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ORIGINAL ARTICLE

Impact of baseline characteristics on glycemic effects of add-on saxagliptin or acarbose to metformin therapy: Subgroup analysis of the SMART study in Chinese patients with type 2 diabetes mellitus

Hui Fang[1,†], Fengmei Xu[2,†], Jin Du[3], Li Liang[4], Wei Li[5], Liya Shen[6], Xueying Wang[7], Chun Xu[8], Fang Bian[9], Yiming Mu[3,*]

[1]Department of Endocrinology, Tangshan Gongren Hospital, Tangshan, China, [2]Department of Endocrinology, Hebi Coal (Group) Co. Ltd, General Hospital, Hebi, China, [3]Department of Endocrinology, Chinese People's Liberation Army General Hospital, Beijing, China, [4]Department of Endocrinology, People's Hospital of Liaoning Province, Shenyang, China, [5]Department of Endocrinology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [6]Department of Geriatrics, Wuhan 6th Hospital, Wuhan, China, [7]Department of Endocrinology, Jinzhou Central Hospital, Jinzhou, China, [8]Department of Endocrinology, Chinese People's Armed Police Force General Hospital, Beijing, China, and [9]Department of Endocrinology, Cangzhou People's Hospital, Cangzhou, China

Keywords
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***Correspondence**
Yiming Mu
Tel.: +86-10-5549-9001
Fax.: +86-10-6693-7711
E-mail address:
muyiming2016@126.com

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ABSTRACT

Aims/Introduction: This secondary analysis of the 24-week SMART study examined the efficacy of add-on saxagliptin or acarbose to metformin across different patient subgroups with type 2 diabetes mellitus, based on baseline characteristics.

Materials and Methods: Randomized patients (n = 481) were classified into subgroups based on their baseline age (<65, ≥65 years), body mass index (BMI; <24, 24–<28, ≥28 kg/m^2), glycated hemoglobin (HbA1c; <8%, 8–<9%, 9–<10%, ≥10%) and renal function (creatinine clearance 50–<80, ≥80 mL/min). Treatment effects on primary outcome (HbA1c) and key secondary outcomes of fasting plasma glucose (FPG), 2-h postprandial glucose and homeostatic model assessment of β-cell function were assessed across patient subgroups.

Results: For saxagliptin, reductions in HbA1c from baseline to week 24 were consistent across different subgroups regardless of baseline age, body mass index, HbA1c and renal function (range −0.66 to −1.16%). Saxagliptin was associated with consistent reductions in FPG (−0.60 to −1.33 mmol/L) and 2-h postprandial glucose (−0.48 to −1.95 mmol/L) across the majority of subgroups studied. The efficacy of acarbose on FPG attenuated progressively with increasing baseline HbA1c (+0.86 to −1.43 mmol/L); an increase from baseline FPG was observed in patients with HbA1c >9%. The effect of acarbose on postprandial glucose was also variable (+0.23 to −3.38 mmol/L).

Conclusions: As add-on to metformin, both saxagliptin and acarbose reduced HbA1c regardless of baseline HbA1c, age, body mass index and renal function; however, only saxagliptin was effective at a stable glycemic control (FPG and PPG). The efficacy of acarbose on FPG and PPG was significantly attenuated in patients with higher baseline HbA1c (≥8%).

INTRODUCTION

According to recent estimates from the International Diabetes Federation, China has the highest number of individuals with diabetes worldwide, with a prevalence of 10.9% (114 million) among adults aged 20–79 years; approximately 90% of these patients have type 2 diabetes[1]. The high prevalence of type 2 diabetes and the corresponding costs of its associated complications place a considerable strain on China's public health services[1-3].

[†]These two authors are co-first authors.

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The management of type 2 diabetes involves optimal control of hyperglycemia through lifestyle modification and drug therapy, with metformin as the preferred choice of monotherapy[4,5]. The international and national clinical practice guidelines, including the Chinese Diabetes Society, recommend a glycated hemoglobin (HbA1c) target of <7% in patients with type 2 diabetes[4,5]. A less stringent target of <8.0% is recommended for patients with a history of severe hypoglycemia, or those with advanced macro- and microvascular complications[4].

The progression of disease eventually necessitates additional glucose-lowering therapies. The Chinese Diabetes Society recommend insulin secretagogues, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors or thiazolidinediones as add-on to metformin[5]. The choice of combination therapy is based on drug-specific and patient characteristics, with emphasis on a patient-centric approach for the management of hyperglycemia[6]. Head-to-head studies comparing different treatment choices provide evidence on potential differences in the efficacy and safety of different drugs, and inform the choice of therapy in clinical practice. The 24-week SMART study, which compared the efficacy and safety of saxagliptin and acarbose as an add-on to metformin in Chinese patients with type 2 diabetes, showed the non-inferiority of saxagliptin to acarbose for the reduction of HbA1c, with a favorable gastrointestinal safety profile[7]. In the present secondary analysis of the SMART study, we sought to examine the impact of baseline age, body mass index (BMI), HbA1c and renal function on the glycemic effects of saxagliptin and acarbose. Identifying the patients who would benefit most from either saxagliptin or acarbose would assist physicians in selecting the optimal second-line therapy according to the individual patient profiles.

METHODS

The design and primary results of the study have been previously described[7]. Briefly, the SMART study (NCT02243176) was a 24-week, multicenter, randomized, parallel-group, open-label phase IV study that compared saxagliptin with acarbose as second-line therapy in Chinese patients with type 2 diabetes inadequately controlled with metformin monotherapy. Male and female patients aged ≥18 years with HbA1c 7.5–11.0% at screening, receiving a stable dose of metformin monotherapy (≥1,500 mg/day or allowed maximum tolerated dose) for at least 8 weeks before screening were enrolled in the study. Key exclusion criteria included a history of acute metabolic complications of diabetes within 6 months before screening; fasting triglycerides >4.5 mmol/L, moderate/severe renal impairment at screening or within 4 weeks before screening; or significant cardiovascular history within 3 months before screening.

Eligible patients were randomized (1:1) to receive saxagliptin (Onglyza®, AstraZeneca, Mölndal, Sweden) 5 mg once daily, or acarbose (Glucobay®, Bayer AG, Leverkusen, Germany) 50 mg three times daily (uptitrated to 100 mg three times daily if appropriate through telephone reminder after 7 days following randomization), as an add-on to their existing metformin therapy for 24 weeks. No adjustments in the metformin dose were allowed unless warranted by the risk of hypoglycemia. The primary end-point was the absolute change in HbA1c at week 24. Key efficacy parameters (HbA1c, fasting plasma glucose [FPG] and 2-h postprandial glucose [2 h-PPG]) were blinded for investigators during the randomized phase of the study. The trial was approved by the independent ethics committee at each study center, and all patients provided written informed consent.

Statistical analysis

For the present analysis to assess the treatment effects on different subgroups of patients with type 2 diabetes, randomized patients were classified into subgroups based on their baseline age (<65, ≥65 years), BMI (<24, 24 to <28, ≥28 kg/m^2), HbA1c level (<8%, 8 to <9%, 9 to <10%, ≥10%) and renal function (creatinine clearance [CrCl] mildly impaired [50 to <80 mL/min], normal [≥80 ml/min]). The BMI subgroups were based on cut-offs recommended by the World Health Organization and Chinese Diabetes Society for overweight (≥24 kg/m^2) and obesity (≥28 kg/m^2)[5,8]. In addition, as each 1% change in HbA1c level is clinically meaningful, we categorized the patients based on each 1% increase from the target HbA1c target (<7%). As there were relatively fewer patients in the HbA1c ≥10% subgroup, we combined the 9 to <10% and ≥10% subgroups, and analyzed the treatment effects across the <8%, 8 to <9%, and ≥9% subgroups. The creatinine clearance subgroups were based on the cut-offs used by Gu *et al.*[9] for normal (CrCl >80 mL/min) and mild renal impairment (50 <CrCl to ≤80 mL/min).

The changes from baseline in the HbA1c (primary outcome), FPG, blood pressure (BP) and serum lipid levels (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol and triglycerides) were assessed across these subgroups using a mixed-model repeated-measures model, adjusting for baseline variables (age or BMI or HbA1c or CrCl), time and baseline values. The changes in 2 h-PPG and homeostatic model assessment of β-cell function (HOMA-β) were analyzed using analysis of covariance, with baseline variables (age or BMI or HbA1c or CrCl) and baseline values of 2 h-PPG and HOMA-β as the covariates. The treatment effect was presented as the least squares mean change (standard error) in outcome measure from baseline to week 24 for each subgroup.

As both saxagliptin and acarbose primarily affect PPG, multivariate linear regression analyses were carried out to determine the factors associated with the treatment effect on 2 h-PPG. In addition, multivariate logistic regression analyses were carried out to identify the factors associated with achieving target HbA1c levels <7%. A stepwise regression model was carried out using glycemic control (HbA1c <7%) or 2 h-PPG as outcome variables for each treatment group, using sex, baseline age, diabetes duration, BMI, HbA1c, FPG, PPG, HOMA-β, insulin and diabetes-related complications as covariates.

RESULTS

The SMART study randomized 488 patients with type 2 diabetes, of whom 481 received at least one dose of the study medications, and had at least one post-baseline efficacy measure (saxagliptin, $n = 238$; acarbose, $n = 243$). At baseline, the mean age of patients was 55.6 years (standard deviation [SD] 10.69 years). The mean BMI was 26.3 kg/m^2 (SD 3.48 kg/m^2) and HbA1c was 8.20% (SD 0.83%). Overall, 406 (84.4%) patients were aged <65 years, and 75 (15.6%) patients were aged ≥65 years; 119 (24.8%) patients had a BMI <24 kg/m^2, 222 (46.2%) between 24 to <28 kg/m^2 and 139 (29.0%) ≥28 kg/m^2. At baseline, 206 (42.8%), 193 (40.1%), 67 (13.9%) and 15 (3.1%) patients had HbA1c < 8%, 8 to <9%, 9 to < 10% and ≥10%, respectively. A total of 382 (80.4%) patients had CrCl ≥80 mL/min, and 93 (19.6%) had CrCl 50 to <80 mL/min. The distribution of patients in both treatment arms was comparable to that of the overall population (Table S1).

Impact of baseline patient characteristics on glycemic efficacy of saxagliptin

Reductions in HbA1c from baseline to week 24 (primary endpoint) were consistent across different subgroups defined by baseline age, BMI, HbA1c and renal function, with no significant differences between the subgroups (Figure 1). The magnitude of HbA1c reduction with saxagliptin was greater in patients with higher baseline HbA1c levels (Figure 1a).

Overall, FPG and PPG were reduced with saxagliptin treatment across all subgroups studied (Figure 2). The magnitude of FPG reduction was consistent in low (<8%, –1.33 mmol/L) and high baseline HbA1c groups (9–10%, –1.20 mmol/L and ≥10%, –1.17 mmol/L), but was diminished in the 8 to <9% subgroup (–0.64 mmol/L; $P = 0.0019$ vs HbA1c <8% subgroup; Figure 2a). Similarly, the magnitude of FPG lowering was reduced in the BMI ≥28 kg/m^2 ($P = 0.0175$ vs <24 kg/m^2 subgroup; Figure 2b). The effects of saxagliptin on HbA1c, FPG and PPG were consistent when analyzed across the HbA1c subgroups: <8%, 8 to <9% and ≥9% (Figure S1a,b).

In the multivariate linear regression analysis, the mean change in 2 h-PPG with saxagliptin significantly and positively correlated with BMI (regression coefficient: +0.175; $P \leq 0.001$) and duration of diabetes (+0.104; $P = 0.010$). Also, the change in 2 h-PPG significantly correlated with baseline HbA1c (–0.642; $P = 0.008$), baseline PPG (– 0.633; $P < 0.001$) and insulin levels (–0.039; $P = 0.028$), indicating a greater reduction in PPG with higher baseline levels of HbA1c, PPG and insulin (Table S2). In addition, increases in HOMA-β with saxagliptin treatment were consistent across most subgroups studied (Figure S2).

Impact of baseline patient characteristics on glycemic efficacy of acarbose

The changes in HbA1c at week 24 were consistent across subgroups based on baseline age, BMI and renal function (Figure 3); however, in the subgroup defined by baseline HbA1c, the magnitude of reduction was lower in patients with baseline HbA1c ≥10% compared with <8% (least squares mean change from baseline: –0.07 vs –0.71%, respectively); however, this difference was not statistically significant (Figure 3).

The efficacy of acarbose on FPG diminished progressively at higher baseline HbA1c levels, with an increase in FPG observed in patients with baseline HbA1c of 9 to <10% and ≥10% (Figure 4a). Changes in FPG were significantly different between lower and higher HbA1c subgroups: <8% (–1.43 mmol/L), 8 to <9% (–0.92 mmol/L; $P = 0.0139$), 9 to <10%, (+0.10 mmol/L; $P < 0.0001$) and ≥10% (+0.86; $P = 0.0005$). Similarly, the effects of acarbose on PPG varied across HbA1c subgroups. Compared with the HbA1c <8% group, the decrease in PPG was lower in patients with baseline HbA1c 8 to <9%, and the difference between the subgroups tended to approach statistical significance (–0.49 mmol/L vs –1.25 mmol/L; $P = 0.0527$). In patients with baseline HbA1c 9 to <10%, there was an increase in PPG levels from baseline to week 24 (+0.23 vs –1.25 mmol/L in those with baseline HbA1c <8%; $P = 0.0092$; Figure 4). In an analysis by subgroups <8%, 8 to <9% and ≥9%, the effects of acarbose on FPG and PPG were significantly and progressively attenuated in patients with HbA1c ≥8% ($P < 0.05$ for all comparisons; Figure S1d).

In the multivariate linear regression analysis, the mean change in 2 h-PPG with acarbose was significantly and directly correlated with the duration of diabetes (regression coefficient: +0.081; $P = 0.032$), and inversely correlated with baseline PPG (–0.714; $P < 0.001$; Table S2). In addition, acarbose treatment was associated with an increase in HOMA-β across the majority of subgroups studied (Figure S3).

Predictors of achievement of glycemic target (HbA1c <7%)

For patients treated with saxagliptin, the duration of diabetes, baseline HbA1c, FPG and 2 h-PPG levels were significant negative factors by univariate analysis ($P < 0.01$; Table 1). However, only the duration of diabetes and HbA1c levels were significant factors by multivariate analysis ($P < 0.05$; Table 1).

For patients treated with acarbose, baseline HbA1c, FPG and 2 h-PPG levels were significant negative factors by univariate analysis ($P = 0.000$), whereas only HbA1c and FPG were significant factors by multivariate analysis ($P \geq 0.008$).

Hemodynamic and metabolic effects of saxagliptin and acarbose

Saxagliptin therapy was associated with a decrease in systolic and diastolic BP from baseline values across the majority of subgroups; however, the magnitude of BP reduction was lower in older patients and in those with a higher BMI (Table S3). In addition, there was a decrease from baseline in total cholesterol and LDL-C levels, and a slight increase in triglycerides across most subgroups (Table S3).

Treatment with acarbose was associated with a decrease from baseline in BP, total cholesterol and LDL-C levels across most of the subgroups. The treatment effect on total cholesterol and

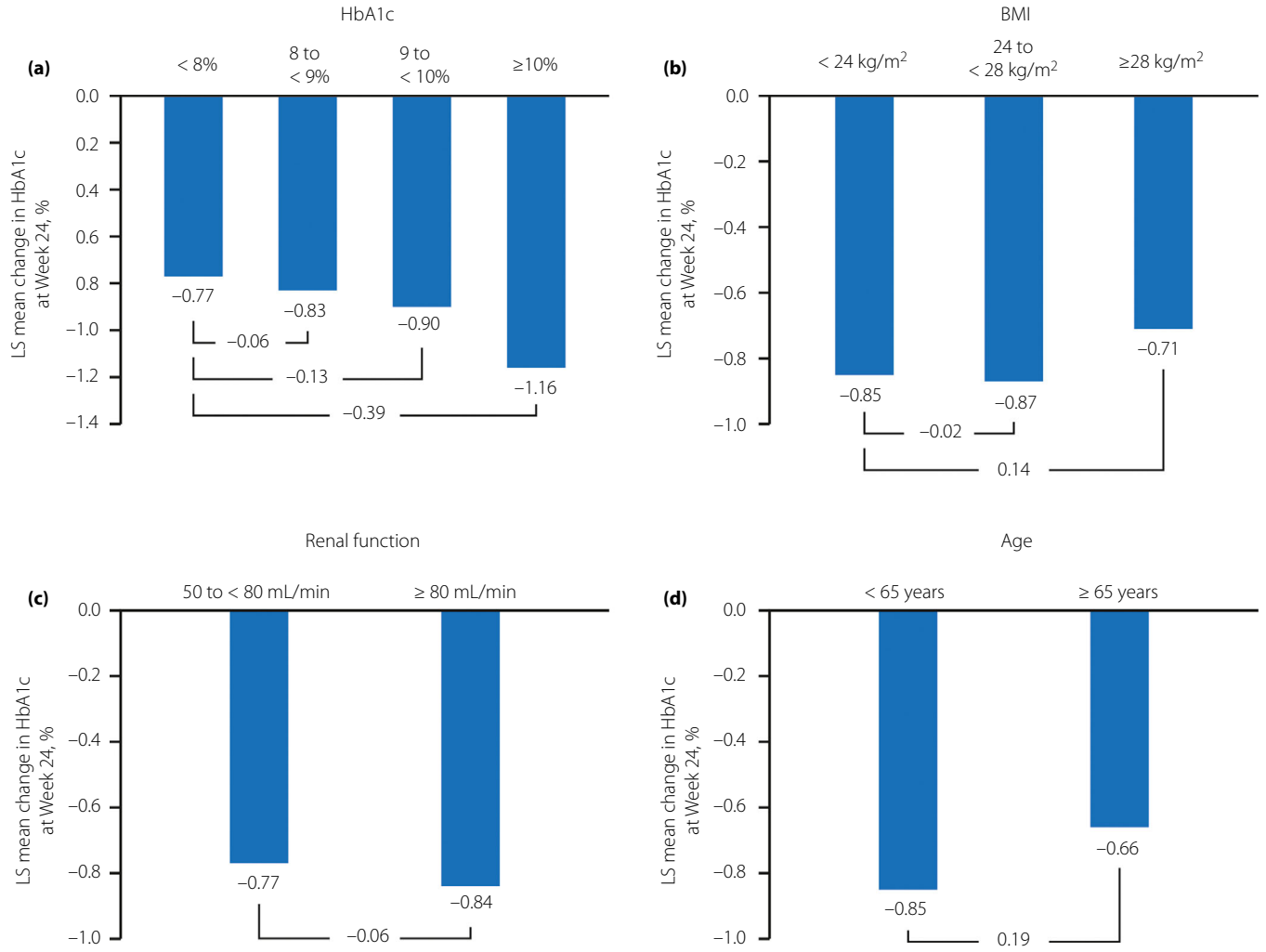

Figure 1 | Saxagliptin arm–least squares (LS) mean changes from baseline to 24 weeks in glycated hemoglobin (HbA1c) across subgroups defined by baseline (a) HbA1c, (b) body mass index (BMI), (c) renal function and (d) age.

LDL-C varied for patients with higher baseline HbA1c levels, with a slight increase from baseline observed in patients with baseline HbA1c ≥10% (Table S2).

DISCUSSION

The 24-week SMART study has previously shown the non-inferiority of saxagliptin to acarbose for glycemic control in Chinese patients with type 2 diabetes inadequately controlled on metformin monotherapy[7]. The present post-hoc analysis of the SMART study showed that saxagliptin is associated with the stable control of hyperglycemia (HbA1c, FPG and PPG) across a range of patient subgroups regardless of baseline HbA1c, age, BMI and renal function. In contrast, acarbose therapy was associated with a reduction in HbA1c across most of the subgroups studied; however, the decrease in HbA1c was attenuated in patients with baseline HbA1c ≥10%. In addition, the efficacy of acarbose on FPG and PPG was progressively and significantly attenuated in patients with baseline HbA1c ≥8%, with an increase from baseline FPG levels observed in patients with baseline HbA1c ≥9%.

The efficacy and safety of saxagliptin as monotherapy or combination therapy in Chinese patients with type 2 diabetes have been established in several studies[9-12]. In the present study, saxagliptin as add-on to metformin has shown consistent glycemic efficacy across a range of patient profiles. These results are similar to those observed in the SUNSHINE (a multi-center, single arm, cohort study to evaluate the efficacy and safety of saxagliptin 5 mg, once daily for 24 weeks, in patients with type 2 diabetes mellitus who are treatment naïve or have inadequate glycemic control on metformin alone) trial, which showed consistent glycemic efficacy of saxagliptin across subgroups stratified by baseline age, CrCl, BMI, HbA1c and treatment status (drug-naïve or metformin uncontrolled)[9].

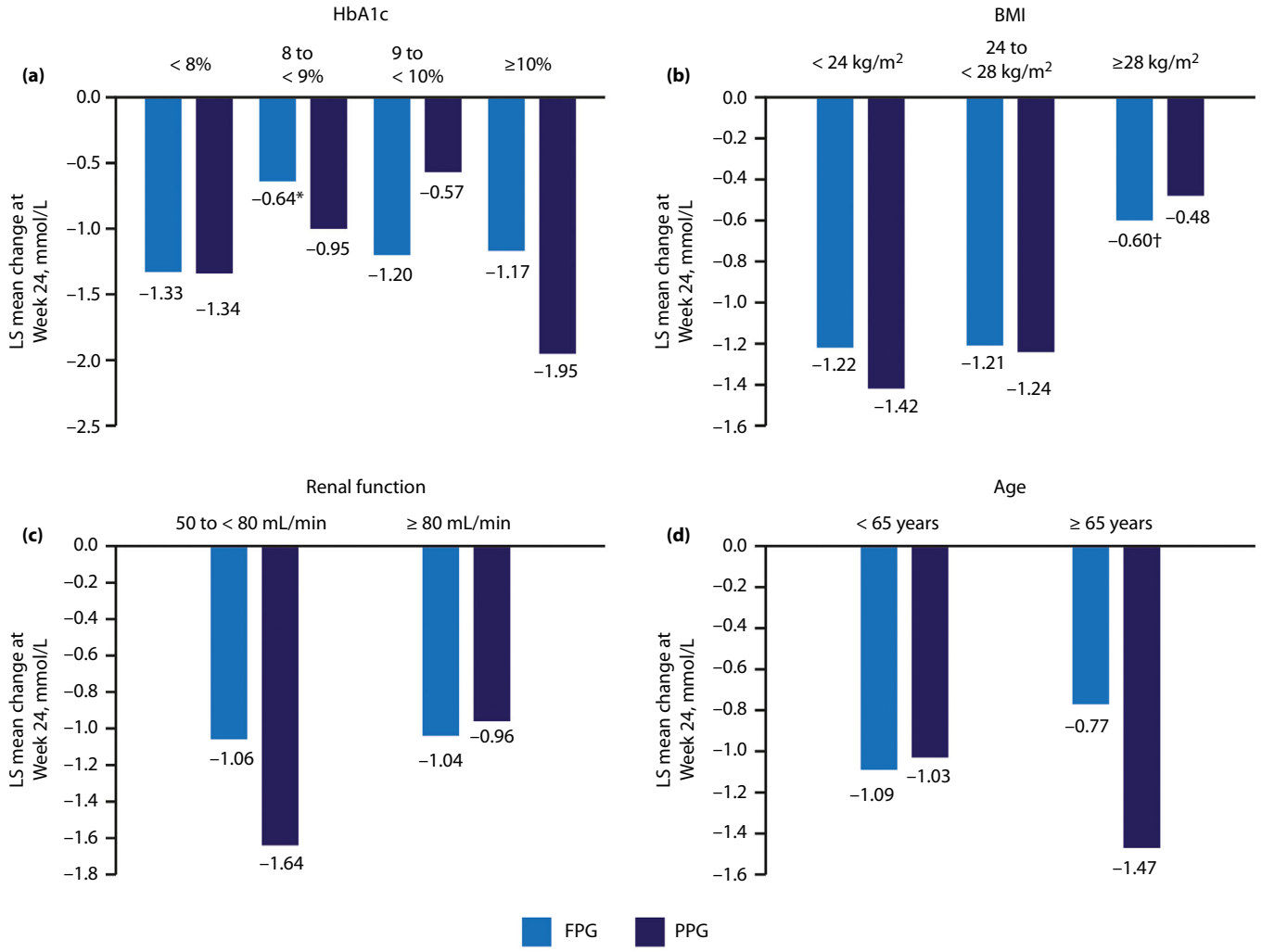

Figure 2 | Saxagliptin arm–least squares (LS) mean changes from baseline to 24 weeks in fasting plasma glucose (FPG) and postprandial glucose (PPG) across subgroups defined by baseline (a) glycated hemoglobin (HbA1c), (b) body mass index (BMI), (c) renal function and (d) age. *P = 0.0019 versus HbA1c <8% subgroup. †P = 0.0175 versus BMI < 24 kg/m^2 subgroup.

The efficacy of glucose-lowering therapies across the HbA1c spectrum is particularly important, as baseline HbA1c is an independent predictor of the likelihood of achieving glycemic control. A meta-regression analysis of 78 randomized controlled trials with 20,053 patients showed that DPP-4 inhibitors have greater efficacy in reducing HbA1c in patients with higher baseline values, with a 0.26% incremental reduction in the HbA1c response for every 1% increase of baseline HbA1c ($P < 0.001$)[13]. Similar results were reported in the SUNSHINE and SPECIFY trials in Chinese patients with type 2 diabetes[9,12]. In the SUNSHINE trial, saxagliptin treatment was associated with larger reductions in HbA1c in patients with higher baseline values – the reductions in HbA1c ranged from –0.78% in patients with baseline HbA1c of <8.0% to –2.90% in those with baseline HbA1c ≥10.0% to ≤11%[9]. In the 48-week SPECIFY trial, the reductions in HbA1c with saxagliptin therapy ranged from –0.56% to –1.80% in patients with baseline HbA1c <8.0% and ≥9.0%, respectively[12]. In the present analysis, the reductions in HbA1c were numerically larger in patients with higher baseline HbA1c values, ranging from –0.77% in patients with HbA1c <8.0 to –1.16% in those with HbA1c ≥10.0%. Furthermore, saxagliptin therapy reduced FPG and PPG across all subgroups. The magnitude of FPG reduction was lower in patients with baseline HbA1c 8 to <9% (vs HbA1c <8% subgroup); however, this might not be clinically relevant, as there was no clear trend in the attenuation of effects on FPG in patients with higher baseline HbA1c (≥9% subgroups). In addition, the magnitude of FPG-lowering with saxagliptin was reduced in patients with BMI ≥28 kg/m^2 (vs <24 kg/m^2 subgroup). This discrepancy in FPG-lowering effect was not observed previously in the SUNSHINE study with a larger sample size (n = 1,423), which showed a consistent reduction in FPG across all BMI subgroups (≥28 kg/m^2, –0.49 mmol/L; ≥24 to <28 kg/m^2,

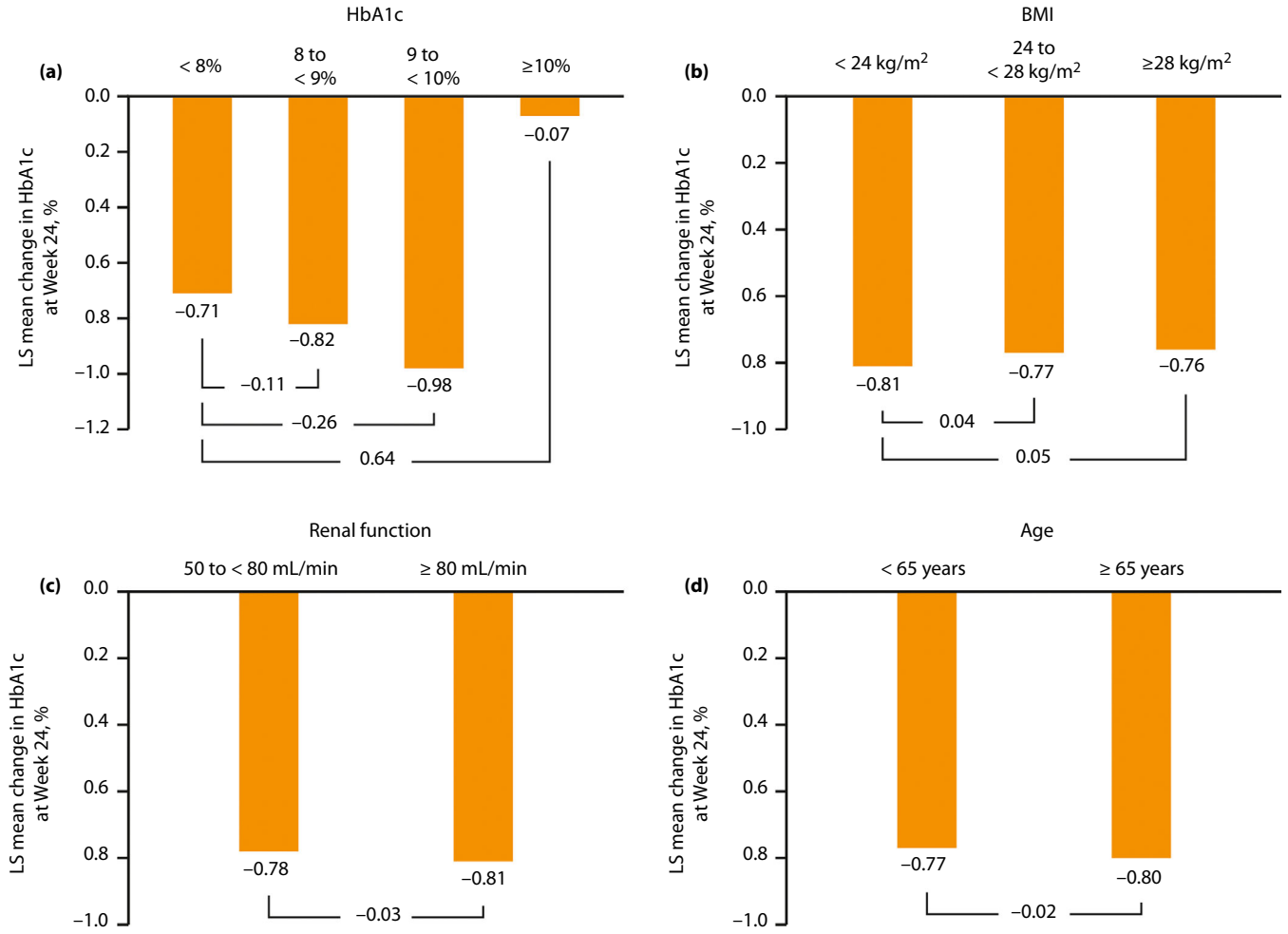

Figure 3 | Acarbose arm–least squares (LS) mean changes from baseline to 24 weeks in glycated hemoglobin (HbA1c) across subgroups defined by baseline (a) HbA1c, (b) body mass index (BMI), (c) renal function and (d) age.

−0.62 mmol/L; <24 kg/m^2, −0.50 mmol/L)[9]. In addition, a pooled analysis of five randomized clinical trials (n = 1,994) showed no association between BMI and glycemic response to saxagliptin treatment[14]. In contrast, a meta-analysis of 55 studies by Kim *et al.*[15] showed a significant correlation between the HbA1c-lowering effect of DPP-4 inhibitors and baseline BMI, especially in studies with average BMI <30 kg/m^2; however, this was not observed for studies with average BMI ≥30 kg/m^2. As multiple factors might affect the efficacy of DPP-4 inhibitors (such as β-cell function, glucagon-like peptide-1 release, DPP-4 activity, glucose uptake and glucagon suppression), these effects cannot be explained by BMI alone. The clinical markers of insulin sensitivity, such as abdominal adiposity, would provide further insights; however, this information was not available from the current study. Furthermore, the discrepancy in the FPG-lowering effect of saxagliptin across BMI subgroups could be due to the smaller sample size of the current study.

The efficacy of acarbose on HbA1c was consistent across subgroups defined by baseline age, BMI and renal function. However, there was a numerically smaller reduction in HbA1c for patients with baseline HbA1c ≥10%, which is a more clinically meaningful cut-off for those receiving combination therapy. The HbA1c reduction was −0.71% in patients with a baseline value <8.0, and −0.07% in those with a baseline value ≥10.0%. The attenuation of HbA1c-lowering efficacy was not observed when patients in the high HbA1c subgroups were combined (9 to <10% and ≥10%; Figure S1c), which suggests the variability in treatment effects with every 1% rise in HbA1c levels. These results are in contrast to previous findings from the MARCH (Metformin and AcaRbose in Chinese as the initial Hypoglycemic treatment) trial, which showed larger reductions in HbA1c in patients with higher baseline HbA1c values (<7%, 7–8% and >8%) with acarbose as initial therapy in newly diagnosed Chinese patients with type 2 diabetes[16]. This could perhaps be due to the lack of patients with high baseline HbA1c in the MARCH trial. In addition, the trial enrolled treatment-naïve patients and evaluated the efficacy of acarbose as monotherapy. The examination of effects on blood glucose

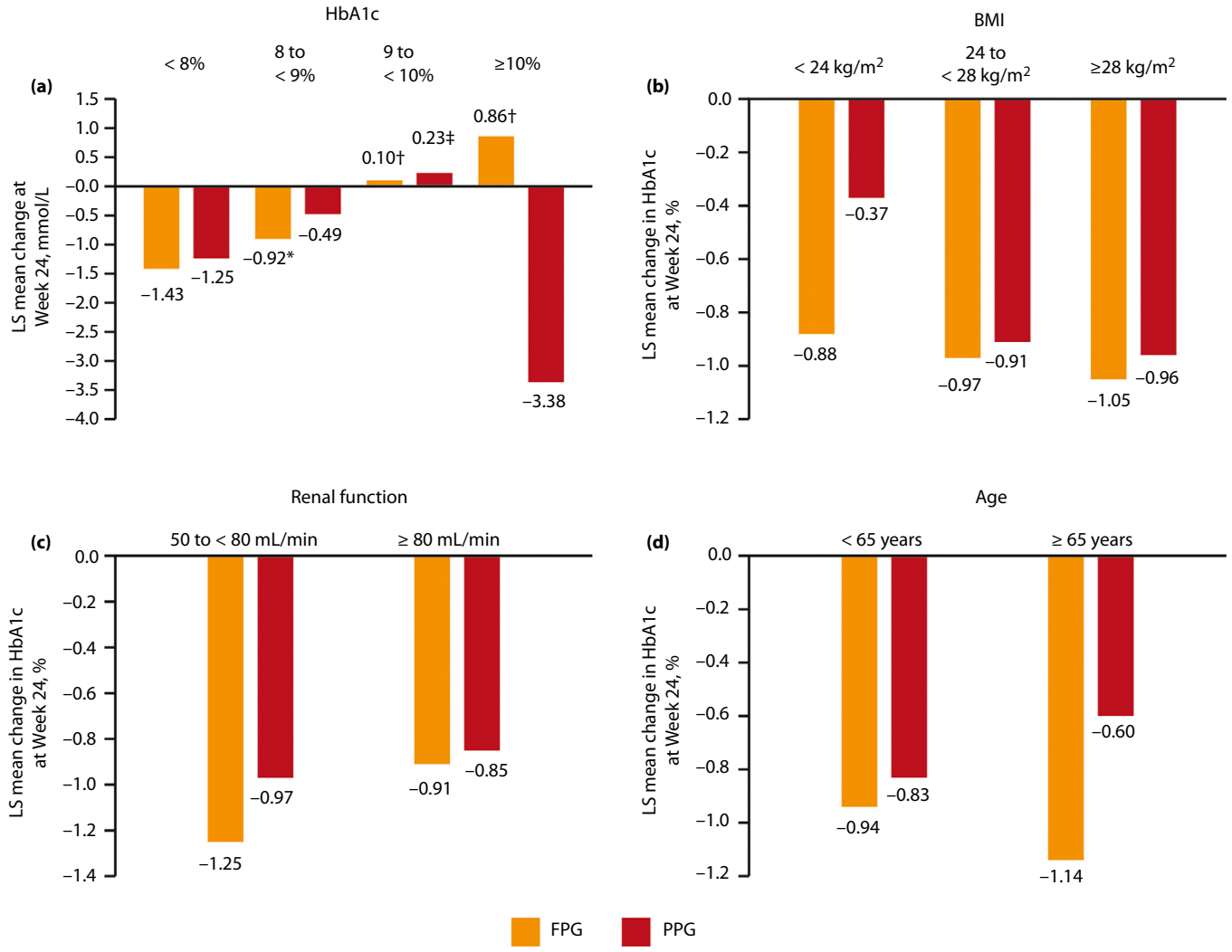

Figure 4 | Acarbose arm–least squares (LS) mean changes from baseline to 24 weeks in fasting plasma glucose (FPG) and postprandial glucose (PPG) across subgroups defined by baseline (a) glycated hemoglobin (HbA1c), (b) body mass index (BMI), (c) renal function and (d) age. *P = 0.0139; †P < 0.001; ‡P = 0.0092 (all comparisons vs HbA1c <8% group).

levels across different HbA1c subgroups provides further insights. There was a progressive and significant attenuation in the efficacy of acarbose on FPG and PPG levels in patients with higher baseline HbA1c, with an increase in FPG levels observed in patients with HbA1c ≥ 9% – the least squares mean changes from baseline in FPG values ranged from–1.43 to +0.86 across the HbA1c subgroups. This is in line with the previous observation from the MARCH trial in which acarbose decreased PPG more effectively than metformin only in patients with low or moderate baseline HbA1c (≤8%)[17].

The importance of PPG in the management of hyperglycemia is well established, particularly in Asian patients who are more likely to show postprandial hyperglycemia. As both saxagliptin and acarbose decrease PPG, we also carried out a multivariate linear regression analysis to identify factors associated with treatment effects on PPG. For the saxagliptin group, the change in PPG was independently and inversely correlated with baseline PPG and insulin levels, showing a higher reduction in PPG with an increase in baseline PPG and insulin levels. In contrast, the change in PPG with acarbose inversely correlated with baseline PPG, showing a higher reduction in PPG with an increase in baseline PPG.

The current study also showed discordance between the effect of acarbose on HbA1c and plasma glucose levels. This could be partly explained by the glycemic variability, as HbA1c levels do not indicate the stability of glycemic control. The glycation of hemoglobin is a non-enzymatic and slow process, and is directly proportional to the time-averaged concentration of glucose[18,19]. Therefore, glycemic fluctuations with intermittent excursions in blood glucose levels might not have a significant impact on HbA1c levels[20]. The glycemic effects of saxagliptin are mediated by glucose-dependent stimulation of insulin secretion and suppression

Table 1 | Logistic regression analyses of patient characteristics that impacted achievement of glycated hemoglobin <7% after 24 weeks of treatment with saxagliptin or acarbose

Baseline variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Saxagliptin						
Sex (male vs female)	1.57	0.90–2.74	0.115	1.85	0.98–3.47	0.057
Age (years)	0.99	0.97–1.02	0.670			
Duration of diabetes (years)	0.91	0.84–0.97	0.007	0.90	0.83–0.98	0.011
BMI (kg/m^2)	0.95	0.87–1.02	0.175			
HbA1c (%)	0.33	0.22–0.50	0.000	0.40	0.25–0.63	0.000
FPG (mmol/L)	0.72	0.62–0.84	0.000	0.86	0.72–1.02	0.077
PPG (mmol/L)	0.85	0.77–0.95	0.002			
HOMA-β (mU/mmol)	1.00	1.00–1.01	0.146			
Insulin (mU/L)	1.00	0.97–1.03	0.933			
Diabetic complications (yes vs no)	0.85	0.34–2.09	0.718			
Acarbose						
Sex (male vs female)	1.07	0.63–1.81	0.808			
Age (years)	1.01	0.98–1.03	0.666			
Duration of diabetes (years)	0.98	0.92–1.03	0.415			
BMI (kg/m^2)	1.03	0.95–1.11	0.470			
HbA1c (%)	0.28	0.18–0.44	0.000	0.37	0.23–0.59	0.000
FPG (mmol/L)	0.65	0.55–0.78	0.000	0.77	0.64–0.94	0.008
PPG (mmol/L)	0.78	0.69–0.87	0.000			
HOMA-β (mU/mmol)	1.00	1.00–1.01	0.096			
Insulin (mU/L)	1.02	0.99–1.05	0.181			
Diabetic complications (yes vs no)	1.63	0.64–4.19	0.307			

BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-β, homeostatic model assessment of β-cell function; OR, odds ratio; PPG, postprandial glucose.

of glucagon[21], which has been shown to effectively control the glycemic variability[22-25]. Although acarbose was also shown to reduce several parameters of glycemic variability[26,27], the current study showed that its efficacy on blood glucose levels appears to diminish at higher baseline HbA1c levels. This could be due to its non-insulin-dependent mechanism of action, which is non-systemic and limited to delaying the intestinal glucose absorption, and is therefore independent of the baseline hyperglycemia. In addition, α-glucosidase inhibitors have no effect on the endogenous glucose production, which increases with higher insulin resistance. This might explain why there was a diminished or no effect of acarbose on FPG and PPG in patients with higher baseline HbA1c levels. Taken together, these results suggest a limited utility of acarbose as an add-on to metformin, with beneficial effects observed only in patients with low HbA1c.

There were no clear trends for the treatment effects on lipid profile and blood pressure. Both saxagliptin and acarbose treatments were associated with slight reductions in total cholesterol and LDL-C and increases in high-density lipoprotein cholesterol and triglyceride levels across most subgroups. There are mixed reports on the effects of DPP-4 inhibitors on lipid profile, with slight improvement to no effect on triglyceride levels[28-30]. In previous studies of patients with type 2 diabetes, saxagliptin was not associated with any significant changes in triglyceride levels[31,32].

Although study data were collected prospectively, the reported analyses were carried out post-hoc and, therefore, subject to the potential biases inherent to such analyses. The randomization in the SMART trial was not stratified according to baseline age, HbA1c, BMI and renal function; therefore, the distribution of patients varied across these subgroups. However, the distribution of patients across the different subgroups was comparable between the treatment groups. This analysis was not designed or powered to evaluate the differences in treatment effects across the subgroups, and hence, the results are exploratory in nature. The evaluation of treatment effects across these subgroups in a larger sample size would provide further evidence on the observed differences. Despite these limitations, the present study was the first to compare the efficacy of saxagliptin and acarbose across a range of patient subgroups. The clinical characteristics, such as age, BMI, baseline HbA1c and renal function, are key patient factors that help in identifying the most appropriate therapy. The findings from the present study will further diversify the clinical evidence to physicians for the selection of optimal second-line treatment for type 2 diabetes patients.

In summary, we carried out the present study to determine the glycemic effects of saxagliptin and acarbose as an add-on to metformin across a range of patient profiles defined by key baseline characteristics. The study showed that although

saxagliptin and acarbose reduced HbA1c regardless of baseline HbA1c, age, BMI and renal function, only saxagliptin was effective for stable glycemic control (as reflected by control of FPG and PPG). The efficacy of acarbose on FPG and PPG was progressively and significantly attenuated in patients with higher baseline HbA1c (≥8%).

DISCLOSURE

HF has been a speaker for Novo Nordisk, AstraZeneca, Sanofi Aventis, Bayer and Eli Lilly. FX has received lecture fees from Novo Nordisk and Eli Lilly, and been a speaker for Eli Lilly and Bayer. JD reports lecture fees from Novo Nordisk and Sanofi. LL has attended advisory boards for Novo Nordisk, Eli Lilly and AstraZeneca, and been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis and Bayer. WL has participated in the clinical trials of Novo Nordisk, Eli Lilly and Sanofi Aventis, and has been a speaker for these companies. LS has participated in clinical trials of Novartis and Takeda, and has been a speaker for Novo Nordisk, Boehringer Ingelheim, Novartis, Takeda, Sanofi Aventis and MSD. XW has been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis and Bayer. CX reports lecture fees from Novo Nordisk. FB reports research grants and lecture fees from Novo Nordisk. YM has attended advisory boards for Novo Nordisk, Eli Lilly and AstraZeneca, has received research grants from Novartis, and has been a speaker for Novo Nordisk, Eli Lilly, AstraZeneca, Sanofi Aventis and Bayer.

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SUPPORTING INFORMATION

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

Figure S1 | Least squares (LS) mean changes from baseline to 24 weeks in, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG) across subgroups defined by baseline HbA1c – saxagliptin (A & B) and acarbose (C & D) arms. $^{*}P = 0.0177$; $^{\dagger}P = 0.0315$; $^{\ddagger}P < 0.0001$; $^{\S}P = 0.0486$ (all comparisons vs HbA1c <8% group).

Figure S2 | Least squares (ls) mean changes from baseline to 24 weeks in homeostatic model assessment of β-cell function (HOMA-β) across subgroups defined by baseline (a) glycated hemoglobin (HbA1c), (b) body mass index (BMI), (c) renal function and (d) age – saxagliptin arm. $^{*}P = 0.0148$ versus CrCl 50 to <80 subgroup. CrCl, creatinine clearance.

Figure S3 | Least squares (LS) mean changes from baseline to 24 weeks in homeostatic model assessment of β-cell function (HOMA-β) across subgroups defined by baseline (a) glycated hemoglobin (HbA1c), (b) body mass index (BMI), (c) renal function and (d) age – acarbose arm. $^{*}P = 0.0038$ versus CrCl 50 to <80 subgroup. CrCl, creatinine clearance.

Table S1 | Patient distribution in the saxagliptin and acarbose arms stratified by baseline characteristics. BMI, body mass index; HbA1c, glycated hemoglobin.

Table S2 | Linear regression analysis for risk factors of change from baseline for 2-h postprandial glucose (mmol/L) at week 24 in patients with type 2 diabetes by univariate and multivariate analyses. BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HOMA-β, homeostatic model assessment of β-cell function; OR, odds ratio; PPG, postprandial glucose; T2DM, type 2 diabetes mellitus.

Table S3 | Impact of baseline patient characteristics on saxagliptin's and acarbose's effects on metabolic parameters. BMI, body mass index; BL, baseline; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; TC, total cholesterol.