

# Comparative assessment of the efficacy and safety of acarbose and metformin combined with premixed insulin in patients with type 2 diabetes mellitus

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## Abstract

This study, a subgroup analysis of the data from the Organization Program of DiabEtes INsullN ManaGement study, aimed to compare the efficacy and safety profiles of acarbose and metformin used in combination with premixed insulin.

This analysis included 80 and 192 patients taking only 1 oral antidiabetic drug, classified into acarbose (treated with acarbose + insulin) and metformin groups (treated with metformin + insulin), respectively. The efficacy and safety data were analyzed for within- and between-group differences. The clinical trial registry number was NCT01338376.

The percentage of patients who achieved target hemoglobin A1c (HbA1c) <7% in the acarbose and metformin groups were 38.75% and 30.73%, respectively, after a 16-week treatment. The average HbA1c levels in the acarbose and metformin groups were comparable at baseline and decreased significantly in both groups at the end of the study. All 7 blood glucose decreased significantly in both groups at endpoint compared with that at baseline. Insulin consumption was higher in the metformin group in terms of total daily amount and units/kg body weight. Incidences of hypoglycemia were similar in both groups. Body weight changed significantly in both groups from baseline to endpoint, but with no significant difference between the groups. Mean scores of Morisky Medication Adherence Scale improved in both groups at endpoint.

Combination of insulin with acarbose or metformin could improve glycemic control in patients with type 2 diabetes mellitus. Acarbose and metformin were found to be comparable in terms of efficacy, weight gain, and incidence of hypoglycemia.

**Abbreviations:** 7-BG = 7 blood glucose, BMI = body mass index, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MARCH = Metformin and AcaRbose in Chinese as the initial Hypoglycaemic treatment, MMAS = Morisky Medication Adherence Scale, OAD = oral antidiabetic drug, OPENING = Organization Program of DiabEtes INsullN ManaGement, PBG = postprandial blood glucose, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides.

**Keywords:** acarbose, efficacy, metformin, premixed insulin, safety, type 2 diabetes mellitus

## 1. Introduction

China has experienced drastic socioeconomic changes in the last 3 decades. The increase in the obese population and westerniza-

tion of lifestyle have resulted in the increased incidence of diabetes. The prevalence of diabetes among adults of >20 years in age increased from 1% in 1980 to 9.7% in 2007–08, making China mainland the country with the largest diabetes prevalence in the world.<sup>[1]</sup> Despite the high prevalence of diabetes, China faces challenges in managing the disease because of low level of awareness, low treatment rate, and even lower controlling rate with regard to diabetes.<sup>[2–4]</sup> Therefore, combining the characteristics of type 2 diabetes mellitus (T2DM) and developing better treatment options for patients have become a national hotspot for many researchers in China.

Patients with T2DM in China have a lower body mass index (BMI) compared with those in the Western countries, suggesting that the functions of pancreatic  $\beta$ -cells may be lower in Chinese patients compared with their Western counterparts.<sup>[5,6]</sup> Moreover, the carbohydrate intake is substantially higher in the Chinese population than in Western countries.<sup>[1,7–9]</sup> These characteristics make the blood glucose spectrum of Chinese patients with T2DM different from that of Western patients. For instance, the proportion of patients with increased fasting blood glucose (FBG) is lower whereas the proportion of the ones with increased postprandial blood glucose (PBG) is higher in Chinese patients than in the Western patients.<sup>[7,9]</sup> Therefore, it is hypothesized that some “Chinese characteristics” influence the treatment of T2DM in Chinese patients.

Editor: Federico Bertuzzi.

The authors declare that they have no conflicts of interest.

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Medicine (2017) 96:35(e7533)

Received: 14 March 2017 / Received in final form: 12 June 2017 / Accepted: 25 June 2017

<http://dx.doi.org/10.1097/MD.0000000000007533>

Metformin is the first-line drug according to almost all guidelines.<sup>[10–12]</sup> However, with the increased understanding of T2DM, the effectiveness of acarbose, an  $\alpha$ -glycosidase inhibitor, has gained wide acceptance in light of the features of T2DM and the diet structure in Chinese patients. Acarbose is now used as the preferred drug for some patients with newly diagnosed T2DM.<sup>[5,13,14]</sup> Acarbose competitively inhibits the  $\alpha$ -glycosidase on the surface of epithelial cells from the duodenum and small intestine, delays the metabolism and assimilation of carbohydrates, and thus effectively decreases PBG as well as the risk of hypoglycemia before the next meal.<sup>[15]</sup> A long-term use of acarbose increases the amount of chyme in the lower intestine and activates  $\alpha$ -glycosidase in the lower intestine and colon, which turns the whole bowel into a site for assimilation of carbohydrates and thus effectively delays the assimilation.<sup>[13]</sup>

The Metformin and AcaRbose in Chinese as the initial Hypoglycaemic treatment (MARCH) study<sup>[7]</sup> was the first one that directly compared the safety and efficacy profiles of metformin or acarbose treatment in patients with newly diagnosed T2DM in China. The findings showed that acarbose and metformin had similar safety and efficacy profiles. Moreover, acarbose showed better body weight-reducing effects compared with metformin, greatly supporting the effectiveness of acarbose in treating Chinese patients with newly diagnosed T2DM.

The Organization Program of DiabEtes INsulin ManaGement (OPENING) study<sup>[16]</sup> compared the effects of a structured educational program on the control rate in patients who switched to insulin treatment after a suboptimal response to oral hypoglycemic drugs. The patients in the structured education group showed a higher decrease in hemoglobin A1c (HbA1c) level, higher HbA1c control rate, and better self-satisfaction compared with the control group. The oral hypoglycemic drugs used in the OPENING study were metformin and/or acarbose. However, the safety and efficacy profiles of combination treatment with acarbose or metformin are unclear for patients who were previously diagnosed with T2DM and needed insulin treatment.

The present study was a subgroup analysis of the data from the OPENING study, which compared the efficacy and safety profiles

of acarbose and metformin when used in combination with premixed insulin.

## 2. Materials and methods

### 2.1. Participants

The design and methods of the OPENING study are described elsewhere.<sup>[16]</sup> A total of 1511 subjects with T2DM from 48 centers throughout China were enrolled and required to discontinue prior oral hypoglycemic treatments except for biguanides and  $\alpha$ -glucosidase inhibitors (acarbose). Injections of isophane recombinant-soluble human insulin pre-mix 30/70 (SciLin M30; Bayer Healthcare, Beijing, China) were started after 2-week screening period. During the 16-week treatment phase, the doses of biguanides (not <1000 mg daily) and acarbose (not <150 mg daily) were not changed, whereas the initial premixed insulin dose injected on the first day of treatment was set at 0.3 to 0.4 IU/kg and adjusted according to the individual preprandial blood glucose level; the target FBG was  $\leq 8.0$  mmol/L, individualized appropriately. The patients who received premixed insulin and 1 drug, namely metformin or acarbose, were eligible for the present study. Finally, 192 patients in the metformin group (treated with metformin + insulin) and 80 patients in the acarbose group (treated with acarbose + insulin) were included for the analysis. All of the patients in the present study, whether metformin or acarbose group, were selected from both education group and control group in the OPENING study. They had taken metformin or acarbose for a long time. Therefore, no drug contraindications such as impaired renal function or existing chronic gastrointestinal diseases were reported in both groups.

This study was approved by the ethic committee of Peking University First Hospital and related hospitals, and informed consent was obtained from all individual participants of the study.

The participant inclusion and exclusion processes are shown in Figure 1.

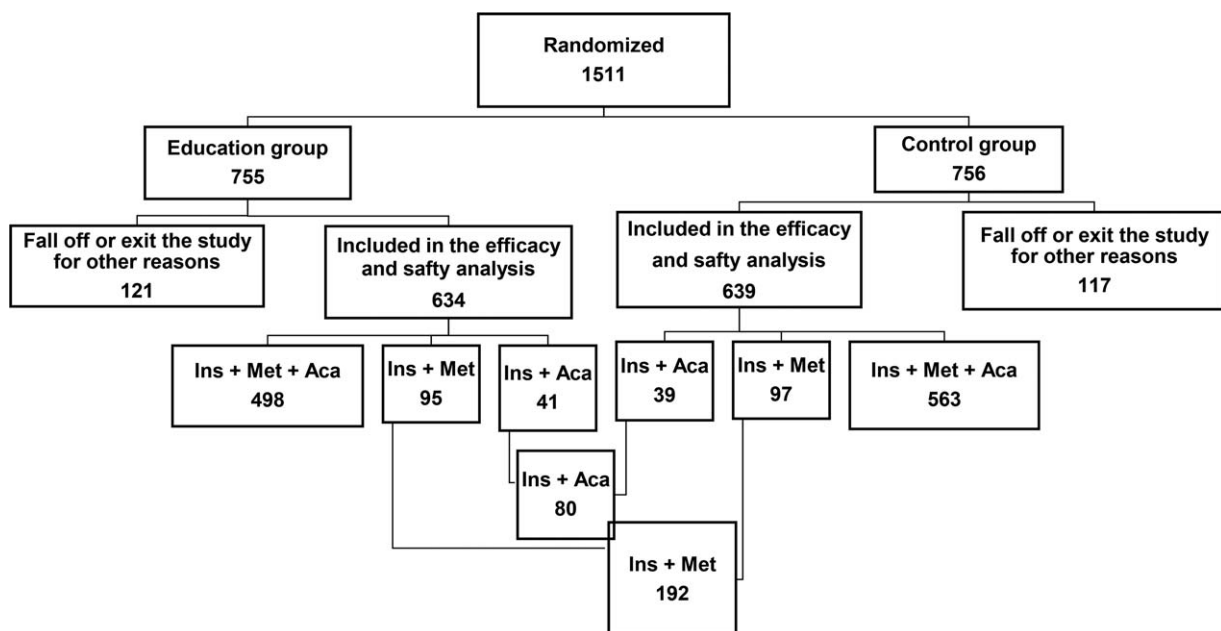


Figure 1. Participant inclusion and exclusion processes. Aca = acarbose, Ins = premixed insulin, Met = metformin.

**Table 1****Baseline demographic data between the treatment groups.**

	Acarbose group	Metformin group	Statistics	P value
Age, y	57.93 ± 10.25	55.96 ± 10.06	1.46	.1455
Gender			0.11	.7421
Male	37 (46.25)	93 (48.44)		
Female	43 (53.75)	99 (51.56)		
Disease duration, y	8.51 ± 5.41	7.51 ± 4.73	1.51	.1318
Weight, kg	67.10 ± 9.87	68.60 ± 10.59	-1.08	.2795
BMI, kg/m <sup>2</sup>	24.66 ± 2.80	25.03 ± 2.67	-1.02	.3071
FBG, mmol/L	9.55 ± 2.91	10.47 ± 3.23	-2.19	.0292
HbA1c, %	9.39 ± 1.85	9.51 ± 1.68	-0.54	.5918
TG, mmol/L	2.19 ± 1.38	2.18 ± 1.83	0.09	.9276
TC, mmol/L	4.96 ± 1.04	8.06 ± 41.73	-1.02	.3073
HDL-C, mmol/L	2.29 ± 8.99	3.67 ± 10.73	-0.97	.3334
LDL-C, mmol/L	5.02 ± 17.25	10.41 ± 30.11	-1.81	.0719

BMI = body mass index, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides.

**2.2. Measurements**

All subjects underwent a clinical assessment at baseline, including body weight, vital signs, FBG and self-monitoring blood glucose (SMBG), HbA1c, lipid profiles (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), daily insulin dose, as well as Morisky Medication Adherence Scale (MMAS) scores. Hypoglycemic events were also recorded during the whole study period. According to oral antidiabetic drug (OAD) treatment, these subjects were divided into 2 groups: metformin and acarbose groups. The changes in the aforementioned parameters for different OAD groups were compared.

The glucometers to perform SMBG at home in the present study were provided and calibrated by the investigators.

**2.3. Statistical analysis**

All analyses were performed using SAS 9.1.3 (TS1M3) for Windows (SAS Institute, NC). The results were expressed as the mean ± standard deviation or as the number of patients in a group, with percentages in parentheses, as appropriate. Changes in parameters from baseline within the group were evaluated using 2-tailed paired *t* tests or Wilcoxon signed-rank tests. Comparison between groups at baseline and after treatment was done using 2-sample *t* tests or chi-squared tests, as appropriate. Statistical significance was inferred when  $P < .05$ , unless stated otherwise.

**3. Results****3.1. Comparison of baseline data between the metformin and acarbose groups**

The treatment groups were comparable in terms of age, gender, duration of diabetes, HbA1c level, and FBG at baseline (Table 1).

**3.2. Comparison of HbA1c level before and after treatment between the two groups**

The HbA1c level in the metformin group decreased by 1.98% ( $9.51 \pm 1.68\%$  vs  $7.53 \pm 1.06\%$ ,  $P < .001$ ), whereas the level in the acarbose group decreased by 2% ( $9.39 \pm 1.85\%$  vs  $7.39 \pm 1.08\%$ ,  $P < .001$ , Table 2), compared with the baseline level. When HbA1c  $\leq 7\%$  was considered as the criteria, the control rate in these 2 groups was 30.73% and 38.75%, respectively; when HbA1c  $\leq 6.5\%$  was considered as the criteria, the control rate in these 2 groups was 16.15% and 17.50%, respectively. No significant difference was found between the 2 groups.

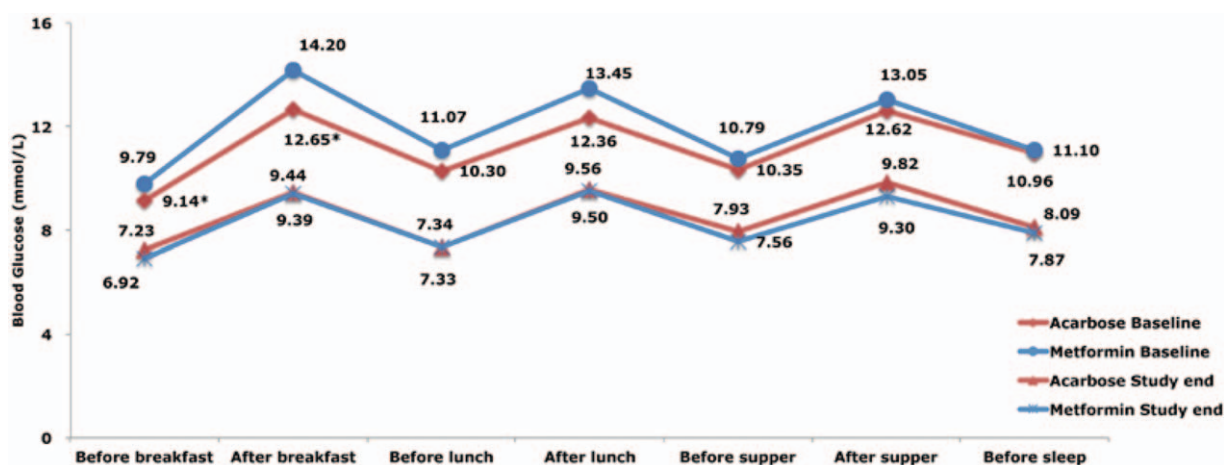
**3.3. Comparison of blood glucose levels at 7 time points before and after the treatment**

At baseline, the FBG was slightly higher in the metformin group than in the acarbose group ( $9.79 \pm 2.83$  vs  $9.14 \pm 2.61$  mmol/L), whereas the blood glucose levels at the other time points were not significantly different between the 2 groups (Fig. 2). After the 16-week treatment, the blood glucose levels at the 7 time points decreased significantly compared with baseline. Moreover, no

**Table 2****Comparison of FBG and changes in HbA1c% before and after treatment between the treatment groups.**

	N (missing)	FBG, mmol/L			Statistical method	HbA1c, %			Statistical method
		Baseline	Study endpoint	Paired <i>t</i> test ( <i>P</i> value)		Baseline	Study endpoint	Paired <i>t</i> test ( <i>P</i> value)	
Acarbose group	80 (0)	9.55 ± 2.91	7.67 ± 2.24	-4.90 (<.0001)	Paired <i>t</i> test	9.39 ± 1.85	7.39 ± 1.08	-1449.50 (<.0001)	Wilcoxon signed-rank test
Metformin group	192 (0)	10.47 ± 3.23	7.47 ± 2.13	-6976.50 (<.0001)	Wilcoxon signed-rank test	9.51 ± 1.68	7.53 ± 1.06	-8312.50 (<.0001)	Wilcoxon signed-rank test
Statistics		-2.19	0.69			-0.54	-1.03		
<i>P</i> value		.0292	.4915			.5918	.3061		

FBG = fasting blood glucose.



**Figure 2.** Comparison of blood glucose levels at 7 time points before and after the treatment between the treatment groups. \* $P < .05$  compared with the metformin group.

significant difference was found between the 2 treatment groups after the treatment (Fig. 2).

### 3.4. Daily insulin dose

The daily insulin dose in the acarbose and metformin groups was 30 and 33 IU, respectively, and the difference between the 2 groups was statistically significant ( $P = .008$ ). The insulin needed for each kilogram of body weight was 0.45 and 0.49 IU for the patients in the acarbose and metformin groups ( $P = .04$ ), respectively. These findings showed that lower doses of insulin were needed for patients in the acarbose group to achieve similar hypoglycemic effects.

### 3.5. Safety profiles

**3.5.1. Incidence of hypoglycemia.** The incidence rate of symptomatic hypoglycemia was 28.75% and 28.65% in the acarbose and metformin groups, respectively, and the difference was not statistically significant between the 2 groups ( $P = .97$ ). Moreover, the incidence rates of symptomatic hypoglycemia throughout the day (2.86% for the acarbose group and 1.9% for the metformin group,  $P = .1393$ ) and nocturnal hypoglycemia (0.19% for the acarbose group and 0.32% for the metformin group,  $P = .3535$ ) were also not significantly different between the 2 groups. No severe hypoglycemic event was reported in either group.

**3.5.2. Body weight.** The body weight of the patients in each group increased slightly (1.18 kg in the acarbose group and 1.13 kg in the metformin group) compared with the baseline level, but the difference was not significant between the 2 groups ( $P = .29$ ).

### 3.6. Medication compliance

The patients in each group showed good medication compliance, as assessed by the MMAS score, with a score of 0 as high adherence, 1 to 2 as medium adherence, and 3 to 4 as low adherence. Mean scores of MMAS improved in both groups at endpoint:  $0.46 \pm 0.73$  versus  $1.29 \pm 1.30$  ( $P < .0001$ ) in the acarbose group and  $0.41 \pm 0.79$  versus  $1.20 \pm 1.46$  ( $P < .0001$ ) in the metformin group, with similar reductions; no significant difference was found between the 2 groups ( $P > .05$ ).

Although some patients withdrew from the OPENING study for various reasons, no patients withdrew or reduced the dose of metformin and acarbose due to gastrointestinal symptoms or other adverse reactions in this subgroup study.

Further, 28.75% (23/80) patients were symptomatic hypoglycemic in the acarbose group and 28.65% (55/195) in the metformin group ( $P = .9862$ ); no severe hypoglycemic episodes were reported in either of the groups.

## 4. Discussion

Metformin is a first-line drug according to the Chinese guideline.<sup>[12]</sup> However, acarbose has now been used as the preferred drug for some patients with newly diagnosed T2DM.<sup>[5,13,14]</sup> Therefore, both metformin and  $\alpha$ -glucosidase inhibitors are commonly accepted and widely used in China either as monotherapy or in combination with other oral agents or insulin for treating T2DM.<sup>[17]</sup>

The MARCH study<sup>[7]</sup> showed that acarbose and metformin were comparable in terms of safety and efficacy profiles in treating Chinese patients. Moreover, Gu et al<sup>[18]</sup> performed a meta-analysis in 2015 to compare the glucose-lowering effect of metformin and acarbose in T2DM. The 2 drugs showed the same glucose-lowering effect on direct comparison, while the effect of metformin was slightly better on indirect comparison. The effect of acarbose was better in the Eastern than in the Western patients, whereas the effect of metformin showed no obvious difference. However, no study has directly compared the efficacy and safety of acarbose and metformin combined with fixed-dose insulin. The present study was a subgroup analysis of the OPENING study, which aimed to compare the efficacy and safety profiles of acarbose and metformin when used in combination with premixed insulin.

A total of 192 patients were treated with premixed insulin 30R and metformin, and 80 patients were treated with premixed insulin 30R plus acarbose in the present study. The total daily dose of insulin in the 2 treatment groups was comparable, while the daily insulin dose in the metformin group was slightly higher than that in the acarbose group (33.88 IU vs 30.00 IU,  $P = .008$ ). After the 16-week treatment, the HbA1c level in each group decreased significantly compared with the baseline level. When HbA1c  $\leq 7\%$  or  $\leq 6.5\%$  was considered as the criteria for HbA1c

control, the control rate between the 2 groups did not show a statistically significant difference. The HbA1c and blood glucose levels in the present study showed that acarbose and metformin were comparable in efficacy when used in combination with premixed insulin.

In terms of safety profiles, hypoglycemic events were found in 28.75% and 28.65% of the patients in the acarbose and metformin groups, respectively, and the difference was not statistically significant ( $P = .97$ ); the difference in hypoglycemic events throughout the day and during the night was also not significant between the 2 groups. Moreover, no severe hypoglycemic event was observed in either group. The body weights of the patients in both groups were found to have increased slightly after the treatment. No severe or life-threatening adverse event was found in either group. The medication compliance, as assessed by the MMAS score, improved in both groups at endpoint with similar reductions, and no significant difference was found between the 2 groups. As a subgroup analysis of the OPENING study, all of the subjects included in the present study had taken metformin or acarbose for a long time. Therefore, a few new gastrointestinal side effects existed during the study in both groups.

In summary, the present study (subgroup analysis of the OPENING study) supported the findings of the MARCH study and showed that the combined application of 30R of premixed insulin and acarbose or metformin showed the comparable efficacy of reducing HbA1c and improving blood glucose at 7 time points for patients with diabetes undergoing treatment for a certain duration and in need of insulin, despite the fact that the total daily dose of insulin was slightly lower in the acarbose group than in the metformin group. In terms of safety profiles, the incidence of hypoglycemic events was comparable between the 2 groups; and the effects on the body weight and MMAS score at endpoint were also similar. Therefore, the findings of the present study suggested that the efficacy and safety profile of acarbose were similar to those of metformin and hence it could be used as a hypoglycemic agent in combination with premixed insulin for Chinese patients with T2DM.

As a subgroup analysis of the OPENING study, this study had some limitations such as small sample size and short duration. Randomized, double-blind, larger-sample, and longer-duration studies should be performed to compare the efficiency and safety of acarbose and metformin combined with premixed insulin.

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