (T2D) treatments in a real-world patient population.

Materials and Methods: This retrospective cohort study used records from the UK Clinical Practice Research Datalink. The cohort consisted of adult patients with T2D newly treated with either gliclazide MR or sitagliptin as second-line treatment added to metformin and with a glycated haemoglobin (HbA1c) level of ≥7.0% (53 mmol/mol). Patients were 1:1 matched using high-dimensional propensity score matching and followed to determine the time taken to reach an HbA1c <7.0%. Secondary outcomes included time to HbA1c ≤6.5% (48 mmol/mol), time to ≥1% (11 mmol/mol) HbA1c reduction from baseline, treatment persistence and durability, and hypoglycaemic events.

Results: Among the 1986 patients included, those on gliclazide MR more likely achieved an HbA1c <7.0% [hazard ratio (HR): 1.35; 95% confidence interval (CI): 1.15-1.57], HbA1c ≤6.5% (HR: 1.51; 95% CI: 1.19-1.92) or had an HbA1c reduction ≥1% from baseline (HR: 1.11; 95% CI: 1.00-1.24) compared with patients on sitagliptin. Durability (log-rank P = .135) and persistence (P = .119) were similar between the two groups. Hypoglycaemic events were uncommon (23 total severe and non-severe events; incidence rate, 3.7 per 1000 patient years), with 4.7 and 2.6 events per 1000 patient years with gliclazide MR and sitagliptin treatment, respectively.

Conclusions: In this real-world study, second-line gliclazide MR was more effective than sitagliptin in reducing HbA1c, with similar durability and persistence and low rates of hypoglycaemic events, in individuals with T2D on metformin treatment and HbA1c above the target of 7.0%.

KEYWORDS

glycaemic control, pharmacoepidemiology, primary care, sitagliptin, sulfonylureas

1 | INTRODUCTION

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder characterized by high blood glucose levels and associated with long-term micro- and macrovascular complications, which increase the burden for both the patient's health and treatment costs.[1]

Glucose-lowering therapies aim at maintaining glycaemic control while reducing the risk of hypoglycaemic events. To this end, current T2D treatment guidelines from the UK National Institute of Health and Care Excellence, the American Diabetes Association jointly with the European Association for the Study of Diabetes, and the European Society on Cardiology recommend individualized patient care, which includes evidenced-based patient education, dietary advice and medication.[2–5] Metformin is generally recommended as a first-line treatment for T2D and, when blood glucose levels remain high, guidelines recommend therapy intensification by the addition of second-line medications. Individualization of second-line medication depends on a number of considerations, including cost, body weight, cardiovascular risk factors and risk of hypoglycaemia.[2–4] Despite the introduction of newer T2D treatments, glycaemic control remains unsatisfactory in many patients.[6]

A recent retrospective study of 10 256 patients with T2D initiating second-line treatment in Germany and the UK found that sulfonylureas (SUs) were selected as add-on therapy in 40.9% of patients and dipeptidyl peptidase-4 (DPP-4) inhibitors in 30.7%.[7] SUs have a long history of clinical use and are recognized as a cost-effective method of blood glucose control.[8] Currently, many different SUs and DPP-4 inhibitors are available for the treatment of T2D. Gliclazide modified release (MR) – a once-daily SU that allows for a progressive release of medication – reduces glycated haemoglobin (HbA1c) in patients with T2D with efficacy similar to the once-daily SU glimepiride, but with significantly fewer hypoglycaemic events.[9] A systematic review of randomized controlled trials shows that gliclazide MR has a significantly reduced risk of hypoglycaemia in comparison with other SUs.[10] A further study shows that, compared with standard glucose control, an intensive glycaemic control with gliclazide MR as the first-line agent and addition to other agents, if required, can achieve a lower mean HbA1c [6.5% (48 mmol/mol) vs. 7.3% (56 mmol/mol)] and reduces the incidence of combined major macro- and microvascular events.[11]

Sitagliptin is a commonly used DPP-4 inhibitor shown in a meta-analysis of randomized controlled trials to have an efficacy similar to SUs grouped as a general medication class.[12] Furthermore, comparison of specific DPP-4 inhibitors and SUs in long-term randomized clinical trials have shown a similar reduction of risk of cardiovascular events in high-risk patients.[13] However, individual SUs, such as gliclazide MR, have been shown to have different treatment properties.[8,10,14] Thus, a direct comparison of individual SUs to DPP-4 inhibitors may more accurately reflect the differences between specific treatments in these two medication classes.

In this study, we used primary care data to compare the effectiveness and safety of gliclazide MR and sitagliptin as second-line T2D treatments after optimal metformin monotherapy in a real-world patient population.

2 | MATERIALS AND METHODS

This retrospective study was conducted following the RECORD-PE guidelines[15] for conducting and reporting studies using routinely collected observational data (checklist in the Appendix) and a protocol approved by an Independent Scientific Advisory Committee (ISAC; protocol No. 19_149). Codes used to define the cohort, medical conditions, medications and outcomes are reported in the Appendix.

2.1 | Patients

Patient records from the UK Clinical Practice Research Datalink (CPRD Gold) database, that were linked to the Hospital Episode Statistics Admitted Patient Care (HES APC) and the Office for National Statistics (ONS) Death Registration databases, were used to determine all patient characteristics and effectiveness outcome data in this study. Adult patients (≥18 years old), with a documented diagnosis of T2D, ≥1 year of 'up-to-standard' follow-up (i.e. ≥1 year from the date the practice data meet minimum quality criteria for research), at least one HbA1c measurement ≥7% (53 mmol/mol) in the 6 months before entry, initiating treatment with gliclazide MR or sitagliptin (first prescription) as an add-on to metformin treatment between 1 January 2010 and 21 October 2019 were included in this study (Table S1). Patients with a diagnosis of type 1 or any other specific diabetes (e.g. gestational, secondary, steroid, mature onset diabetes of the young) were excluded.

2.2 | Exposures

Treatment initiation was defined as ≥2 prescriptions of the study drug without a ≥90-day gap between the termination of the first prescription and initiation of the second.

2.3 | Outcomes

The primary outcome was time to HbA1c level of <7.0% (53 mmol/mol). Secondary outcomes included time to an HbA1c level of ≤6.5% (48 mmol/mol) and to a ≥1% (11 mol/mol) HbA1c reduction from baseline. Further secondary outcomes included treatment duration as measured by both durability (the treatment duration until stop, switch, or add-on of a new glucose-lowering drug) and persistence (the treatment duration until stop or switch, regardless of add-on glucose-lowering drug). A switch was defined as the prescription of a new glucose-lowering drug occurring after the last prescription of index drug and within 90 days after index drug discontinuation; a stop as the absence of switch within 90 days after the index drug discontinuation; and an add-on as the initiation of a new glucose-lowering drug with at least two prescriptions before the index drug discontinuation. Hypoglycaemic events (defined both in HES – severe episodes resulting in hospital admission, and in CPRD – severe and non-severe

episodes recorded in clinical practice records) were also measured as a secondary outcome.

2.4 | Assessment window

Following an on-treatment approach, patient records were followed from study entry (1 January 2010) until treatment stop, switch or end of study (21 October 2019). The HbA1c assessment window started 60 days after a patient's index date (i.e. treatment initiation with index drug) and ended 30 days after treatment stop, switch or add-on of a new glucose-lowering drug. As HbA1c measurement may reflect the past 2-3 months of treatment, this window was designed to capture effects of the former drug with no interference from the newly initiated drug. The hypoglycaemic event assessment window started upon treatment initiation and ended with treatment stop, switch or add-on of a new glucose-lowering drug. Baseline characteristics were captured any time before the index date for medical conditions and ethnicity, and as the closest information preceding the index date, within: any time for smoking; 3 years for body mass index; and 1 year for alcohol intake, medications and biochemical tests. The practice-level index of multiple deprivation, a weighted score calculated from several indicators (income, employment, education, skills and training, health and disability, crime, barriers to housing services and living environment), was estimated in 2015.

2.5 | Statistical analysis

All statistical analyses were performed in Stata (version 16.0). To mitigate confounding because of underlying differences in baseline characteristics, high-dimensional propensity score (hd-PS) was used to match patients who initiated gliclazide MR with those who initiated sitagliptin. hd-PS matching was performed on the study population without missing data (Table S2). This was based on a logistic regression model using baseline covariates, which were deemed a priori confounders of the association between treatment and outcome (Table S2), and 300 empirical covariates identified from the data dimensions clinical, referral and drug prescriptions.[16] To exclude patients treated most contrary to prediction, symmetric propensity score trimming was performed and assessed with various cut points. To compare all primary and secondary outcomes, new users of gliclazide MR were matched with <0.12 calliper to new users of sitagliptin with a fixed ratio 1:1; differences between the two groups in baseline characteristics were estimated before and after matching as standardized differences.

The Cox proportional hazards model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CI) for all HbA1c outcomes. Durability and persistence were compared using the log-rank test. For hypoglycaemia, incidence rates were estimated in gliclazide MR and sitagliptin groups; the first event recorded during the hypoglycaemia assessment window was considered. We used both HES APC data, which records patients admitted to hospital with a diagnosis of hypoglycaemia, and CPRD records, which captures both severe and non-severe events.

Exploratory subgroup analyses for the primary effectiveness outcome were performed in the full hd-PS-matched cohort according to the baseline characteristics of age, diabetes duration and HbA1c as continuous variables; and sex, ethnicity, kidney disease and cardiovascular disease (chronic coronary syndromes, cerebrovascular accident, heart failure, peripheral vascular disease, other vascular diseases) as categorical variables. The likelihood ratio test was used to compare the two models without and with an interaction term between treatment and baseline characteristics.

We have conducted several supplementary analyses to confirm the robustness of the main results: these investigations are summarized in Table S3.

3 | RESULTS

3.1 | Patient flow and baseline characteristics

In total, 6686 patients were selected for analysis before hd-PS matching, i.e. 1207 patients newly treated with gliclazide MR and 5479 patients newly treated with sitagliptin (Figure 1; Table S4). hd-PS matching was performed with a 0.12 calliper and 5% trim (Figure S1); 214 patients (18%) from the gliclazide MR group and 4486 patients (82%) from the sitagliptin group were excluded, leaving 993 patients in each group with a treatment duration of up to 9 years for outcome analysis (Figure 1). Following matching, baseline characteristics, including patient sex, age, baseline HbA1c, duration of diabetes and concomitant therapy were largely overlapping between patients newly treated with gliclazide MR or sitagliptin (Table 1).

3.2 | Effectiveness outcomes

3.2.1 | Glycated haemoglobin outcomes

Overall, patients treated with gliclazide MR were 35% more likely to achieve the target of <7.0% (53 mmol/mol) HbA1c more than patients in the sitagliptin group (HR: 1.35; 95% CI: 1.15-1.57). There was a rapid separation of probability curves, with patients in the gliclazide MR group more likely to achieve HbA1c control starting at approximately 3 months (Figure 2A). Patients treated with gliclazide MR were 51% more likely to achieve the target of HbA1c ≤6.5% (48 mmol/mol) (HR: 1.51; 95% CI: 1.19-1.92); as with the primary outcome, rapid separation of probability curves was also observed (Figure 2B). Patients treated with gliclazide MR were also slightly more likely to achieve an HbA1c reduction ≥1% (11 mmol/mol) from baseline (HR: 1.11; 95% CI: 1.00-1.24; Figure 2C).

Treatment duration, as measured by both durability and persistence, was largely similar for gliclazide MR and sitagliptin. The median durability times were 2.6 and 2.5 years for gliclazide MR and sitagliptin, respectively, with a log-rank test $P = .135$; corresponding

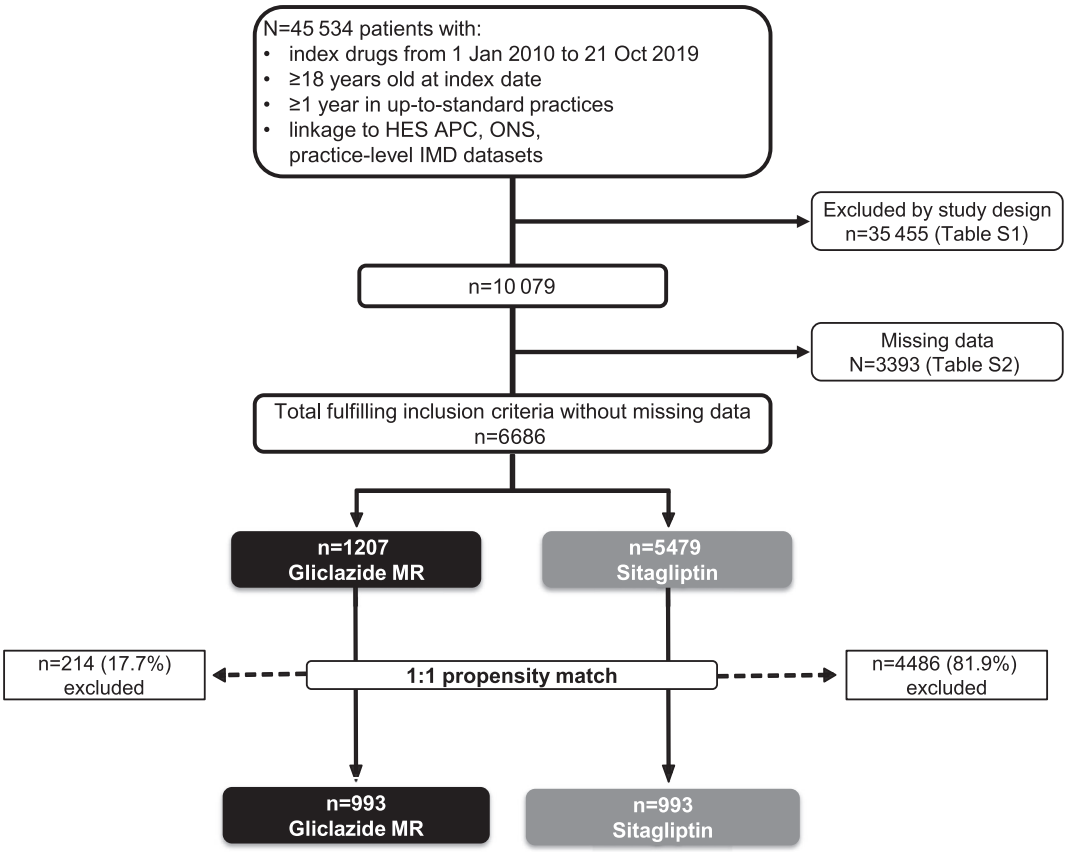

FIGURE 1 Patient flow. HES APC, Hospital Episode Statistics Admitted Patient Care; IMD, index of multiple deprivation; MR, modified release; ONS, Office for National Statistics

estimates for persistence were 2.7 and 2.5 years, with a log-rank test $P = .119$ (Figure 3).

3.3 | Effect of patient characteristics on the primary effectiveness outcome

Exploratory analysis showed that results of the primary outcome were maintained across subgroups of ethnicity and presence of kidney disease (Table 2). There was a possible larger effect of gliclazide MR versus sitagliptin in patients with baseline cardiovascular disease (HR: 1.73; 95% CI: 1.28-2.34) compared with those without (1.23; 1.02-1.47; P for interaction, .056). The difference between gliclazide MR and sitagliptin was consistent regardless of baseline HbA1c ($P = .986$) and age ($P = .116$), while was higher for a longer duration of diabetes ($P = .029$).

3.4 | Hypoglycaemic events

Overall, few severe and non-severe hypoglycaemic episodes occurred (23 events in 6241 patient years of follow-up; incidence rate, 3.7 events per 1000 patient years). In patients taking gliclazide MR, 15 hypoglycaemic events [four severe (HES); 11 severe or non-severe (CPRD)] occurred during 3201 person-years of follow-up, corresponding to 4.7 events per 1000 patient years. Respective estimates for sitagliptin were: eight events (one severe; seven severe or non-severe), in 3039 patient years, and 2.6 events per 1000 patient years.

3.5 | Supplementary analyses

The main results were confirmed in several sensitivity analyses (Tables S3, S5-S12; Figure S2), including: the comparison between gliclazide MR and sitagliptin as monotherapy (Table S5), multiple imputation to account for missing data (Table S6), time-to-event analysis using interval censored data (Table S7), regression adjustment (Table S9) or inverse probability of treatment weighting (Table S10). There was no evidence of a higher risk of hypoglycaemia with gliclazide MR versus sitagliptin across various definitions of hypoglycaemic events and statistical modelling (Table S8). Lastly, explorative interactions were assessed for all outcomes (Table S11) and results for HbA1c considered as a continuous outcome were consistent with those of the main analysis [mean HbA1c difference, gliclazide MR vs. sitagliptin: −0.14% ($P = .011$) at 1 year; −0.12%

TABLE 1 Baseline characteristics after high-dimensional propensity score matching

Characteristics	Gliclazide MRN = 993	SitagliptinN = 993	Standardized difference
Male (n, %)	583 (58.7%)	593 (59.7%)	0.02049
Age (years)	63.3 (53.4-71.6)	63.1 (54.8-71.5)	0.01847
Diabetes duration (years)	4.4 (2.1-7.3)	4.4 (2.0-7.6)	0.01326
Body mass index (kg/m^2)	30.8 (27.7-34.8)	31.3 (27.8-35.0)	−0.01718
HbA1c (%)	8.5 (7.8-9.7)	8.6 (7.8-9.8)	0.03784
HbA1c (mmol/mol)	69 (62-83)	70 (62-84)	—
Practice level IMD (tenths)			0.08857
1 (least deprived)	41 (4.1%)	39 (3.9%)	
2	7 (0.7%)	3 (0.3%)	
3	63 (6.3%)	64 (6.4%)	
4	47 (4.7%)	49 (4.9%)	
5	12 (1.2%)	12 (1.2%)	
6	37 (3.7%)	45 (4.5%)	
7	43 (4.3%)	41 (4.1%)	
8	52 (5.2%)	62 (6.2%)	
9	78 (7.9%)	73 (7.4%)	
10 (most deprived)	43 (4.3%)	38 (3.8%)	
Missing	570 (57.4%)	567 (57.1%)	
Comorbidities			
Previous hypoglycaemia	6 (0.6%)	6 (0.6%)	0.00000
Chronic coronary syndrome	159 (16.0%)	169 (17.0%)	0.02712
Chronic obstructive pulmonary disease	63 (6.3%)	76 (7.7%)	0.05133
Cerebrovascular accident	43 (4.3%)	53 (5.3%)	0.04697
Dementia	11 (1.1%)	13 (1.3%)	0.01843
High blood pressure	585 (58.9%)	584 (58.8%)	0.00205
Heart failure	31 (3.1%)	30 (3.0%)	0.00584
Kidney disease	155 (15.6%)	161 (16.2%)	0.01652
Liver disease	14 (1.4%)	14 (1.4%)	0.00000
Peripheral vascular disease	24 (2.4%)	26 (2.6%)	0.01286
Dyslipidaemia	1 (0.1%)	2 (0.2%)	0.02593
Foot complications	6 (0.6%)	7 (0.7%)	0.01249
Neuropathy	12 (1.2%)	10 (1.0%)	0.01924
Retinopathy	141 (14.2%)	153 (15.4%)	0.03403
Other vascular complications	74 (7.5%)	71 (7.2%)	0.01161
Ethnicity			0.02407
Black	17 (1.7%)	16 (1.6%)	
South-east Asian	30 (3.0%)	32 (3.2%)	
White	343 (34.5%)	348 (35.0%)	
Other	15 (1.5%)	13 (1.3%)	
Missing	588 (59.2%)	584 (58.8%)	
Smoking status			0.03440
Non-smoker	469 (47.2%)	454 (45.7%)	
Ex-smoker	368 (37.1%)	384 (38.7%)	
Smoker	156 (15.7%)	155 (15.6%)	
Alcohol assumption			0.02871
No	153 (15.4%)	146 (14.7%)	

(Continues)

TABLE 1 (Continued)

Characteristics	Gliclazide MRN = 993	SitagliptinN = 993	Standardized difference
Ex	35 (3.5%)	38 (3.8%)	
Yes	320 (32.2%)	315 (31.7%)	
Missing	485 (48.8%)	494 (49.7%)	
Concomitant therapy			
Anticoagulant therapy	59 (5.9%)	62 (6.2%)	0.01263
Antihypertensive therapy	688 (69.3%)	691 (69.6%)	0.00656
Antiplatelet therapy	321 (32.3%)	352 (35.4%)	0.06599
Lipid-lowering therapy	769 (77.4%)	766 (77.1%)	0.00721
Consultation (no. previous year)	39 (30-54)	40 (30-55)	0.03049
Total cholesterol (mmol/L)	4.3 (3.6-5.0)	4.2 (3.7-5.0)	0.00429
HDL cholesterol (mmol/L)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	0.00750
LDL cholesterol (mmol/L)	2.2 (1.7-3.0)	2.3 (1.7-3.0)	−0.01452
Triglycerides (mmol/L)	1.9 (1.4-2.6)	1.9 (1.4-2.7)	0.02202
HDL/LDL	3.8 (3.1-4.6)	3.8 (3.1-4.6)	0.02304
Creatinine (μmol/L)	76 (65-89)	75 (66-89)	−0.02424

Note: All values expressed as n (%) or median (interquartile range).
Abbreviations: HbA1c, glycated haemoglobin; HDL/LDL, high/low-density lipoprotein; IMD, index of multiple deprivation; MR, modified release.

(P = 0.017) at 2 years; and −0.09% (P = .039) at 3 years; Figure S2], with virtually identical frequencies of HbA1c measurements over time (Table S12).

4 | DISCUSSION

International guidelines recommend individualizing glycaemic control in patients with T2D to reduce long-term risks of microvascular and macrovascular complications.[2–5] In patients whose blood glucose remains high after evidenced-based patient education, dietary advice and first-line metformin, current T2D guidelines recommend addition of a second medication to ensure glycaemic control and avoid therapeutic inertia.[2–5] Recent reports from database studies in the UK and Germany found that SUs and DPP-4 inhibitors are the most commonly prescribed second-line T2D treatments.[7] Although there is a wealth of studies comparing general classes of treatments such as SUs and DPP-4 inhibitors with other classes or individual medications,[12,17–19] the properties of individual medications in a class can vary,[8,10,14] and studies comparing the effectiveness of individual medications are needed to help inform clinical decision making.

Thus far, conflicting results have been reported when comparing SUs and DPP-4 inhibitors as general medication classes. A study in large hd-PS matched populations from claims data have shown no difference in effectiveness between the general categories of SUs and DPP-4 inhibitors for lowering HbA1c <7.0% (53 mmol/mol), although the study did not report the SUs used.[18] One meta-analysis of randomized clinical trials found that patients treated with SUs have a significantly greater reduction in HbA1c and would probably achieve HbA1c <7.0% (53 mmol/mol) more than patients treated with DPP-4 inhibitors.[17] However, another meta-analysis specifically comparing sitagliptin with SUs other than gliclazide MR showed no difference in glycaemic control of T2D.[20] To our knowledge, here we present the first study directly comparing the real-world effectiveness of two common, orally administered T2D medications, gliclazide MR and sitagliptin. SUs such as gliclazide MR have been used to treat T2D for over 60 years and have a well-characterized risk/benefit profile.[8] However, therapies such as DPP-4 inhibitors have entered the market over the past decade, and individual studies are needed to elucidate comparative effectiveness.

In this study, treatment of hd-PS matched, real-world patients with gliclazide MR led to a greater probability of patients achieving HbA1c <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol), with a treatment effect already evident at 3 months. This rapid reduction of HbA1c levels can help prevent long-term risk of complications. Recent studies have reported a legacy effect associated with glucose-lowering treatment in terms of macrovascular and mortality outcomes.[21,22] Laiteerapong et al. showed that patients with HbA1c ≥6.5% (48 mmol/mol) during the first year of treatment were at a higher risk of micro- and macrovascular events, while those with ≥7.0% (53 mmol/mol) during the first year had a higher mortality risk.[21] Because early achievement of glycaemic control has been associated with better long-term outcomes ('legacy effect'),[23] time to HbA1c <7.0% (53 mmol/mol) was originally chosen as the primary outcome for this study. However, patients treated with gliclazide MR also had greater reductions in mean HbA1c over time. Of note, for both gliclazide MR and sitagliptin, patients had the highest probability of achieving HbA1c reductions during the first year of treatment, with very few outcome events during the following years: these findings indicate a progressively lower probability of glucose control in individuals who did not reach the target during the initial 12 months, as

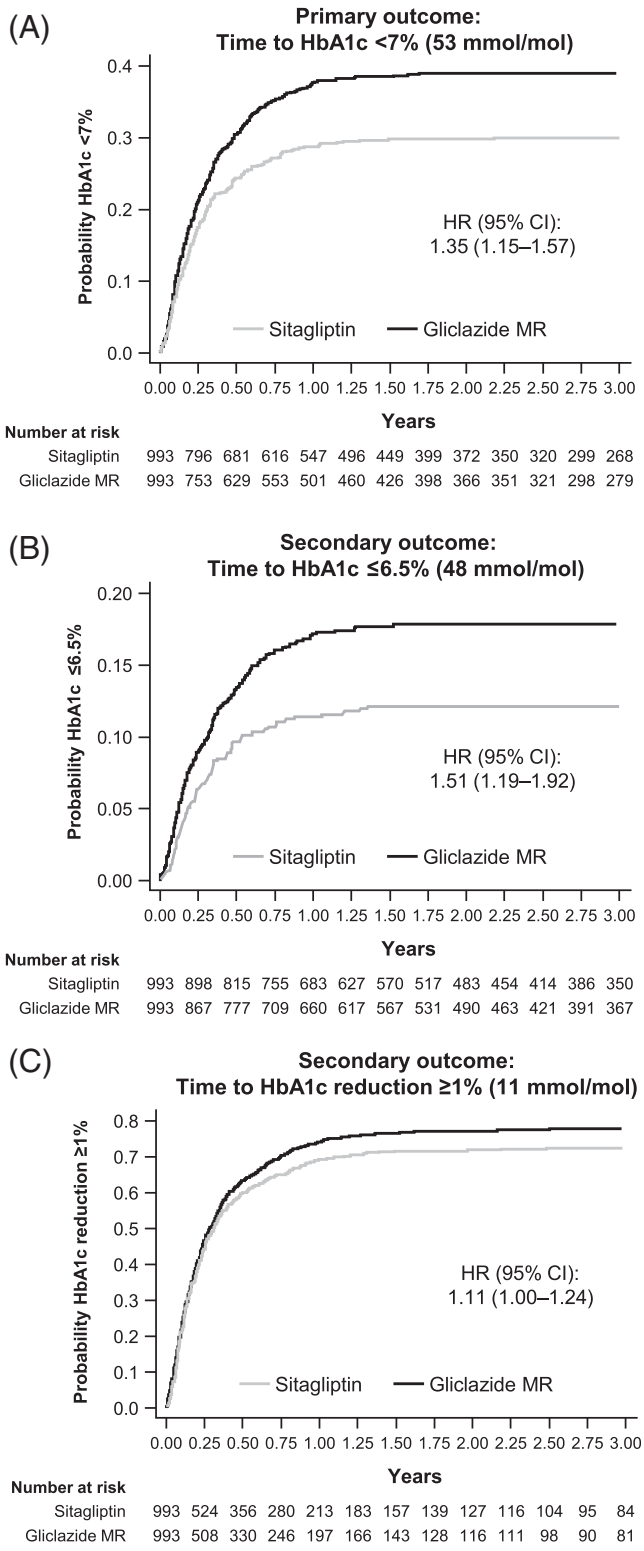

FIGURE 2 Kaplan-Meier curves for HbA1c control. Probability of achieving a reduction of HbA1c in patients with T2D treated with gliclazide MR or sitagliptin. A, <7% (53 mmol/mol). B, ≤6.5% (48 mmol/mol). C, ≥1% (11 mmol/mol) reduction from baseline. CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; MR, modified release; T2D, type 2 diabetes mellitus

further confirmed by the progressively smaller difference in HbA1c when analysed as a continuous outcome.

Durability and persistence of glycaemic control for T2D treatment can be indicative of a number of endpoints, including treatment adherence, decline in β-cell function over time and tolerability over time. As a general class, concerns have been raised over the effect of SUs on β-cell exhaustion, leading to poor durability. However, because of its mechanism of action, gliclazide has shown a significantly longer time to treatment failure than other SUs.[24,25] Furthermore, real-world studies show that general SUs are more durable than DPP-4 inhibitors as both first-[26] and second-line treatments.[27] Here, in a direct comparison using hd-PS matching, gliclazide MR and sitagliptin had comparable median durability and persistence of ≥2.5 years.[27]

Currently, SUs are perceived as having an increased risk of hypoglycaemic events compared with DPP-4 inhibitors and other T2D treatments. While this may be true for SUs as a general class,[17,28,29] studies of gliclazide report a significantly lower risk of hypoglycaemic events than other SUs,[9,10] and a risk similar to other insulinotropic agents.[10] Here, hypoglycaemic events reported for patients treated with gliclazide MR and sitagliptin were uncommon, albeit numerically higher in patients on gliclazide MR. The present study was restricted to patients with ≥2 prescriptions of the study drug without a ≥90-day gap between termination of the first prescription and initiation of the second. This criterion was important to ensure sufficient exposure to the study drug, as HbA1c levels reflect glycaemic levels for the previous 2-3 months, and to limit misclassification of exposure, as patients with renewed prescriptions have probably taken the medications. However, this means that patients with hypoglycaemic events early in the course of treatment that stopped the study drug after one prescription were not captured and may have led to a depletion of susceptibles bias. Notwithstanding, depletion of susceptibles was not an issue in this study: of the 860 patients excluded for having <2 study drug prescriptions that met all other inclusion criteria, only three patients (two on gliclazide MR, one on sitagliptin) had a hypoglycaemic event within the first 90 days following the first study drug prescription. Moreover, similar low rates of hypoglycaemic events with gliclazide MR treatment have been seen in other real-world studies.[30]

Taken together, these results showing low rates of hypoglycaemic events combined with rapid response to gliclazide MR may help to inform clinical decision making among second-line interventions for T2D globally, providing important evidence where there is lack of data from randomized clinical trials. Although randomized clinical trials currently provide the highest standard of evidence for decision making, they have restrictive inclusion and exclusion criteria and may exclude patients perceived as more vulnerable or with a less homogeneous profile because of age, disease severity or comorbid disease. Other non-interventional studies often include these patients, better representing real-world clinical populations. However, real-world studies comparing various treatments may be unbalanced because of variable factors such as geographical location, prescription bias, clinical severity of disease, patient age, or the number and type of comorbidities

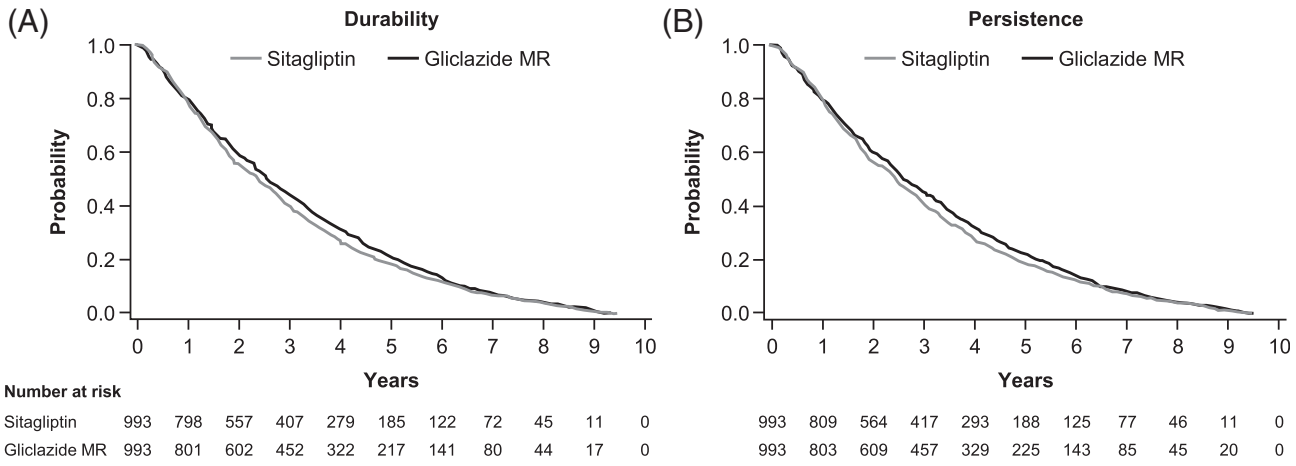

FIGURE 3 Kaplan-Meier curves for durability and persistence. A, Treatment durability, defined as the treatment duration until stop, switch or add-on of a new glucose-lowering drug. B, Treatment persistence, defined as the treatment duration until stop or switch, regardless of add-on glucose-lowering drug. MR, modified release. Log-rank test: durability, $P = .135$; persistence, $P = .119$

TABLE 2 Comparison of the probability of achieving glycated haemoglobin level of <7.0% (53 mmol/mol) with gliclazide MR versus sitagliptin in subgroups according to baseline characteristics

	Gliclazide MR vs. sitagliptin			
	HR (95% CI)	Number of participants	Number of events	*P*-value for interaction
Sex				
Men	1.47 (1.20, 1.79)	1176	391	0.187
Women	1.18 (0.93, 1.52)	810	255	
Ethnicity				
South-east Asian	1.11 (0.46, 2.67)	62	20	0.656
White European	1.37 (1.05, 1.78)	691	224	
Baseline kidney disease				
Yes	1.33 (0.92, 1.93)	316	113	0.954
No	1.35 (1.14, 1.60)	1670	533	
Baseline CVD[a]				
Yes	1.73 (1.28, 2.34)	558	177	0.056
No	1.23 (1.02, 1.47)	1428	469	

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MR, modified release.
[a]Chronic coronary syndromes, cerebrovascular accident, heart failure, peripheral vascular disease, other vascular diseases.

between populations. hd-PS matching of populations from claims or other databases uses algorithms to select covariates and match patients, mitigating selection bias and managing confounding factors, resulting in real-world treatment groups with similar characteristics.[16] As randomized trials comparing all combinations of individual T2D medications are not feasible, hd-PS matching is a cost-effective tool that can be used to examine comparative effectiveness in electronic health record databases.[16]

Because of the non-interventional nature and similarly to other investigations using routinely collected electronic health records, this study has limitations. Data quality of outcomes and other covariates were not standardized across all centres contributing to the CPRD. Thus, there may be variation in data entry or methods used to record measurements for the baseline covariates used for hd-PS matching. HbA1c measurements in patients with controlled glycaemia may be less frequently reported in real-world studies. Furthermore, while we used three HbA1c outcomes to compare the two medications, it should be noted that individualized HbA1c targets are increasingly suggested and used in clinical practices. Background information on metformin dose was also not well recorded for most of the included participants; therefore, a proportion of patients may have received lower doses of metformin because of factors such as gastrointestinal side effects at the time of prescription of a second-line therapy. Physicians may be more likely to prescribe an SU to patients on low-dose metformin because of gastrointestinal side effects than other medications that might worsen gastrointestinal side effects. Similarly, data

were sparse on the doses of the two index medications. Weight and body mass index were not recorded over time, preventing analysis of difference in these outcomes. Furthermore, the ascertainment of hypoglycaemic events was based on those recorded in clinical practice records and events leading to hospitalization. The HES APC reported severe events (i.e. resulting in hospitalization), which may lead to under-reporting of non-severe events. The CPRD, on the other hand, reports both severe and non-severe hypoglycaemic events, but makes no distinction between classifications. Finally, although the durability and persistence of glycaemic control may reflect adherence to T2D drug therapy, medication adherence was not directly measured in this study.

Overall, to our knowledge, this was the first study directly comparing the real-world effectiveness of gliclazide MR and sitagliptin as second-line treatments for patients with T2D. In this hd-PS matched population, gliclazide MR was more effective than sitagliptin for reducing HbA1c <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol), with numerically higher but low rates of hypoglycaemic episodes and similar durability and persistence. These data provide evidence that gliclazide MR has an important role in clinical practice and further investigations on dose, other safety outcomes and patient weight are needed to elucidate the entire risk-benefit profile of this medication.

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CONFLICT OF INTEREST

F.Z. is speaker for Napp Pharmaceuticals. E.J. and V.C. are employees of Servier. F.T. reports nothing to disclose. S.S. reports personal fees from NAPP, Amgen, Astra Zeneca, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Boehringer Ingelheim, Sanofi-Aventis, grants from AstraZeneca, Sanofi-Aventis, Servier and Janssen, outside the submitted work. M.J.D. has served as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen; speaker for Mitsubishi Tanabe Pharma Corporation. Grants in support of investigator and investigator-initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly. KK has served as a consultant and participated in speaker bureaus for, or received research support from, Amgen, AstraZeneca, Berlin-Chemie AG/Menarini Group, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Napp, Novartis, Novo Nordisk, Roche, Sanofi and Servier. Data sharing statement. This study was conducted using CPRD GOLD and linked data subject to protocol approval (ISAC No. 19_149). The data controller for CPRD (Department of Health and Social Care) does not allow sharing of raw data. Codes used to define the cohort, medical conditions, medications and outcomes are reported in the Appendix. Statistical codes are available from the corresponding author (F.Z.).

AUTHOR CONTRIBUTIONS

Francesco Zaccardi: study design; data collection and cleaning; statistical analysis; manuscript draft. Freya Tyrer, Kamlesh Khunti: study design; writing manuscript; critical revision for important intellectual content. Emmanuelle Jacquot, Viviana Cortese, Samuel Seidu, Melanie J. Davies: writing manuscript; critical revision for important intellectual content.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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