Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea

Hye-soon Kim1, Doo-man Kim2, Bong-soo Cha3, Tae Sun Park4, Kyoung-ah Kim5, Dong-lim Kim6, Choon Hee Chung7, Jeong-hyun Park8, Hak Chul Jang9, Dong-seop Choi10*

1Department of Internal Medicine, Keimyung University School of Medicine, Daegu, 2Department of Internal Medicine, Hallym University College of Medicine, 3Department of Internal Medicine, Yonsei University College of Medicine, 4Department of Internal Medicine, Konkuk University School of Medicine, 5Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, 6Department of Endocrinology and Metabolism, Chonbuk National University Hospital, Jeonju, 7Department of Internal Medicine, Dongguk University College of Medicine, Goyang, 8Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, 9Paik Institute for Clinical Research, Department of Internal Medicine, College of Medicine, Inje University, Busan, and 10Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Keywords
Glimepiride/metformin combination, Korea, Type 2 diabetes mellitus

*Correspondence
Dong Seop Choi
Tel.: +82-2-920-5421
Fax: +82-2-953-9355
E-mail address: cdongs@kumc.or.kr

J Diabetes Invest 2014; 5: 701–708
doi: 10.1111/jdi.12201

ABSTRACT
Aims/Introduction: To compare the efficacy and safety of early combination therapy with glimepiride/metformin to metformin uptitration in reducing glycated hemoglobin (HbA1c) levels in Korean type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy.

Materials and Methods: In a randomized, open label, parallel group, multicenter study, 209 Korean type 2 diabetic patients (HbA1c 7.0–10.0%, on metformin 500–1,000 mg/day) received glimepiride/metformin fixed-dose combination (G/M FDC) or metformin uptitration treatment (Met UP). The primary end-point was the change in HbA1c from baseline to week 24.

Results: G/M FDC therapy provided significantly greater adjusted mean decreases vs Met UP therapy in HbA1c (~1.2 vs ~0.8%, P < 0.0001), and fasting plasma glucose (~35.7 vs ~18.6 mg/dL, P < 0.0001). A significantly greater proportion of patients with G/M FDC therapy achieved HbA1c <7% (74.7 vs 46.6%, P < 0.0001) at the end of the study. More patients experienced hypoglycemia with G/M FDC therapy compared with Met UP therapy (41 vs 5.6%, P < 0.0001), but there was no serious hypoglycemia in any group. A modest increase in mean bodyweight occurred in the patients who were treated with G/M FDC therapy (1.0 kg), whereas a slight decrease was observed in the patients who were treated with Met UP therapy (~0.7 kg).

Conclusion: The present study showed that glimepiride/metformin fixed-dose combination therapy was more effective in glycemic control than metformin uptitration, and was well tolerated in type 2 diabetic patients inadequately controlled by low-dose metformin monotherapy in Korea. This trial was registered with ClinicalTrial.gov (no. NCT00612144).
INTRODUCTION

Type 2 diabetes mellitus is one of the most common metabolic diseases, with its prevalence increasing worldwide. The pathophysiology of this disease is characterized by defective insulin secretion and increased insulin resistance. The importance of blood glucose control was shown in the UK Prospective Diabetes Study (UKPDS), showing that early intensive blood glucose control from the time of diagnosis of diabetes mellitus reduced micro- and macrovascular complications, as well as mortality. Oral hypoglycemic drugs with various mechanisms, such as enhancing the pancreatic function to secrete insulin, reducing insulin resistance of the body tissues or increasing glucagon-like peptide-1, have been developed and are currently in use. However, monotherapy of a glucose-lowering agent shows an increasing failure of blood glucose control over time, eventually requiring a number of antidiabetic medications in combination or insulin. Of the medication mentioned, combination therapy using sulfonylurea and metformin, which respectively promotes insulin secretion and improves insulin resistance, is an effective and complementary method that improves both of the main causes of type 2 diabetes, and has been reported by UKPDS and other clinical studies to be more effective than monotherapy of both drugs.

Unlike in Western countries, type 2 diabetes in Asia is characterized by onset at a relatively young age without obesity. The risk of type 2 diabetes starts at a lower body mass index for Asians than for Europeans. Also, it has been reported that insulin secretory impairment might be induced by insufficient β-cell mass, functional defects of β-cells, or both. To reflect such pathophysiological differences between Asians and Caucasians and individual differences, the Korean Diabetes Association recommends using not only metformin as the primary drug, but also using all possible medication according to patient characteristics. According to a clinical trial that compared glimepiride, metformin and rosiglitazone monotherapy in 349 Korean patients with type 2 diabetes, the blood glucose lowering effect was not significantly different among the three drugs, and a sufficient glucose-lowering effect was observed at half-maximal dose. Therefore, it seems advisable to use combination therapy with a complementary mechanism rather than increasing to the maximal dose in type 2 diabetes patients inadequately controlled by monotherapy. For this reason, sulfonylurea is the most commonly used primary drug or secondary add-on drug when glycemic goal is not achieved by using metformin monotherapy, especially in Asian countries and also many other countries.

Considering the compliance and cost-effectiveness, the use of a fixed-dose combination pill of sulfonylurea and metformin monotherapy uptitration at an early stage in Korean type 2 diabetes patients inadequately controlled by low-dose metformin monotherapy.

The purpose of the present study was to compare the efficacy and safety of glimepiride/metformin fixed-dose combination (G/M FDC) and metformin uptitration (Met UP) in type 2 diabetes patients who had failed to achieve glycemic goal with low-dose metformin monotherapy.

MATERIALS AND METHODS

Participants

The participants of the present trial were patients with type 2 diabetes mellitus diagnosed at least 3 months before enrollment as having glycated hemoglobin (HbA1c) levels between 7 and 10%, and who had been treated with metformin 500–1,000 mg alone for at least 4 weeks. Female patients with childbearing potential had to have negative results of their serum human chorionic gonadotropin tests. All patients signed informed consent forms before their participation in the trial. Of these eligible patients, only those who were capable of and willing to complete subject diaries to record self-monitored blood glucose (SMBG) levels were selected for the present study. Patients who had acute complications, such as diabetic ketoacidosis or hyperglycemic hyperosmolar state, within 3 months, or those who had clinically significant renal or hepatic disorders were excluded from the study.

Study Design and Protocol

In this multicenter, randomized, parallel group and open labeled clinical study, participants were registered from December 2007 to May 2009 in ten institutions. The study period was 13 weeks at a minimum and 26 weeks at a maximum, consisting of a screening period (1–2 weeks), titration period (2–14 weeks) and maintenance period (10 weeks). Participants who met the inclusion and exclusion criteria were randomly assigned to the G/M FDC group (initial dosage 1/250 mg b.i.d.) or Met UP group (initial dosage 500 mg b.i.d.). During the titration period consisting of biweekly follow-up schedules, participants were considered to be administrated with dose titration on every visit. For dose titration, SMBG levels were measured for 7 days before the next scheduled visit. The average SMBG level was calculated from six measured SMBG levels closest to the next scheduled visit, three measured before having breakfast and three measured before dinner. According to the titration algorithm (Figure 1), the treatments were titrated based on the average SMBG level and hypoglycemia. When the previous dose was maintained or a patient underwent the maximum titration period of 14 weeks, the maintenance period started without any further dose titration. The study drugs dispensed at each follow-up visit ranged from level-1 (G/M FDC group 1/250 mg/day, Met UP group 750 mg/day) to level 6 (G/M FDC group 8/2,000 mg/day, Met UP group...
were to be taken with daily breakfast and dinner meals. All participants were instructed to stay on a regular diet and exercise, and were encouraged to keep at least 80% compliance.

The study protocol and amendments were approved by an independent ethics committee or institutional review board at each participating site. All participants provided written informed consent. The study was carried out in accordance with ethical principles based on the Declaration of Helsinki.

**Study Measurements**

The primary efficacy end-point was the change in HbA1c from baseline to the study end (minimum 12 weeks, maximum 24 weeks). Secondary efficacy end-points included changes in fasting plasma glucose (FPG) and postprandial glucose (PPG) from baseline to the study end, and the rate of response to HbA1c and FPG at the study end. Response rate was defined as the proportion of patients with each HbA1c <7% and FPG <140 mg/dL.

For safety evaluation, a physical examination including height and weight was carried out at baseline and the end of the study, and vital signs, adverse events and hypoglycemia were checked at each visit. In addition, a hematological examination, blood chemistry test and urine test were carried out.

Symptomatic hypoglycemia was defined as signs and symptoms consistent with hypoglycemia with or without documented glucose measurement. When the blood glucose level measured by SMBG was <60 mg/dL, it was counted as hypoglycemia with or without hypoglycemic signs and symptoms at the investigator’s discretion. To confirm hypoglycemia, all participants were trained to carry out SMBG to check and document their blood glucose level every time they had hypoglycemia signs or symptoms.

**Statistical Analysis**

Efficacy outcomes were analyzed on the intent-to-treat (ITT) population defined as all randomized patients who had received at least one dose of study medication, and had a baseline efficacy data and at least one post-baseline efficacy data. Missing data were handled using the last observation carried forward methodology. Treatment groups were compared using an analysis of covariance (ANCOVA) model with baseline value as a covariate. The response rate was carried out on the ITT population, and the treatment groups were compared using the Cochran–Mantel–Haenszel test.

Safety was analyzed using the safety population composed of all randomized patients who had at least one dose of study medication. Between-group differences in the incidence of adverse events (AE) were analyzed by Fisher’s exact test, and in the incidence of hypoglycemia were analyzed by the Cochran–Mantel–Haenszel test.

**RESULTS**

**Patient Disposition and Baseline Characteristics**

The patient disposition is shown in Figure 2. A total of 265 patients enrolled. Of these, 209 type 2 diabetes patients were randomly assigned to the G/M FDC group (101 participants) and Met UP group (108 participants). Among them, 189 patients completed the present study. Six participants in the G/M FDC group were withdrawn, and the main cause was hypoglycemia (three participants). A total of 14 participants in the Met UP group were withdrawn, and the main causes were adverse events, protocol violation, lack of efficacy and failure to follow up.

For efficacy evaluation, the ITT population of 99 participants from the G/M FDC group and 103 participants from the Met Up group were included. For safety evaluation, 100 participants...
from the G/M FDC and 108 participants from the Met UP group were included. There was no statistically significant difference in the demographic data between the two groups (Table 1).

The average daily dose of the medications were 2.5 mg/627 mg for the G/M FDC group and 1313.1 mg for the Met UP group. The titration period was longer in the Met UP group with 95.7–29.6 days than the G/M FDC group with 88.4–16.9 days.

Primary Efficacy Variable
The HbA1c levels at the baseline visit presented no significant difference between the two groups; 7.9% in the G/M FDC group and 7.8% in the Met UP group. At the end of the study, the final HbA1c levels were 6.6% in the G/M FDC group and 7.0% in the Met UP group, and the adjusted mean difference between groups was 0.4% with statistical significance ($P < 0.0001$; Table 2). Additional analysis of the subgroup who had HbA1c > 8% at the baseline showed that the adjusted mean changes in the G/M FDC group and Met UP group were −1.8 and −1.3%, respectively.

Secondary Efficacy Variables
The mean changes of fasting plasma glucose were −35.7 mg/dL (from 156.7 to 117.3 mg/dL) in the G/M FDC group, and −18.6 mg/dL (from 148.1 to 133.0 mg/dL) in the Met UP group. The adjusted mean difference between the two groups was −17.1 mg/dL with statistical significance ($P < 0.0001$; Table 2).

The 2-h postprandial blood glucose level was changed from 233.6 to 180.9 mg/dL in the G/M FDC group with a mean decrease of 50.6 mg/dL. In the Met UP group, the level was changed from 228.0 to 187.4 mg/dL with a mean decrease of 42.5 mg/dL. The adjusted mean difference of the two groups was 8.1 mg/dL ($P = 0.2681$; Table 2).

The response rate achieving HbA1c < 7.0% was significantly higher in the G/M FDC group, being 74.7%, than in the Met Up group, being 46.6% ($P < 0.0001$). Additionally, the response rate calculated by the percentage of patients achieving

Table 1 | Baseline characteristics of the participants

|                | G/M FDC (n = 101) | Met UP (n = 108) |
|----------------|-------------------|------------------|
| Age (years)    | 55.2 ± 8.4        | 56.1 ± 9.6       |
| Male/female (%)| 51.5/48.5         | 47.2/52.8        |
| Weight (kg)    | 66.5 ± 10.6       | 66.9 ± 12.1      |
| Height (cm)    | 161.4 ± 9.1       | 161.0 ± 9.3      |
| BMI (kg/m²)    | 25.5 ± 3.5        | 25.7 ± 3.2       |
| HbA1c (%)      | 7.9 ± 0.8         | 7.8 ± 0.7        |
| Median duration of diabetes (years) | 3.0 (range 0.0–21.0) | 3.0 (range 0.0–30.0) |
| Age at onset of diabetes (years) | 51.2 ± 8.5 | 51.8 ± 8.7 |

All values are mean ± standard deviation except where indicated. BMI, body mass index; G/M FDC, glimepiride/metformin fixed-dose combination; HbA1c, glycated hemoglobin; Met Up, metformin up-titration treatment.
end-point FPG <140 mg/dL was significantly higher in the G/M FDC group compared with the Met UP group (84.7 vs 65.1%; \( P = 0.0013 \)).

**Safety and Tolerability Profile**

Treatments were generally well tolerated in both groups during the trial. One or more AEs were reported by a similar percentage of patients in each treatment group, and there was no significant difference between the rate of events (\( P = 0.7678 \)). The highest rate of AEs occurred from the gastrointestinal tract being 10.1%, followed by infection (9.6%), without difference between the two groups. Serious adverse events (SAEs) occurred in four participants; one participant from the G/M FDC group and three participants from the Met UP group. All SAEs were evaluated to be unrelated to the study drugs.

A total of 100 cases of hypoglycemic events occurred in 41 patients from the G/M FDC group, and six cases occurred in six patients from the Met UP group. Overall, hypoglycemic events occurred significantly more frequently in the G/M FDC group. However, severe hypoglycemia was not observed in any of the groups. Analysis of hypoglycemia for which SMBG was available showed that only one patient of the G/M FDC group had a blood glucose level below 50 mg/dL (Table 3).

Bodyweight was increased by 1.0 kg in the G/M FDC group and decreased by 0.7 kg in the Met UP group with a statistically significant difference (\( P < 0.0001 \)).

**DISCUSSION**

In the present study, the HbA1c lowering effect was statistically superior in the G/M FDC group compared with the Met UP group in Korean type 2 diabetes patients who had failed blood glucose control by low-dose metformin monotherapy. The response rate, defined as the ratio of patients achieving each HbA1c <7% and FPG <140 mg/dL, was significantly higher in the G/M FDC group and also, the titration period was shorter in the G/M FDC group than the Met UP group. Even though the uptitration dosage was not escalated in equal potency between the groups (G/M FDC group 250 mg vs Met UP group 500 mg, and G/M FDC group 1250 mg vs Met UP group 250 mg), the present study was to prove the efficacy and safety of early combination therapy with complimentary drugs, and it was shown that the G/M FDC group could reduce the dosage of each composition and shorten the titration period to reach the significant response rate. These results suggest that early combination therapy with glimepiride and metformin could provide the benefit of a legacy effect through earlier glucose lowering.

---

### Table 2 | Adjusted mean changes in glycated hemoglobin, fasting plasma glucose and 2-h postprandial plasma glucose

| Group       | n   | Baseline Mean ± SD | End of study Mean ± SD | Adjusted mean change from baseline (95% CI) | Change G/M FDC vs Met UP (95% CI) | P-value |
|-------------|-----|--------------------|------------------------|--------------------------------------------|----------------------------------|---------|
| HbA1c (%)   |     |                    |                        |                                            |                                  |         |
| G/M FDC     | 99  | 7.9 ± 0.8          | 6.6 ± 0.7              | −12 (−13 to −11)                           | −0.4 (−0.6 to −0.3)              | <0.0001 |
| Met UP      | 103 | 7.8 ± 0.7          | 7.0 ± 0.7              | −0.8 (−0.9 to −0.6)                        |                                  |         |
| FPG (mg/dL) |     |                    |                        |                                            |                                  |         |
| G/M FDC     | 98  | 156.7 ± 33.2       | 117.3 ± 21.0           | −35.7 (−39.7 to −31.7)                     | −17.1 (−22.8 to −11.5)           | <0.0001 |
| Met UP      | 103 | 148.1 ± 26.9       | 133.0 ± 20.3           | −18.6 (−22.5 to −14.6)                     |                                  |         |
| PPG (mg/dL) |     |                    |                        |                                            |                                  |         |
| G/M FDC     | 97  | 233.6 ± 66.7       | 180.9 ± 57.3           | −50.6 (−60.8 to −40.3)                     | −8.1 (−22.4 to 6.3)              | 0.2681  |
| Met UP      | 102 | 228.0 ± 69.0       | 187.4 ± 52.1           | −42.5 (−52.5 to −32.5)                     |                                  |         |

CI, confidence interval; G/M FDC, glimepiride/metformin fixed-dose combination; Met Up, metformin uptitration treatment; SD, standard deviation.

---

### Table 3 | Summary of clinical adverse events and hypoglycemia

| AE Category                      | G/M FDC (n = 100) | Met UP (n = 108) |
|----------------------------------|------------------|-----------------|
| Abdominal pain upper             | 4 (4.0)          | 1 (0.9)         |
| Diarrhea                         | 1 (1.0)          | 5 (4.6)         |
| Chest pain                       | 2 (2.0)          | 2 (1.9)         |
| Nasopharyngitis                  | 7 (7.0)          | 5 (4.6)         |
| Upper respiratory tract infection| 0                | 5 (4.6)         |
| Headache                         | 3 (3.0)          | 0               |

**Hypoglycemia, n (%)/event**

| Hypoglycemia event                | G/M FDC | Met UP |
|-----------------------------------|---------|--------|
| Any hypoglycemia                  | 41 (41.0)/100 | 6 (5.6)/6 |
| Titration period                  | 19 (19.0)/31   | 3 (2.8)/3 |
| Maintenance period                | 29 (29.0)/68   | 2 (1.9)/2 |
| Symptomatic hypoglycemia          | 39 (39.0)/96   | 4 (3.7)/4 |
| Nocturnal hypoglycemia            | 2 (2.0)/2     | 0/0    |
| Severe hypoglycemia               | 0/0     | 0/0    |

**Hypoglycemia checked with SMBG, no. events (%)**

| Hypoglycemia event                | G/M FDC | Met UP |
|-----------------------------------|---------|--------|
| Hypoglycemia checked with SMBG    | 81 (100) | 4 (100) |
| <50 mg/dL                         | 1 (1.2) | 0 (0.0) |
| 50–60 mg/dL                       | 9 (11.1) | 1 (25.0) |
| 60–70 mg/dL                       | 24 (29.6) | 1 (25.0) |
| ≥70 mg/dL                         | 47 (58.0) | 2 (50.0) |

*Adverse events (AEs) excluding hypoglycemia. G/M FDC, glimepiride/metformin fixed-dose combination; Met Up, metformin uptitration treatment; SMBG, self-monitored blood glucose.
cohol control, avoiding negative glycemic memory related to micro- and macro-vascular complications. In contrast, we expected more mean FPG decrease in the Met UP group than in the G/M FDC group considering their average daily metformin dose. However, significant superiority was observed in the G/M FDC group. The effect of glimepiride on FPG can be explained by direct and indirect inhibition of hepatic glucose production through an increase in insulin secretion. In PPG evaluation, the G/M FDC group failed to prove its efficacy over the Met UP group with statistical significance, but the trend of greater reduction was also detected.

As found in the present study, insulin secretagogue enables an efficient control of blood glucose in Korean type 2 diabetic patients who develop type 2 diabetes mainly as a result of insulin secretory impairment. A study carried out by Fukushima et al. showed similar results. The authors concluded that Japanese type 2 diabetic patients are characterized by a larger decrease in insulin secretion and show less attribution of insulin resistance. Other studies on type 2 diabetes patients in Asia also showed that insulin secretion is the sole or more important factor in pathogenesis of diabetes in type 2 diabetes patients who are not obese or without Metabolic Syndrome. Patients with impaired glucose tolerance and even patients with normal glucose tolerance showed a decrease in insulin secretion of β-cells. Such impaired insulin secretion is explained by smaller β-cell size or functional defect in Asians. Also, in the case of normal glucose tolerance and type 2 diabetes patients, β-cell mass has a high linear correlation with body mass index. The studies showed that a decrease in insulin secretion during the early stage of diabetes played an important role in the pathogenesis of type 2 diabetes patients in Korea and other Asian countries, and they provided the basis for effective glucose control by using sulfonylurea, which stimulates insulin secretion, at an early stage of diabetes.

Glimepiride and metformin are the most common and widely used oral hypoglycemic agents in the world. Metformin improves insulin resistance, and is recommended as the first choice medication for newly diagnosed type 2 diabetes patients by most guidelines. Glimepiride is a third generation sulfonylurea that stimulates insulin secretion. Unlike conventional sulfonylurea, glimepiride has high selectivity toward the pancreatic ATP-sensitive potassium channel, increases glucose transport, and shows various extrapancreatic effects in muscle and fat cells. For these benefits, glimepiride is prescribed as a primary monotherapy or additional medication when metformin monotherapy has failed. Most existing studies have been carried out for patients who have failed blood glucose control, even when using metformin at the maximum dose or higher. The combination therapy with metformin and glimepiride showed superior efficacy than metformin or glimepiride monotherapy in type 2 diabetes patients who had failed glucose control with metformin 2,550 mg. However, metformin shows a dose-dependent blood glucose lowering effect only up to 1,500 mg, and the dose above that shows no significant additional response. Considering the importance of the insulin secretory function in Korean type 2 diabetes patients, the importance of early intensive glucose control and the dose–response relationship of metformin, we consider it to be more beneficial to add glimepiride to patients who have failed to control their blood glucose with low-dose metformin rather than maximizing the dose of metformin.

The rate of hypoglycemia occurrence in the present study was comparable to existing studies. As expected, more cases of hypoglycemia were observed in the G/M FDC group. Of the 100 cases of hypoglycemia that occurred in the G/M FDC group, 81 cases had blood glucose levels that were measured by SMBG in a patient diary. Of the 81 cases, 47 cases (58%) had a blood glucose level above 70 mg/dL, and one case (1.2%) below 50 mg/dL. As an insulin secretagogue, sulfonylureas tend to cause more hypoglycemia compared with other classes of medication, but glimepiride has a lower occurrence rate for any and severe hypoglycemia compared with conventional sulfonylureas, which is thought to be due to glimepiride not stimulating inappropriate insulin secretion when blood glucose is low.

Several studies have reported dose-dependent gastrointestinal AEs of metformin. Gastrointestinal AE is a clinically important factor, as it decreases patient compliance and causes discontinuance of the treatment. In the present study, ten patients (10.0%) in the G/M FDC group and 11 patients (10.2%) in the Met UP group experienced gastrointestinal AEs, which was lower than previous clinical trials. This can be attributed to a relatively lower metformin dose in the present study compared with other studies.

The limitation of the present study was the short period of 24 weeks, so further long-term study is required to prove the efficacy and safety of G/M FDC therapy over Met UP therapy. Also, the titration algorithm was not designed to equal potency, so it was difficult to investigate the direct comparison between two groups per protocol. However, the present study was carried out to verify the benefits of early combination of complimentary drugs, so the results that G/M FDC therapy reduced each component’s dosage and shortened the titration period are an important outcome providing evidence to clinicians for applying early combination therapy to their clinical practice.

In summary, G/M FDC therapy showed a superior blood glucose-lowering effect, comparable safety and tolerability compared with Met UP therapy. Considering pathogenetic characteristics of Korean type 2 diabetes, glimepiride/metformin fixed-dose combination therapy is concluded to be an effective therapeutic strategy to minimize side-effects from high-dose metformin and to reduce exposure to hyperglycemia in type 2 diabetes patients who have inappropriate blood glucose control by low-dose metformin treatment.

ACKNOWLEDGMENTS

This study was sponsored by Handok Inc. None of the authors have any financial support that might pose a conflict of interest.
REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854–865.

2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–853.

3. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577–1589.

4. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005–2012.

5. Hermann LS, Scherstén B, Bitzén PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care 1994; 17: 1100–1109.

6. U.K. Prospective Diabetes Study Group. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. Diabetes Care 1998; 21: 87–92.

7. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009; 301: 2129–2140.

8. Korean Diabetes Association. Treatment Guideline for Diabetes. Korean Diabetes Association, 2011. Available from URL: http://www.diabetes.or.kr/pro/publish/sub04.php?mode=list

9. Yoon KH, Shin JA, Kwon HS, et al. Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in Korean drug-naive type 2 diabetic patients: the practical evidence of anti-diabetic monotherapy study. Diabetes Metab J 2011; 35: 26–33.

10. Melikian C, White TJ, Vanderplas A, et al. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002; 24: 460–467.

11. Best JD, Judzewitsch RG, Pfeifer MA, et al. The effect of chronic sulfonylura therapy on hepatic glucose production in non-insulin-dependent diabetes. Diabetes 1982; 31: 333–338.

12. Fukushima M, Usami M, Ikeda M, et al. Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. Metabolism 2004; 53: 831–835.

13. Kim DJ, Lee MS, Kim KW, et al. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001; 50: 590–593.

14. Chen KW, Boyko EJ, Bergstrom RW, et al. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. 5-Year follow-up of initially nondiabetic Japanese-American men. Diabetes Care 1995; 18: 747–753.

15. Matsumoto K, Miyake S, Yano M, et al. Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. Diabetes Care 1997; 20: 1562–1568.

16. Rattarasarn C, Soonthornpan S, Leelawattana R, et al. Decreased insulin secretion but not insulin sensitivity in normal glucose tolerant Thai subjects. Diabetes Care 2006; 29: 742–743.

17. Park YW, Allison DB, Heymsfield SB, et al. Larger amounts of visceral adipose tissue in Asian Americans. Obes Res 2001; 9: 381–387.

18. Yoon KH, Ko SH, Cho JH, et al. Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 2003; 88: 2300–2308.

19. Geisen K, Végh A, Krause E, et al. Cardiovascular effects of conventional sulfonylureas and glimepiride. Horm Metab Res 1996; 28: 496–507.

20. Müller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas – a comparison between glimepiride and conventional sulfonylureas. Diabetes Res Clin Pract 1995; 28: S115–S137.

21. National Collaborating Centre for Chronic Conditions (UK). Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). Royal College of Physicians (UK), London, 2008.

22. Charpentier G, Fleury F, Kabir M, et al. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabet Med 2001; 18: 828–834.

23. Fujioka K, Brazg RL, Raz I, et al. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. Diabetes Obes Metab 2005; 7: 28–39.

24. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose–response trial. Am J Med 1997; 103: 491–497.

25. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009; 32: 187–192.

26. Sherifali D, Ponthakee Z. To lower or not to lower? Making sense of the latest research on intensive glycaemic control and cardiovascular outcomes. Evid Based Med 2009; 14: 34–37.
27. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; 373: 1765–1772.

28. González-Ortiz M, Guerrero-Romero JF, Violante-Ortiz R, et al. Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus. *J Diabetes Complications* 2009; 23: 376–379.

29. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev* 2001; 17: 467–473.

30. Szoke E, Gosmanov NR, Sinkin JC, et al. Effects of glimepiride and glyburide on glucose counterregulation and recovery from hypoglycemia. *Metabolism* 2006; 55: 78–83.

31. Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996; 334: 574–579.