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Real-world experience of treatment individualization based on a fixed-dose combination of gliclazide extended release+ metformin extended-release in type 2 diabetes mellitus

ABSTRACT

Background. To evaluate the efficacy of gliclazide extended-release (XR) 60 mg + metformin XR 500 mg fixed-dose combination (FDC) with metformin as an add-on (as needed) in real-world clinical practice.

Methods. This prospective observational study was performed in patients with type 2 diabetes mellitus uncontrolled on metformin (group M) or on conventional gliclazide XR 60 mg + metformin XR 500 mg (group GM), and newly diagnosed or untreated patients with HbA1c >9% (group U) at 6 out-patient diabetes care units. Patients received gliclazide XR 60 mg + metformin XR 500 mg FDC and metformin (as needed) at baseline for 30 days. Up-titration with gliclazide capped at 120 mg and metformin every 30 days till day-90. The proportion of patients achieving target FPG was the primary endpoint.

Results. Of 455 patients (mean age: 51.9 ± 11.3 years; mean BMI 26.7 ± 6.2 kg/m²), 261 patients had a family

history of diabetes and 161 patients had hypertension. Target FPG was achieved with 1 tablet each of gliclazide XR 60 mg + metformin XR 500 mg FDC and metformin by 73.09%, 74.26%, and 60.66% patients in groups M, GM, and U, respectively. Only 29.23% of patients required up-titration to 1 tablet of FDC + 2 tablets each of metformin and FDC at days 60 and 90. Mean FPG, PPG and HbA1c significantly reduced at day-90 (P < 0.001).

Conclusions. It can be concluded from this real-world primary-care practice study that the use of gliclazide XR 60 mg + metformin XR 500 mg FDC and metformin (as needed) was effective and well-tolerated, and >3 out of 5 patients achieved target glycaemic control within 30 days in all groups. (Clin Diabetol 2021; 10; 4: 337-341)

Key words: gliclazide, diabetes mellitus, metformin, glycaemic control, fixed-dose combination

Introduction

Diabetes has become a major healthcare issue imposing a huge economic burden, with about 77 million cases reported in India [1]. Evidence shows that most patients receive oral hypoglycaemic agents, but their poor adherence poses a major challenge in achieving glycaemic control. In Indian primary care

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settings, most patients are diagnosed and treated by general physicians and increasing the effectiveness of diabetes treatment at these centres has remained a priority. Most diabetes management guidelines recommend metformin-based dual drug combination to achieve target glycaemic control [2, 3]. Despite the availability of newer classes of antihyperglycemic agents, sulfonylureas (particularly gliclazide) have been commonly used in combination with metformin owing to its proven safety, efficacy, familiarity, guideline recommendations, cost and coverage [4]. A fixed-dose combination (FDC) of gliclazide extended-release (XR) 60 mg plus (+) metformin XR 500 mg is available in India as a scored and breakable tablet making its up-titration easier for better glycaemic control.

The present study aimed to assess glycaemic control in patients with type-2 diabetes mellitus (T2DM) receiving gliclazide XR 60 mg + metformin XR 500 mg FDC and metformin separately in addition, when required, in daily clinical practice.

Material and methods

This was a multi-centre, prospective observational study conducted between November 2017 and March 2018. The study was approved by a central ethics committee and all patients provided written informed consent. Patients with T2DM who received treatment per the clinical discretion of investigators as a part of routine clinical care with gliclazide XR 60 mg + metformin XR 500 mg FDC and add-on metformin XR 500 mg (as per patient profile) were selected. These patients were categorized into three groups: newly diagnosed or untreated patients with HbA1c > 9% (Group U), those uncontrolled on metformin 500 mg (Group M) and patients uncontrolled on conventional gliclazide XR 60 mg + metformin XR 500 mg (Group GM). Individuals who were pregnant or breastfeeding exhibited hypersensitive reaction to sulfonylureas, displayed severe hepatic or renal failure (creatinine clearance < 30 mL/min), demonstrated contraindication to gliclazide, presented with uncontrolled and clinically significant disease(s) or known malignancy or had a high probability of lost-to-follow-up, were excluded.

All patients were prescribed 1 tablet containing gliclazide XR 60 mg + metformin XR 500 mg FDC plus metformin 500 mg (as per need) for 30 days at baseline. Treatments were up-titrated at the discretion of the investigators, based on fasting plasma glucose (FPG) levels measured at days 30, 60 and 90. Dosing was capped at 120 mg for gliclazide and 1500 mg for metformin daily.

Data were collected from the patient's medical records maintained by the investigators. This included

Table 1. Demographic characteristics

Demographic characteristics of patients, n = 455	
Age, years	51.9 (11.3)
Male	244 (53.6)
BMI, kg/m ²	26.7 (6.2)
Systolic Blood Pressure, mm Hg	132.5 (15.7)
Diastolic Blood Pressure, mm Hg	81.3 (8.1)
Risk factors	
Smoking	47 (10.3)
Obesity	137 (30.1)
Clinical history	
Previous myocardial infarction	20 (4.4)
Previous congestive heart failure	1 (0.2)
Previous stroke	4 (0.9)
Family history of diabetes	261 (57.4)
History of other CVD	45 (9.9)
Hypertension	161 (35.4)
Dyslipidaemia	103 (22.6)

Data are shown as mean (SD) or n (%); BMI: Body mass index; CVD: cardiovascular disease

baseline demographic and clinical characteristics. FPG and postprandial plasma glucose (PPG) levels were taken at baseline and days 30, 60 and 90, and HbA1c at baseline and at the end of study (day-90).

Statistical analyses

The primary endpoint was the number of patients achieving glycaemic control (FPG 90-130 mg/dL) on an intention to treat basis at follow-up visits in each group. Other endpoints were changes in FPG, PPG and HbA1c from baseline at day 90. Categorical data were presented as percentages with their 95% CI, and changes in FPG along with their 95% CI. Statistical analyses were conducted using SAS version 9.1.

Results

This study enrolled a total of 455 patients (group M: 197, group GM: 136 and group U: 122) at 6 centres across India. Patients had a mean age of 51.9 ± 11.3 years and a mean BMI of 26.7 ± 6.2 kg/m² (Table 1). More than half (n = 261) the patient population had a family history of diabetes, 35.4% (n = 161) patients had hypertension, 30.1% (n = 137) had obesity, 22.6% (n = 103) had dyslipidaemia and 9.9% (n = 45) had history of cardiovascular diseases.

Of 197 patients in group M, target FPG was achieved by 73.09% (n = 144) with 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC plus 1 tablet

of metformin at day-30 (Fig. 1A). About 15.29% and 15.38% of patients received up-titration to 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC plus 2 tablets of metformin to achieve glycaemic control at day-60 and day-90, respectively. Only 5.90% and 6.41% of patients required 2 tablets of gliclazide XR 60 mg + metformin XR 500 mg FDC to achieve glycaemic control at day-60 and day-90, respectively (Figure 1A). Approximately 74.26% ($n = 101$) patients in group GM achieved glycaemic control with gliclazide XR 60 mg + metformin XR 500 mg FDC plus 1 tablet of metformin at day-30; and approximately 12–15% required up-titration to 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC plus 2 tablets of metformin at third and fourth follow-up visits. Only 0.87% patients required 2 tablets of gliclazide XR 60 mg + metformin XR 500 mg FDC at day-60. None of the patients required 2 tablets of gliclazide XR 60 mg + metformin XR 500 mg FDC at day-90 (Fig. 1B). The proportion of patients who were newly diagnosed or untreated with HbA1c > 9% (group U) and achieved target FPG with 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC plus 1 tablet of metformin at day-30 was 60.66% ($n = 74$). Around 12–14% of patients received up-titration to 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC plus 2 tablets of metformin at day-60 and day-90. About 12–19% of patients required 2 tablets of gliclazide XR 60 mg + metformin XR 500 mg FDC to achieve glycaemic control at days 60 and 90 (Fig. 1C). Collectively, the majority of patients achieved target FPG with 1 tablet of gliclazide XR 60 mg + metformin XR 500 mg FDC with 1 tablet of metformin at day-30 and only 29.23% (133/455) required the up-titration of treatment. Moreover, only a few patients remained uncontrolled at the end of the study across three groups (Fig. 1).

In patients uncontrolled on conventional gliclazide XR 60 mg + metformin XR 500 mg (group GM), mean FPG reduced from 159.85 ± 39.12 mg/dL at baseline to 105.38 ± 20.24 mg/dL at day-90 ($P < 0.001$; Figure 2A). Similarly, PPG decreased from 231.43 ± 52.35 mg/dL to 162.19 ± 26.4 mg/dL ($P < 0.001$; Fig. 2B), and HbA1c from 8.01 ± 0.69 % to 7.21 ± 0.57 % ($P < 0.001$; Fig. 2C). In patients uncontrolled on metformin (group M), mean FPG was reduced from 168.12 ± 37.21 mg/dL at baseline to 107.69 ± 21.22 mg/dL at day-90 ($P < 0.001$; Figure 2A). Similarly, PPG decreased from 246.52 ± 63.27 mg/dL to 155.53 ± 28.7 mg/dL ($P < 0.001$; Figure 2B), and HbA1c from 8.29 ± 1.01 % to 7.21 ± 0.61 mg/dL ($P < 0.001$; Figure 2C). In the last group of patients who are newly diagnosed or untreated with HbA1c > 9% (group U), mean FPG was reduced from 182.35 ± 48.32 mg/dL at baseline to $109.45 \pm$

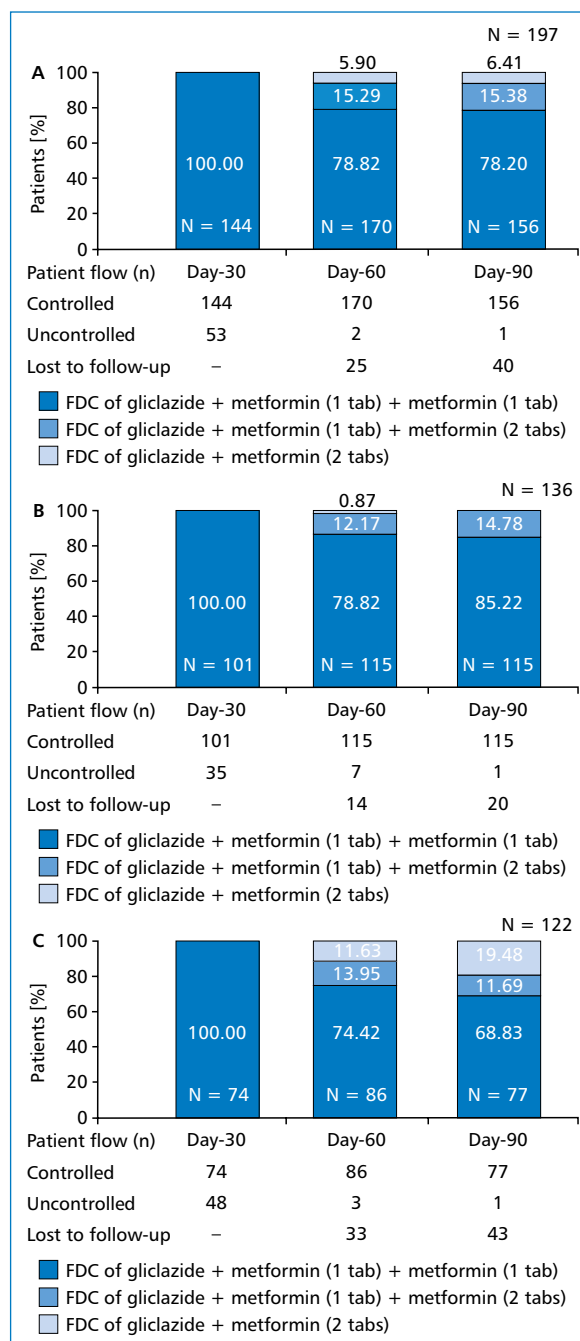


Figure 1. Glycaemic control rate and pattern of FDC use. The bar graph shows the pattern of FDC use in patients who achieved glycaemic control and the table represents the overall glycaemic control rate; **A.** Group M, patients uncontrolled on metformin 500 mg ($n = 197$); **B.** Group GM, patients uncontrolled on conventional gliclazide + metformin ($n = 136$); **C.** Group U, newly diagnosed or untreated patients with HbA1c > 9% ($n = 122$)

18.79 mg/dL at day-90 ($P < 0.001$; Fig. 2A). Similarly, PPG decreased from 267.2 ± 67.32 mg/dL to 169.14 ± 25.62 mg/dL ($P < 0.001$; Fig. 2B), and HbA1c from 89.53 ± 1.87 % to 7.44 ± 0.87 % ($P < 0.001$; Fig. 2C).

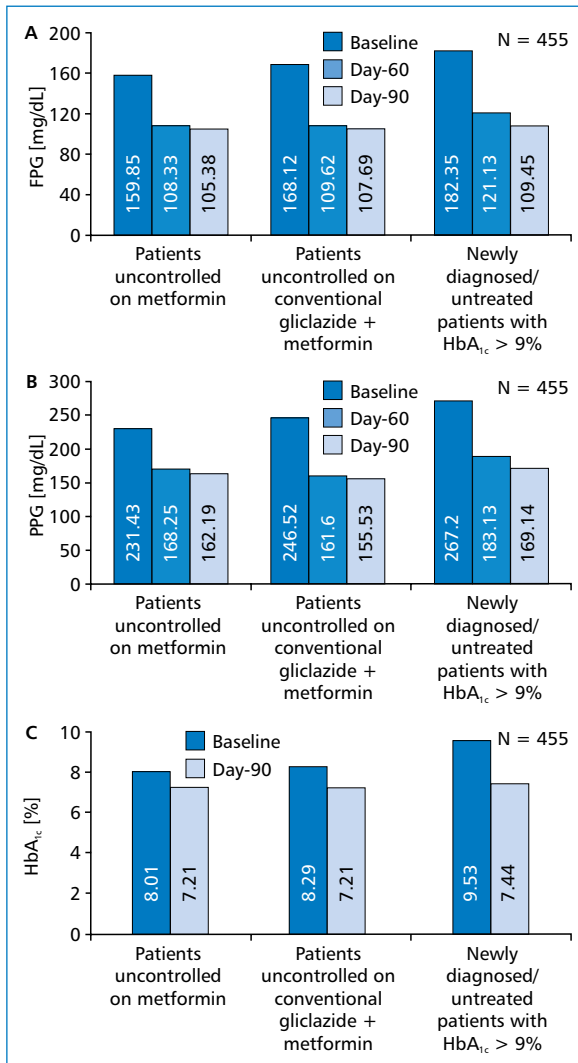


Figure 2. Glycaemic control in patients receiving the gliclazide XR 60 mg + metformin XR 500 mg and metformin XR 500 mg based up-titration; **A:** Mean FPG at baseline and follow-up visits; **B:** Mean PPG at baseline and follow-up visits; **C:** Mean HbA_{1c} at baseline and follow-up visits. FPG, PPG, and HbA_{1c} were significantly reduced ($P < 0.001$) at Day-60 and Day-90 compared to respective baseline values; FPG: fasting plasma glucose; PPG: postprandial glucose

Overall, as expected, the decrease in glycaemic parameters were greater in Group U compared to Group M and Group GM. Altogether, the gliclazide XR 60 mg and metformin XR 500 mg-based combination treatment, up-titrated at the discretion of physician for 3 months, significantly reduced FPG, PPG and HbA_{1c} from baseline in all 3 patient categories.

Discussion

In this study, treatment of type 2 diabetes with gliclazide XR 60 mg + metformin XR 500 mg FDC and metformin-improved glycaemic control in all three

groups. For patients who were uncontrolled on metformin alone or with conventional gliclazide XR 60 mg + metformin XR 500 mg, approximately more than 50% of patients achieved target FPG within 30 days at the first visit. Moreover, about 37% of patients who were newly diagnosed or untreated, with HbA_{1c} > 9%, achieved target FPG by 30 days.

A line of evidence indicates that gliclazide reduces HbA_{1c} better than other insulinotropic agents [5]. Gliclazide is also cardio safe and has lower hypoglycaemia risk [5, 6]. In the GUIDE (GLUcose control in type 2 diabetes: Diamicon MR vs glimepiride) randomized, head-to-head trial, its hypoglycaemic risk was found to be lower compared to that of glimepiride [7]. A systematic review and meta-analysis of 18 studies including 1,67,327 patients with diabetes reported superior cardiovascular (CV) safety of gliclazide [6]. Danish registry of 1,07,806 patients with diabetes with or without myocardial infarction who initiated single-agent treatment with insulin secretagogues or metformin, also showed lower CV and all-cause mortality risk with gliclazide at 9-year follow-up [8]. Similarly, in the Steno-2 randomized trial conducted in 160 patients with diabetes, microalbuminuria, an intensive gliclazide therapy showed a median 7.9 years of life gain with + 8.1 years free from-CV-events at 21.2 years of median follow-up [9]. Unlike other SUs, greater selectivity of gliclazide for pancreas rather than myocardial sulfonylureas receptors, along with its fibrinolytic properties (which are independent of its glucose-lowering action) could be attributed to better CV safety [10].

Reductions in glycaemic parameters were in line with previously reported studies. Moreover, the results showing the feasibility and effectiveness of gliclazide XR 60 mg + metformin XR 500 mg FDC are in line with other studies conducted in India [11, 12].

Clinical practice guidelines including the latest WHO guidelines for diabetes management prefers gliclazide among other SUs, to be used with metformin as a combination therapy [2, 3]. However, compliance to therapy remains a challenge. Treatment with FDC improves compliance and increases the probability of achieving target glycaemic control [13]. In this study, > 70% of patients achieved target FPG in a short duration and could explain the ease of up-titration using gliclazide XR 60 mg + metformin XR 500 mg FDC with metformin (when required). This could help all patient groups to achieve glycaemic control, faster.

A major limitation of this study is that patients did not receive randomized treatment. The medication regimen was at the discretion of prescribing physicians. However, these results represented the real-world primary-care practice data for efficient up-titration of

the therapy using gliclazide XR 60 mg + metformin XR 500 mg FDC with metformin (as per patient profile).

Above all, the presented findings suggest that a gliclazide-metformin-based combination treatment, up-titrated at the discretion of physician for 3 months, significantly reduced FPG, PPG and HbA1c levels from baseline in patients either uncontrolled on metformin alone or conventional gliclazide XR 60 mg + metformin XR 500 mg, and in newly diagnosed patients or untreated patients with HbA1c > 9%. Overall, the treatment was well tolerated by the patients.

Conclusion

It can be concluded from this real-world primary-care practice study that efficient up-titration of therapy using gliclazide XR 60 mg + metformin XR 500 mg FDC plus metformin (as per individual patient need), can be an effective option to achieve optimal glycaemic control in daily clinical practice.

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Conflict of interest

The authors declare no conflict of interest.

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