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GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients

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Abstract

Background Progressive β-cell failure is a characteristic feature of type 2 diabetes; consequently, β-cell secretagogues are useful for achieving sufficient glycaemic control. The European GUIDE study is the first large-scale head-to-head comparison of two sulphonylureas designed for once-daily administration used under conditions of everyday clinical practice.

Design Eight hundred and forty-five type 2 diabetic patients were randomized to either gliclazide modified release (MR) 30–120 mg daily or glimepiride 1–6 mg daily as monotherapy or in combination with their current treatment (metformin or an α-glucosidase inhibitor) according to a double-blind, 27-week, parallel-group design. Efficacy was evaluated by HbA1c and safety by hypoglycaemic episodes using the European Agency definition.

Results HbA_{1c} decreased similarly in both groups from 8·4% to 7·2% on gliclazide MR and from 8·2% to 7·2% on glimepiride. Approximately 50% of the patients achieved HbA1c levels less than 7%, and 25% less than 6·5%. The mean difference between groups of the final HbA_{1c} was –0·06% (noninferiority test $P < 0·0001$). No hypoglycaemia requiring external assistance occurred. Hypoglycaemia with blood glucose level < 3 mmol L^{-1} occurred significantly less frequently ($P = 0·003$) with gliclazide MR (3·7% of patients) compared with glimepiride (8·9% of patients). The distribution of the sulphonylurea doses was similar in both groups.

Conclusions This study provides new insights into therapeutic strategies using sulphonylureas. It shows that gliclazide MR is at least as effective as glimepiride, either as monotherapy or in combination. The safety of gliclazide MR was significantly better, demonstrating approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride.

Keywords Glucose control, HbA_{1c}, hypoglycaemia, sulphonylureas, type 2 diabetes.
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Introduction

Sulphonylureas are widely used in the management of type 2 diabetes, as impaired insulin secretion plays an important role in the pathophysiology of hyperglycaemia [1]. Tight glycaemic control is essential in order to prevent or delay diabetes complications [2,3]. One deterrent to tight glycaemic control is the risk of hypoglycaemia [2]. Moderate hypoglycaemia induces cognitive impairment [4] and many complex attention tasks relevant to everyday life may be impaired [5]. Recurrent severe hypoglycaemia may induce impaired awareness of hypoglycaemia and possibly long-term sequelae in the form of cumulative cognitive impairment [6,7]. Intensive therapy frequently means multiple medications, negatively impacting treatment adherence. Studies have demonstrated that adherence depends on the frequency of doses: fewer intakes lead to higher compliance [8]. Gliclazide modified release (MR) and glimepiride are the two once-daily sulphonylureas used most frequently in type 2 diabetes treatment in many European countries [9]. Gliclazide MR has demonstrated efficacy and safety [10–12]; a smaller incidence of hypoglycaemia has been reported with gliclazide than with other sulphonylureas in several studies [13–15]. Glimepiride demonstrated equivalent efficacy to glibenclamide, with a lower incidence of hypoglycaemia during the first weeks of treatment [16,17]. Despite sulphonylureas being a widely used class of oral antidiabetics [9], few direct comparisons have been performed. GUIDE (GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride) is a large scale prospective double-blind, randomized study comparing gliclazide MR and glimepiride, over 27 weeks in type 2 diabetic patients. The study was designed first to assess the efficacy of these sulphonylureas, following current recommendations for dose adaptation and second to obtain reliable information on sulphonylurea-related hypoglycaemia when glycaemic control is improved.

Methods

Subjects

Inclusion criteria were: type 2 diabetic patients (according to World Health Organization criteria), >35 years old, treated for at least 3 months with diet alone or in combination with metformin or an α-glucosidase inhibitor (acarbose or miglitol), with glycated haemoglobin (HbA_{1c}) between 6·9% to 11·5%, and able to perform home blood glucose monitoring. Exclusion criteria were: currently treatment with insulin-secreting agents or thiazolidinediones, contraindication to study drugs, no effective contraception in women with child-bearing potential, elevated transaminases more than threefold the upper normal range or calculated creatinine clearance (CCl) using the Cockroft formula: CCl < 20 mL min^{-1}.

Study design

After confirmation of eligibility, patients were randomized to either gliclazide MR or glimepiride either as monotherapy in patients previously treated with diet alone or in combination with their current treatment (metformin or an α-glucosidase inhibitor maintained at stable dosage) for a 27-week double-blind treatment period that comprised a 9-week dose titration period followed by an 18-week maintenance period. The randomization of treatments was balanced, using permutation blocks of four and stratified on the centres.

The four dosages of gliclazide MR, from 30 to 120 mg daily, and the five dosages of glimepiride, from 1 to 6 mg daily, currently recommended in European countries were used. Tablets were masked in capsules. It was checked that the blinding method using capsules did not modify the dissolution kinetics of the tablets. Capsules were taken once daily, just before or during breakfast as follows (gliclazide MR/glimepiride): dose 1 (30 mg or 1 mg); dose 2 (60 mg or 2 mg); dose 3 (90 mg or 3 mg); dose 4 (120 mg or 4 mg); and dose 5 (120 mg or 6 mg). Patients started double-blind medication with the lowest dose of gliclazide MR 30 mg or glimepiride 1 mg. During the titration period, the dose of study medication could be increased every 3 weeks up to dose 4 until metabolic control was achieved [therapeutic goal defined as fasting plasma glucose (FPG) between 5 and 7·8 mmol L^{-1}]. Visits were then scheduled every 9 weeks (W). The product monograph for glimepiride states that the usual maintenance dose is 1–4 mg and the maximal dose of 6 mg allowed in most European countries improves blood glucose control only in exceptional cases. However, glimepiride 6 mg (dose 5) could be prescribed at visit W18 based on HbA_{1c} and the investigator's judgement. Dose 5 for gliclazide MR corresponded like dose 4–120 mg. Throughout the study, the dose could be decreased in case of hypoglycaemia according to the investigator's judgement or more than 3 episodes within 1 month.

The trial was approved by the Medical Ethical Review Committees of participating centres and conducted in accordance with the revised Declaration of Helsinki (Edinburgh revision, 2000). All patients gave their written informed consent to participate in the study. One hundred and fifty-four clinical centres in Austria, Belgium, the Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Slovakia, Spain, and the United Kingdom were involved.

All fasting blood samples were analyzed in a central laboratory (MDS-Pharma Services, France), except for FPG during the titration period, which was analyzed in local laboratories (W3, W6, and W9).

Central HbA_{1c} and FPG were assessed at baseline (W0), at the end of the titration period (W9), and during the maintenance period (W18 and W27). HbA_{1c} was assayed with the high-performance liquid chromatography (HPLC) Biorad Variant. The lipid profile [including total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low-density lipoprotein (LDL) cholesterol, and triglycerides, using an enzymatic method] and biochemical safety screen

(serum creatinine, transaminases, alkaline phosphatase) were assessed at W0 and at the last visit.

Adverse events were recorded at each visit after examination and questioning of patients.

All patients were provided with the same blood glucose monitoring device with a memory (Glucotrend, Roche Diagnostics) and were trained to recognize symptoms suggestive of hypoglycaemia. Patients systematically measured capillary blood glucose 1 day per week (three times daily: before breakfast, lunch, and dinner). At any occurrence of symptoms they were instructed to measure their blood glucose level (BGL) and to record the event in a diary, which was reviewed by the investigator at each visit.

The definitions used to classify suspected hypoglycaemia were those recommended by the European Agency for the Evaluation of Medicinal Products (EMEA) [18]: (i) severe hypoglycaemia, defined as symptomatic episodes requiring external assistance owing to severe impairment in consciousness or behaviour, with BGL < 3 mmol L^{-1}; (ii) hypoglycaemia with BGL < 3 mmol L^{-1} being either symptomatic with no need for external assistance, or asymptomatic; and (iii) episodes suggestive of hypoglycaemia, where blood glucose measurements are not available. Additionally the blood glucose threshold of less than 4 mmol L^{-1} was also used to describe hypoglycaemia, following the Canadian guidelines [19].

Statistical analysis

The primary efficacy endpoint was HbA_{1c}. Secondary endpoints included FPG, lipid levels, and hypoglycaemic episodes.

Sample size was estimated based on the final value of HbA_{1c}, using the one-sided Student's *t*-test at 2·5% type I error (noninferiority limit set at 0·5%); 400 patients per group were needed to conclude noninferiority of gliclazide MR compared with glimepiride with a SD of 1·5% and a power greater than 90%. This figure was also appropriate to evaluate differences in the incidence of hypoglycaemic episodes.

All efficacy analyses were performed on the intention-to-treat population, defined as all patients exposed to study medication with one baseline and at least one postbaseline efficacy evaluation on treatment, and the per-protocol population defined as completed patients without deviation interfering with primary efficacy criterion. Safety analyses were performed on all patients who were exposed to at least one dose of study medication. Final values for withdrawn patients corresponded to the final values on treatment (final observation on treatment carried forward). Data are expressed as mean ± SD.

For efficacy analyses, covariance analysis on the last value including the baseline value as covariate and country and concomitant antidiabetic treatment as factors was used. A 95% confidence interval (CI) for differences between the least-squares means (gliclazide MR – glimepiride) obtained from the covariance analysis were calculated as well as an exact *P*-value (using a noncentred Student's *t*-test). Changes from baseline to last value were analyzed in each treatment group using a paired Student's *t*-test. Changes from baseline were tested in each treatment group using one-way analysis of variance for repeated measures on time factor and completed by a Dunnett *t*-test (baseline as reference).

For hypoglycaemic episodes, the percentage of patients reporting at least one episode and the distribution of the number of episodes were compared between treatment groups using Fisher's exact test. The time of occurrence of the first event was compared between the two treatment groups using a model for survival curves (Kaplan–Meier estimator) and Wilcoxon test.

Analyses were also performed on prespecified subgroups according to concomitant antidiabetic treatment, age (≤ 65, and > 65 years, > 75 years), CCl < 50, 50–80, and > 80 mL min^{-1}, and body mass index (BMI) (≤ and > 30 kg m^{-2}).

All statistical analyses were performed using SAS software (Statistical Analysis System, version 8·2, SAS Institute, Cary, NC). Data management and statistical analysis were performed by a professional institute independent from the sponsor (UMANIS, Levallois-Perret, France).

Results

Demographic and baseline characteristics

A total of 845 patients were randomized in the study. The two groups were comparable for all baseline characteristics (Table 1). Of the 845 patients, 842 were exposed to at least one dose of study medication corresponding to the safety population. Of them, 815 had at least one HbA_{1c} value on study medication corresponding to the intention-to-treat population.

Overall, 778 of 845 patients (92%) completed the study. Thus, 67 patients withdrew from the study (35 gliclazide MR/32 glimepiride): 23 owing to adverse events other than hypoglycaemia (12 gliclazide MR/11 glimepiride), 10 owing to hypoglycaemia (1 gliclazide MR/9 glimepiride), two owing to lack of efficacy (one in each treatment group), 25 for a nonmedical reason (16 gliclazide MR/9 glimepiride), and seven because of a protocol deviation (five gliclazide MR/2 glimepiride).

Efficacy

Over the 27 weeks of treatment, improvement in blood glucose control was statistically significant in both groups with decreases in HbA_{1c} of 1·1–1% (Table 2) and in FPG of 1·4–1·3 mmol L^{-1} in the gliclazide MR and glimepiride groups, respectively. Mean adjusted differences between groups were – 0·06% (95% CI –0·19 to 0·07) for HbA_{1c} and –0·05 mmol L^{-1} (95% CI –0·33 to 0·23) for FPG with noninferiority tests, both $P < 0·0001$. The time course of the changes in mean HbA_{1c} and FPG in each treatment group were similar with an early decrease at 9 weeks (Fig. 1).

Table 1 Baseline characteristics in the randomized population

	Gliclazide MR 405 patients	Glimepiride 440 patients
Age (years)	60·5 ± 9·9	60·6 ± 10·5
Sex (M/F) (%)	51/49	52/48
Body weight (kg)	83·1 ± 14·3	83·8 ± 16·0
Body mass index (kg m^{-2})	30·5 ± 4·8	30·6 ± 4·9
Blood pressure (mmHg)	136 ± 13/81 ± 8	137 ± 14/81 ± 8
Known duration of diabetes (years)	5·6 ± 5·9	5·8 ± 5·8
HbA_{1c} (%)	8·4 ± 1·1	8·2 ± 1·0
Fasting plasma glucose (mmol L^{-1})	10·2 ± 2·6	10·1 ± 2·6
Hypertension (%)	61	64
Dyslipidemia (%)	49	49
Macrovascular complications (%)	22	21
Microvascular complications (%)	10	11
Antihypertensive agents (%)	60	62
Lipid-lowering agents (%)	30	33
Anti-platelet agents (%)	21	21

Data are mean ±SD.

Table 2 Change in glycated haemoglobin (%) in the intention-to-treat population

	Gliclazide MR				Glimepiride			
	n	Baseline	Final	Change	*n*	Baseline	Final	Change
Whole population	388	8·4 ± 1·1	7·2 ± 1·1	−1·1 ± 1·1*	427	8·2 ± 1·0	7·2 ± 1·1	−1·0 ± 1·1*
Subgroups								
Treatment regimen								
Monotherapy	129	8·3 ± 1·1	7·0 ± 0·9	−1·3 ± 1·1*	150	8·1 ± 1·0	6·9 ± 0·9	−1·2 ± 1·0*
Combination therapy								
Metformin	219	8·4 ± 1·1	7·4 ± 1·2	−1·0 ± 1·1*	250	8·3 ± 1·0	7·4 ± 1·2	−0·9 ± 1·1*
α-glucosidase inhibitor	40	8·4 ± 1·0	7·3 ± 1·1	−1·1 ± 1·2*	27	8·2 ± 1·1	7·3 ± 1·1	−0·9 ± 1·2*
Age								
≤ 65 years	253	8·4 ± 1·1	7·3 ± 1·2	−1·2 ± 1·1*	276	8·3 ± 1·0	7·2 ± 1·1	−1·1 ± 1·1*
> 65 years	135	8·4 ± 1·1	7·2 ± 1·0	−1·1 ± 1·2*	151	8·1 ± 0·9	7·2 ± 1·1	−0·9 ± 1·0*
Creatinine clearance‡								
> 80 mL min^{-1}	218	8·4 ± 1·1	7·2 ± 1·1	−1·2 ± 1·1*	229	8·3 ± 1·1	7·2 ± 1·1	−1·1 ± 1·1*
50–80 mL min^{-1}	151	8·4 ± 1·1	7·3 ± 1·1	−1·0 ± 1·1*	176	8·2 ± 0·9	7·3 ± 1·1	−0·9 ± 1·1*
< 50 mL min^{-1}	16	8·4 ± 1·2	7·0 ± 1·0	−1·4 ± 1·6†	22	8·1 ± 0·9	7·0 ± 1·3	−1·0 ± 1·0*
BMI								
≤ 30 kg m^{-2}	201	8·4 ± 1·2	7·3 ± 1·1	−1·2 ± 1·2*	216	8·2 ± 1·0	7·3 ± 1·1	−1·0 ± 1·2*
> 30 kg m^{-2}	187	8·4 ± 1·1	7·2 ± 1·0	−1·1 ± 1·1*	211	8·4 ± 1·1	7·2 ± 1·0	−1·0 ± 1·0*

Data are mean ± SD.
*$P < 0·001$; †$P < 0·01$.
‡Calculated using the Cockroft formula; missing data for three patients.

Improvement of blood glucose control was observed as early as W9 with HbA1c of 7·5 (1·1%) and 7·4 (1·0%) at W9 and 7·3 (1·1%) and 7·2 (1·1%) at W18 in the gliclazide MR and glimepiride groups, respectively, and a mean FPG of 8·6 (2·3) mmol L^{-1} at W9 and 8·7 (2·3) mmol L^{-1} at W18 in both groups. The evolution of HbA_{1c} was similar in all subgroups according to concomitant antidiabetic treatment, age, renal function and BMI (Table 2). In both treatment groups, approximately 50% of patients achieved HbA_{1c} levels less than 7%, and 25% less than 6·5% by the end of study treatment.

The method in which the final doses were distributed was similar in the gliclazide MR/glimepiride groups: dose 1 (32%/32·8%); dose 2 (18%/19·2%); dose 3 (14·2%/16·9%); dose 4 (15·5%/14·3%), and dose 5 (20·3%/16·8%). Mean (± SD) final daily dosages were 76·2 (38·1) mg for gliclazide MR and 2·9 (1·8) mg for glimepiride. In patients in whom the glimepiride dose was increased from 4 to 6 mg at W18, the mean HbA_{1c} (± SD) remained stable at 8·5 (1·4)% at W18 and 8·4 (1·2)% at W27. HbA_{1c} values were 8·4 (1·2)% and 8·2 (1·2)%, respectively, over the same period in patients receiving dose 5 of gliclazide MR (same dosage as dose 4, i.e. 120 mg).

Lipid parameters remained stable throughout the study, with minimal changes in LDL-cholesterol from 3·3 to 3·2 mmol L^{-1} and from 3·2 to 3·2 mmol L^{-1} and of

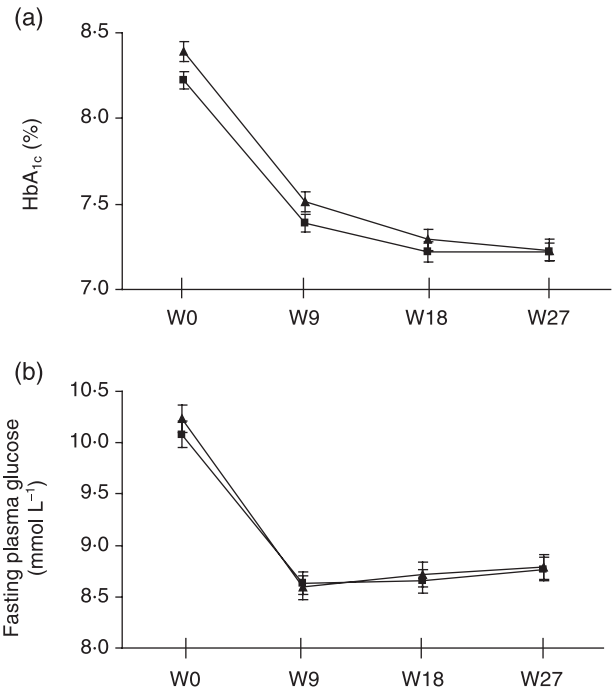

Figure 1 Changes in HbA_{1c} (a) and fasting plasma glucose (b). Data are means ± SEM. ▲: gliclazide MR; ■: glimepiride. non-inferiority test, $P < 0{\cdot}0001$.

triglycerides from 2·2 to 2·1 mmol L^{-1} and from 2·3 to 2·2 mmol L^{-1} in the gliclazide MR and glimepiride groups, respectively.

Identical results were observed in the per-protocol population for all efficacy criteria.

Safety and tolerability

Overall, 66% and 69% of symptoms of hypoglycaemia were documented with blood glucose measured before sugar intake on gliclazide MR and glimepiride, respectively.

Hypoglycaemia with BGL < 3 mmol L^{-1} occurred significantly less frequently ($P = 0{\cdot}003$) in the gliclazide MR group (3·7%) compared with the glimepiride group (8·9%) with an odds ratio of 2·5 (95% CI, 1·4–4·7) (Table 3). Episodes suggestive of hypoglycaemia (symptoms with no blood glucose measurement) also occurred less frequently on gliclazide MR [34 patients (8·4%) experienced 45 episodes in total] compared with glimepiride [52 patients (11·8%) experienced 82 episodes in total].

The occurrence of hypoglycaemic episodes was evenly distributed during the 27-week study (Fig. 2). No episodes requiring external assistance or nocturnal symptomatic episodes occurred. On both drugs, most of the hypoglycaemic episodes occurred in the late morning (58% between 11:00 and 13:00) and early afternoon (17% between 13:00 and 15:00) (Fig. 3). Hypoglycaemic symptoms led to nine patients on glimepiride withdrawing from the study vs.

Table 3 Hypoglycaemia with blood glucose level < 3 mmol L^{-1} in the safety population

	Gliclazide MR			Glimepiride		
	Patients exposed (*n*)	*n* (%) Patients	Episodes	Patients exposed (*n*)	(%) Patients (*n*)	Episodes
Whole population	403	15 (3·7)*	22†	439	39 (8·9)*	56†
Subgroups						
Age						
≤ 65 years	264	10 (3·8)*	12	284	25 (8·8)*	39
> 65 years	139	5 (3·6)‡	10	155	14 (9·0)‡	17
Creatinine clearance§						
> 80 mL min^{-1}	226	10 (4·4)‡	12	232	13 (5·6)‡	23
50–80 mL min^{-1}	157	5 (3·2)*	10	182	23 (12·6)*	27
< 50 mL min^{-1}	17	0 (0)‡	0	25	3 (12·0)‡	6
Treatment details						
Treatment regimen						
Monotherapy	133	7 (5·3)‡	8	156	15 (9·6)‡	19
Combination therapy						
Metformin	229	6 (2·6)*	12	255	22 (8·6)*	35
α-glucosidase inhibitor	41	2 (4·9)‡	2	28	2 (7·1)‡	2
Final HbA_{1c} (%)¶						
≤ 6·5	97	2 (2·1)	2	114	20 (17·5)	24
6·5–7	91	6 (6·6)	11	108	7 (6·5)	10
7–7·5	81	3 (3·7)	4	80	8 (10·0)	14
7·5–8	48	1 (2·1)	1	50	3 (6·0)	6
> 8	71	3 (4·2)	4	75	0	0

Between-group comparisons: *$P \leq 0{\cdot}02$, †$P = 0{\cdot}007$, ‡non-significant, §calculated using the Cockroft formula; the three patients with missing creatinine clearance did not experience hypoglycaemia with a blood glucose level < 3 mmol L^{-1}.

¶Data on safety population except for final HbA_{1c} (intention-to-treat population; final HbA_{1c} missing in 15 patients on gliclazide MR and 12 patients on glimepiride, one patient reported two hypoglycaemic episodes in the glimepiride group).

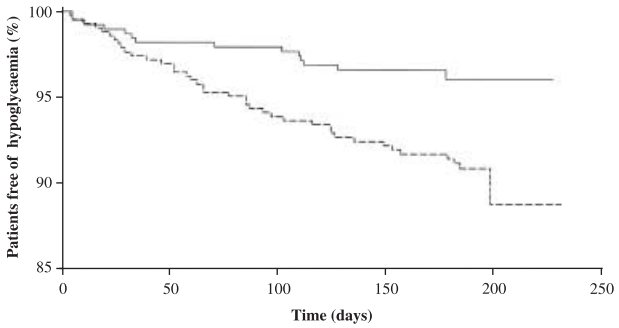

Figure 2 Kaplan–Meier curves for time to appearance of the first hypoglycaemia with blood glucose level < 3 mmol L^{-1}. —: gliclazide MR; - -: glimepiride. Wilcoxon test, $P = 0{\cdot}004$.

one patient on gliclazide MR. Study-treatment dose was decreased for one patient only, who experienced one episode with no blood glucose measurement.

The 3 mmol L^{-1} threshold for BGL complies with the EMEA recommendation of having a high level of specificity in the diagnosis of hypoglycaemia in clinical trials. When considering patients with symptoms and a BGL between 3 and 4 mmol L^{-1} (hypoglycaemia in clinical practice), there was also a 50% difference between gliclazide MR and glimepiride [for gliclazide MR, 31 patients (7·7%) experienced 45 episodes in total; for glimepiride, 63 patients (14·4%) experienced 108 episodes in total; $P = 0{\cdot}002$].

Table 3 displays hypoglycaemia with BGL < 3 mmol L^{-1} according to age, renal function, concomitant antidiabetic treatment, and final HbA_{1c} achieved. Among the 75 patients with baseline $HbA_{1c} \leq 7\%$, 2·3% and 12·5% of patients in the gliclazide MR and glimepiride groups, respectively, experienced hypoglycaemia with BGL < 3 mmol L^{-1} (data not shown). In patients > 75 years (23 on gliclazide MR and 30 on glimepiride), 0 and 3 reported hypoglycaemia with BGL < 3 mmol L^{-1}, respectively. Most episodes occurred at the lowest treatment doses, 13 and two out of 22 episodes on 30 mg and 60 mg gliclazide MR, respectively, and 21 and 27 out of 56 episodes on glimepiride 1 and 2 mg. No hypoglycaemia was observed on glimepiride 6 mg.

At least one adverse event other than hypoglycaemia was reported in 40·9% and 40·1% of patients in the gliclazide MR and glimepiride groups, respectively. Fifty-six serious adverse events occurred: 28 in each group. The most frequent were cardiovascular events at similar frequencies and judged to be nonrelated to the treatment by the investigator. There were no significant changes in the biochemical safety screen. Body weight was stable during the study with mean changes from 83·1 to 83·6 kg and 83·7 to 84·3 kg on gliclazide MR and glimepiride, respectively.

Discussion

Significant improvements in blood glucose control were obtained in this study, with sulphonylureas used as first-line therapy or in combination with metformin or α-glucosidase inhibitors. From a mean baseline value of 8·3%, half the population attained a final HbA_{1c} value less than 7%, and 25% less than 6·5%. Gliclazide MR and glimepiride, used under identical glucose level target titration, were similarly effective in improving blood glucose control with early decreases after 9 weeks of treatment. Sulphonylureas provide long-lasting improvement in blood glucose control [20], but this entails a risk of hypoglycaemia. This study provides detailed data on hypoglycaemia in well-trained patients performing home blood glucose monitoring on a regular basis. The confirmation of hypoglycaemic episodes by capillary blood glucose enhances the value of the data. The safety of gliclazide MR was significantly better, demonstrating approximately 50% fewer hypoglycaemic episodes in comparison with glimepiride. It is worth noting that the incidence of hypoglycaemia was particularly low in the gliclazide MR-treated patients whose HbA_{1c} was either moderately elevated at baseline (≤ 7%) and/or decreased less than 6·5% on treatment and who were at higher risk for hypoglycaemia [21]. This shows that gliclazide MR can be used following current recommendations of aggressive treatment to obtain HbA_{1c} targets between 6·5% and 7% [19,22,23]. Data suggest that even mild impairment of

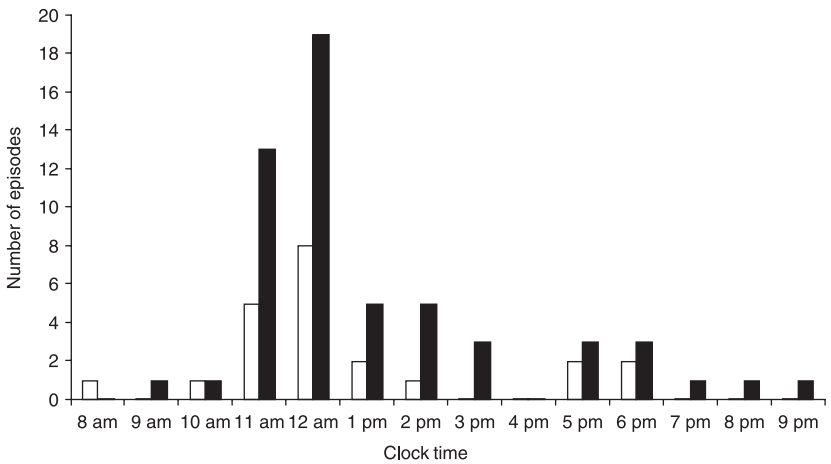

Figure 3 Time of occurrence of hypoglycaemia with blood glucose level < 3 mmol L^{-1}. □: gliclazide MR; ■: glimepiride.

renal function increases the incidence of hypoglycaemia on glimepiride and not on gliclazide MR. This might contribute to the difference between the drugs considering the high prevalence of patients with creatinine clearance less than 80 mL min^{-1}.

No episodes of severe hypoglycaemia were reported during the study in patients carefully trained in the management of hypoglycaemia. However, in routine practice severe hypoglycaemia is encountered in patients with type 2 diabetes. It should be noted that risk factors for severe hypoglycaemia recorded in a recent survey in acute care units are consistent with the nonsevere hypoglycaemia in this study, in particular low HbA_{1c} and renal impairment for glimepiride [21].

The observed difference in hypoglycaemic risk between the two sulphonylureas may be explained by the pharmacokinetic and pharmacodynamic properties of gliclazide MR and glimepiride. First, the two drugs show different pharmacokinetic profiles with the occurrence of an active metabolite eliminated by the kidney for glimepiride [16] and no circulating active metabolite for gliclazide MR [10], consistent with the higher incidence of hypoglycaemia in patients with impaired renal function. Moreover, the course of the drug concentration profile over time is different, with a progressive increase in gliclazide plasma concentrations over 6 h after drug administration [10,24] contrasting with a broad and sharp increase to maximal concentration for glimepiride [16,25]. The time to reach peak plasma concentration (t_{max}) of glimepiride, by 2–4 h, is also consistent with the peak of appearance of hypoglycaemia in the late morning [16]. The same time of appearance was reported for severe episodes on glimepiride [21]. Second, these agents show different binding behaviour to the sulphonylurea receptor of the pancreatic β cell with a rapidly reversible interaction for gliclazide [26] and prolonged binding for glimepiride, with prolonged cell stimulation [27]. Third, the two drugs induce a different insulin secretion profile. In the classic model of isolated rat pancreas, perfused with glucose 5 or 8·3 mmol L^{-1} and exposed to therapeutic concentrations of sulphonylureas, glimepiride produces a prolonged second phase of insulin secretion [28,29], whereas it returns more quickly to basal values with gliclazide [30].

In conclusion, using a current therapeutic strategy, gliclazide MR and glimepiride have been shown to be effective alone or in combination with metformin or α-glucosidase inhibitors, with a better safety profile for gliclazide MR. In the context of recommended early intensive therapy in type 2 diabetes [3,19,22,23], the availability of a once-daily effective sulphonylurea with a good safety profile is of relevant clinical interest.

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