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Triple combination of insulin glargine, sitagliptin and metformin in type 2 diabetes: The EASIE post-hoc analysis and extension trial

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ABSTRACT

Aim: We examined the effects of adding glargine to metformin–sitagliptin (MS + G) or sitagliptin to metformin–glargine (MG + S) therapy in type 2 diabetic persons uncontrolled after 24-week MS or MG dual therapy.
Methods: Subjects with A1c ≥ 7% on MS or MG treatment were respectively given glargine (0.2 U/kg starting dose) or sitagliptin (100 mg daily) for 12 weeks. The primary endpoint was number of subjects attaining A1c goal defined as <7%.
Results: After receiving 24-week MS or MG dual therapy in the original EASIE Study, 42% (104/248) on MS and 68% (152/224) on MG attained A1c < 7% ($p < 0.0001$). The reduction in A1c was negatively associated with baseline fasting blood glucose (FBG) only in the MG group. Reduction in A1c was not related to baseline postprandial blood glucose (PPBG) in either the MG or MS group. Amongst 194 eligible patients, 57.7% (n = 111) entered the 12-week extension trial [MS + G:74/131, 57.3%; MG + S:37/63, 58.7%) with 55 (51.9%) subjects attaining goal [MS + G:59.2%; MG + S:37.1%] at week 12. The final insulin dosage was similar in both groups [MS + G: 0.46 U/kg; MG + S: 0.45 U/kg] with a higher rate of hypoglycemia in the MG + S (6.5 events/patient-year) than the MS + G group (3.2 events/patient-year), although neither group had severe hypoglycemia.
Conclusion: In metformin-treated type 2 diabetes patients, high fasting BG predicted greater A1c reductions with the addition of glargine, but not with sitagliptin. In subjects uncontrolled with 6-month dual therapy of MS or MG, 50% attained A1c < 7% with triple therapy of MS + G or MG + S in 12 weeks. The increased rate of hypoglycemia with MG + S (but not with MS + G) underlines the need to take measures to avoid the hypoglycemia.

Clinical Trial Registry: NCT00751114.

Conflict of Interest: J.C.N. Chan, P. Aschner, D.R. Owens, M. Vincent, M-P. Dain, V. Pilorget, A. Echtay and V. Fonseca served on the steering committee. S. Picard served on the International Titration Committee. V. Pilorget and V. Loizeau conducted the statistical analyses with assistance from C. Candelas and S. Kraft from Sanofi. All authors contributed to the interpretation of the data. J.C.N. Chan drafted the paper with comments from all co-authors who jointly made the decision to submit the paper for publication. J.C.N. Chan has served on the advisory board for Amylin, AstraZeneca, Bayer Healthcare, Eli Lilly and Company, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Pfizer and Sanofi and on the speaker bureau for AstraZeneca, Bayer Healthcare, Eli Lilly and Company, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Pfizer, Sanofi and Takeda. She has received research support from Amylin, AstraZeneca, Bayer HealthCare, Eli Lilly and Company, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Sanofi and Takeda. P. Aschner has served on the advisory board of AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Janssen, Merck, Sharpe & Dohme, Novartis, and Sanofi and on the speaker bureau for AstraZeneca, Eli Lilly and Company, Merck, Sharpe & Dohme, Novartis and Sanofi. D.R. Owens has served on the advisory board and the speaker bureau for Roche and Sanofi and has received research support from Boehringer Ingelheim, Roche and Sanofi. S. Picard has served on the advisory board, as a board member and as a consultant for Medtronics, Novo Nordisk and Sanofi and on the speaker bureau for Eli Lilly & Co, Lifescan, Medtronic, Merck-Serono, Novartis, Pierre Fabre, Novo Nordisk, Sanofi and Solvay. M. Vincent, M-P. Dain and V. Pilorget are employees of Sanofi. V. Loizeau is a consultant to Sanofi. A. Echtay has served on the advisory board of Merck, Sharpe & Dohme and on the speaker bureau of AstraZeneca, Eli Lilly and Company, Merck & Co., Merck, Sharpe & Dohme, Novartis, Novo Nordisk and Sanofi. V. Fonseca has served as a consultant and on the speaker bureau for AstraZeneca, Daiichi Sankyo, Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk, Pamlabs, Sanofi, Takeda and Xoma.

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1. Introduction

The Evaluation of insulin glArgine versus Sitagliptin in Insulin-naivE patients (EASIE) trial compared the efficacy, safety and tolerability of the basal insulin (insulin glargine), versus the dipeptidylpeptidase-4 (DPP-4) inhibitor (sitagliptin), in persons with type 2 diabetes previously uncontrolled with metformin. After 24 weeks of combination treatment, 50% of subjects attained A1c < 7% with a greater A1c reduction achieved in the metformin plus glargine (MG group, −1.7%) compared to metformin plus sitagliptin (MS) group (−1.1%, $p < 0.001$). More subjects in the MG group attained A1c < 7% than the MS group (68% versus 42%; $p < 0.0001$) (Aschner, Chan, Owens, et al., 2012). Subjects not controlled on MS or MG combination treatment (A1c ≥ 7%) were invited to participate in a 12-week extension trial with the addition of the other therapy. We performed a post-hoc analysis on the relationships between fasting/postprandial blood glucose (FBG/PPBG) on responses to MS/MG treatment, if any, and the efficacy and safety of triple therapy (MS + G or MG + S) in those uncontrolled on dual therapy.

2. Methods

2.1. Study design

This was a 3-month extension of the original EASIE study, with clinic visits at weeks 0, 4, 8 and 12 and phone calls at weeks 1, 3, 6, 8 and 10. Laboratory data including A1c and lipids were recorded at weeks 0, 4 and 12. All participants were asked to perform self-monitoring of blood glucose (SMBG) with measurement of FBG daily and 7-point SMBG profiles at weeks 0, 8 and 12. Body weight was recorded at weeks 0, 4, 8 and 12. The study was approved by local ethics committees and conducted in accordance to the Declaration of Helsinki. Written informed consent was obtained from all participants before commencement of data collection.

2.2. Study population and procedures

Persons with type 2 diabetes with A1c ≥ 7% on completion of the 24-week original EASIE study (Aschner et al., 2012) were invited to enter the extension trial although some centers did not participate due to small number of enrolled or eligible patients at each site and/or administrative reasons. Subjects in the MG + S subgroup were given a fixed oral dose of 100 mg sitagliptin once daily taken in the morning either with or without food and asked to continue to titrate their insulin glargine dose according to the original study as described below (Aschner et al., 2012). No change in sitagliptin dose was allowed during the study. In the MS + G group, participants were started on an initial subcutaneous dose of 0.2 U/kg for glargine injected at dinner or bedtime using a prefilled SoloSTAR® pen (sanofi-aventis, Frankfurt, Germany). Subjects were asked to self-titrate insulin glargine twice-weekly aiming at a self-monitored fasting blood glucose (SMFBG) of 3.9–5.5 mmol/l (>70 and ≤100 mg/dl). The dose was decreased by 2 U if SMFBG was <4.0 mmol/l with or without symptomatic hypoglycemia, or increased by 2 U if SMFBG was 5.6–7.7 mmol/l or by 4 U if SMFBG was >7.7 mmol/l, based on the intermediate value of three daily values of SMFBG. The EASIE international titration committee reviewed the titration data weekly via a website and the study investigators were contacted by email if titration was inadequate. Minor departures from the algorithm were allowed.

2.3. Efficacy endpoints

The primary efficacy endpoint was the number of subjects attaining A1c goal defined as <7%. Secondary endpoints included A1c, SMFBG, 7-point SMBG profile and mean daily SMBG, hypoglycemia, body weight and overall safety. During the structured 7-point SMBG profile at weeks 0, 8 and 12, capillary SMBG values were recorded before and 2-h after breakfast, lunch and dinner and at bedtime. Mean daily SMBG was calculated as the mean of the 7-point SMBG profile. Symptomatic hypoglycemia was defined as typical symptoms with or without confirmation of SMBG < 4.0 mmol/l. Severe symptomatic hypoglycemia was defined as symptoms of hypoglycemia, requiring assistance from a third person for administration of oral carbohydrate, injected glucagon or other counter measures together with a measured SMBG < 2.0 mmol/l or recovery attributable to the restoration of BG to normal.

2.4. Statistical analysis

2.4.1. Post hoc analysis of 24-week EASIE Study

We first explored the relationships between changes in A1c (ΔA1c) at week 24 and baseline FBG and PPBG in subjects who completed the original EASIE Trial randomized to the MS and MG group separately. We then performed logistic regression to identify predictors for attainment of A1c < 7% at week 24 using independent variables including treatment assignment (glargine versus sitagliptin), median age (≤54 versus >54 years), median A1c (<8.3 versus ≥8.3%), FBG (<8.8 mmol/L versus ≥8.8 mmol/L) and PPBG (<10.8 mmol/L versus ≥10.8 mmol/L) at baseline with adjustment for heterogeneity due to countries. Covariables with significance level of 0.15 were entered and kept in the model for significance level of 0.05. Significant variables were further tested for interaction and expressed as odds ratio (OR) with 95% confidence intervals (CIs).

2.4.2. 12-week EASIE Extension trial

In this 12-week extension trial, since participants were not randomized at baseline of the extension trial, no statistical comparison between subgroups was therefore made. Descriptive summary statistics were provided for continuous variables and number and percentage of subjects for categorical variables. Proportions (95% CI) of persons with primary efficacy variable were reported in the whole group and subgroups in the modified intent-to-treat (m-ITT) population. The m-ITT population included all who received ≥1 dose of the third drug, i.e. glargine in the MS group or sitagliptin in the MG group and with ≥1 on-treatment assessment of any primary or secondary efficacy variables. The safety population included all who received ≥1 dose of the third drug. Descriptive statistics were provided for secondary efficacy variables and for the rate of hypoglycemia expressed as event per person-year with 95% CIs. Treatment-Emergent Adverse Events (TEAEs) were defined as AEs that developed, worsened or increased in severity from the addition of the first dose of the third drug to 7 days after the last dose. This trial was registered at ClinicalTrials.gov, NCT00751114.

3. Results

3.1. Predictors for A1c < 7% at the end of the 24-week EASIE Trial

At the end of the 24-week original EASIE Trial, overall 50% of subjects attained A1c < 7% with 42% (104/248,) from the MS and 68% (152/224) from the MG group ($p < 0.0001$). Using regression analysis, the slope of ΔA1c against FBG was significant in the MG group ($p < 0.001$) but not in the MS group ($p = 0.5325$) with significant between-group difference ($p = 0.0304$). The slope of ΔA1c against PPBG was not significant in either the MG ($p = 0.0970$) or MS group ($p = 0.2711$) (Supplementary Fig. 1). Table 1 shows the results of the logistic regression analysis to identify predictors for A1c < 7% including the interaction between treatment and FBG/PPBG. In model (A) where PPBG was held as an independent predictor, the MS group was less likely to reach A1c goal than the MG group especially in those with high FBG (OR = 0.15) versus low FBG (OR = 0.36) with significant between-group difference stratified by FBG ($p < 0.001$). In the MG group, FBG did not have effect on A1c response to glargine (OR = 0.9) while MS-treated patients with high FBG (OR = 0.38) were less likely to be controlled than those

Table 1
Multivariable analysis to identify predictors for A1c < 7% in metformin-treated type 2 diabetic subjects given additional glargine or sitagliptin for 24 weeks. Model 1A included interactions between treatment and fasting blood glucose and Model 1B included interaction between treatment and postprandial blood glucose.

Predicting factors (Multivariate analysis)	OR (95% CI)	p-value
Model 1A		
Treatment		<.0001
Sitagliptin vs Insulin glargine with baseline FBG < 8.8 mmol/L	0.36 (0.18; 0.70)	
Sitagliptin vs Insulin glargine with baseline FBG ≥ 8.8 mmol/L	0.15 (0.08; 0.30)	
Age at baseline		0.0114
>54 years vs ≤54 years with baseline A1c < 8.3%	1.05 (0.52; 2.08)	
>54 years vs ≤54 years with baseline A1c ≥ 8.3%	3.38 (1.75; 6.53)	
A1c value at baseline		0.0001
≥8.3%% vs < 8.3%% with baseline age ≤54 year	0.20 (0.10; 0.40)	
≥8.3%% vs < 8.3%% with baseline age >54 years	0.65 (0.33; 1.30)	
FBG at baseline		0.0412
≥8.8 mmol/L vs <8.8 mmol/L with Insulin glargine	0.90 (0.44; 1.84)	
≥8.8 mmol/L vs <8.8 mmol/L with Sitagliptin	0.38 (0.19; 0.75)	
PP BG at baseline		
≥10.8 mmol/L vs <10.8 mmol/L	0.42 (0.25; 0.69)	0.0006
Age at baseline × A1c value at baseline		0.0132
Treatment arm × FPG value at baseline		0.0767
Number of patients included in the analysis		429
Test of adequacy of model: Hosmer–Lemeshow		0.4475
Quality of predictive model: AUC		0.796
Model 1B		
Treatment		<.0001
Sitagliptin vs Insulin glargine with baseline PPBG < 10.8 mmol/L	0.22 (0.11; 0.44)	
Sitagliptin vs Insulin glargine with baseline PPBG ≥10.8 mmol/L	0.24 (0.13; 0.45)	
Age at baseline		0.0122
>54 years vs ≤54 years with baseline A1c < 8.3%	1.05 (0.53; 2.09)	
>54 years vs ≤54 years with baseline A1c ≥ 8.3%	3.31 (1.73; 6.35)	
A1c value at baseline		0.0001
≥8.3%% vs < 8.3%% with baseline age ≤54 year	0.21 (0.10; 0.41)	
≥8.3%% vs < 8.3%% with baseline age >54 years	0.65 (0.33; 1.29)	
FBG at baseline		
≥8.8 mmol/L vs < 8.8 mmol/L	0.57 (0.34; 0.95)	0.0296
PPBG at baseline		0.0006
≥10.8 mmol/L vs <10.8 mmol/L with Insulin glargine	0.40 (0.19; 0.83)	
≥10.8 mmol/L vs <10.8 mmol/L with Sitagliptin	0.43 (0.23; 0.82)	
Age at baseline × A1c value at baseline		0.0145
Treatment arm × PPBG value at baseline		0.8607
Number of patients included in the analysis		429
Test of adequacy of model: Hosmer–Lemeshow		0.9241
Quality of predictive model: AUC		0.792

Odds Ratio (95% Wald Confidence Interval; PPBG = post prandial blood glucose; FBG = fasting blood glucose. Stepwise method was used for Step 1 and 2 with significance level of 0.15 for entry and significance level of 0.05 for stay. In Step 1, treatment was forced into the model with all other covariates entered or excluded from the model according to Wald chi square test. In Step 2, interaction terms were introduced according to Wald chi square test. The factor country was kept for adjustment in the model but not presented.

with low FBG with borderline significant FBG × treatment interaction ($p = 0.08$). Older subjects with high A1c were 3.8-fold more likely than their young counterparts to attain A1c goal. Subjects with high A1c were not likely to attain A1c goal although the older subjects (OR = 0.65) were more likely to be controlled than the young subjects (OR = 0.20) with significant age × A1c interaction ($p = 0.0132$). In model (B) which identifies FBG as an independent predictor, the MS group was less likely to attain A1c goal than the MG group, whether PPBG was high (OR = 0.24) or low (OR = 0.22). In subjects with high PPBG, glycemic control was not likely in either the MG (OR = 0.40) or MS (OR = 0.43) group compared to those with low PPBG. Older subjects with high A1c were 3.3-fold more likely to attain A1c goal than the young ones while subjects with high A1c were not likely to achieve control although the older subjects (OR = 0.65) had a higher odds to do so than the young subjects (OR = 0.21) with significant age × A1c interaction ($p = 0.0145$).

3.2. Baseline characteristics of patients entering the 12-week extension phase

Amongst the 515 randomized patients (250 to glargine and 265 to sitagliptin), 445 patients completed the 24-week original EASIE study. Of these, 131/233 (56.2%) treated with MS combination and 63/212 (29.7%) treated with MG combination remained uncontrolled with A1c ≥ 7% (Fig. 1) (Aschner et al., 2012). In the MS group, 75 of 131 eligible (57.3%) persons received MS + G combination therapy while 37 of the 63 eligible persons (58.7%) in the MG group received MG + S combination treatment, giving a total of 112 subjects for safety analysis in the 12-week extension trial. One person withdrew from the study before receiving additional glargine, with 111 remaining in the m-ITT population for efficacy analysis (74 in MS + G group and 37 in MG + S group).

Table 2 shows the characteristics of the participants at enrolment to the original EASIE study and their glycemic control at the end of the 24-week study period, prior to entry to the 12-week extension trial. Amongst those who entered the extension trial, 20% had one or more diabetic complications, and more than 85% were taking at least one concomitant medication for other risk factors. The 82 eligible non-participants had lower mean A1c at baseline, mean daily SMFBG, mean 7-point SMBG including SMBG at dinner and bedtime as well as diastolic blood pressure than participants of the EASIE extension trial (data not shown). Participation was entirely voluntary. The reasons for the relatively high non-participation rate were mainly due to too few enrolled or eligible subjects for the extension trial at each site or other administrative reasons.

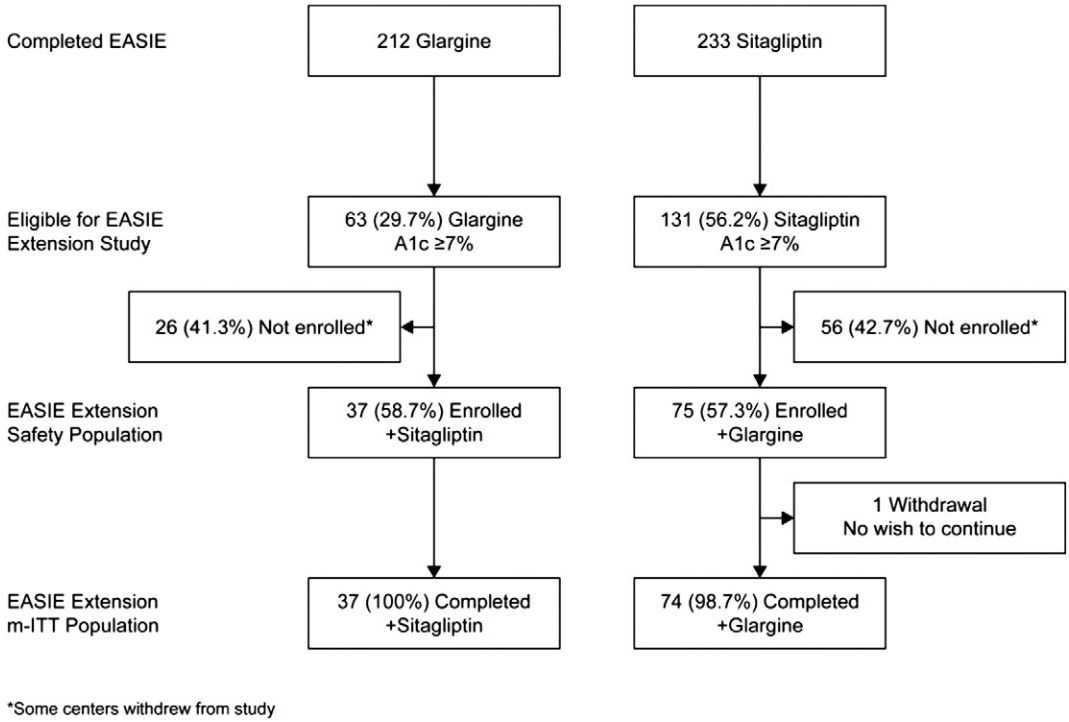

Fig. 1. A flow chart showing the disposition of metformin-treated type 2 diabetic subjects who have completed 24-week treatment with additional glargine or sitagliptin invited to participate in a 12-week extension trial for triple treatment using metformin, glargine and sitagliptin.

3.3. Glycemic control and insulin dose

In the m-ITT population, after 12 weeks of triple treatment with MS + G or MG + S, the overall mean A1c levels fell from 8.0% to 7.2% (Fig. 2A) with a mean A1c change of −0.8% (Table 3) and attainment of A1c < 7% in 55 patients (51.9%). On subgroup analysis, in the MS + G group, the A1c fell from 8.1% to 7.1% with a change of −1.0% whereas in the MG + S group, the A1c fell from 7.8% to 7.4% with an A1c change of −0.4% (Fig. 2A and Table 2). In the MS + G group, 42 (59.2%) and in the MG + S group, 13 (37.1%) attained A1c < 7% at the end of the 12 week extension trial.

The improvement in A1c was accompanied by reductions in SMFBG and 7-point SMBG profile. After 12 weeks, in the m-ITT group, the mean SMFBG fell from 8.0 mmol/l to 6.1 mmol/l (Fig. 2B) and the mean daily SMBG, from 9.2 mmol/l to 7.5 mmol/l (Fig. 2C) with concomitant changes at all times during the 7-point SMBG monitoring (Fig. 3A). In the MG + S group, mean SMFBG was 6.1 mmol/l and did not change further while in the MS + G group, SMFBG declined from 9.0 mmol/l to 6.0 mmol/l (Fig. 2B). The mean 7-point SMBG values in the MG + S group fell from 8.3 mmol/l to 7.6 mmol/l (Fig. 2C) whereas in the MS + G subgroup, values declined from 9.6 to 7.5 mmol/l (Fig. 2C). Fig. 3B and C showed the 7-point SMBG profiles which improved in both groups with numerically greater reduction in the MS + G than the MG + S group (Table 3). In the MS + G group, the dose increased from 0.19 ± 0.03 U/kg to 0.46 ± 0.21 U/kg at the end of the 12-week extension trial. In the MG + S group, the respective dose was 0.45 ± 0.18 U/kg which was similar to the dose at 12-week after insulin initiation in the original EASIE trial and remained stable during the extension trial (Fig. 4).

3.4. Safety

The mean body weight increased by 1.2 kg in the whole group with an increase of 1.3 kg in the MS + G group and 0.9 kg in the MG + S group (Table 3). Serum fasting triglyceride declined in both groups with a

Table 2
Clinical characteristics of type 2 diabetic subjects at enrolment and after 24 week combination treatment with metformin–glargine or metformin–sitagliptin prior to the 12-week extension trial with addition of glargine (MS + G) or sitagliptin (MG + S) for 12 weeks.

	m-ITT group (N = 111)	MG + S (n = 37)	MS + G (n = 74)
At entry of the original 24-week EASIE trial			
Age, years	52.4 (9.3)	51.5 (9.5)	52.9 (9.3)
Women, n (%)	56 (50.5)	20 (54.1)	36 (48.6)
Duration of diabetes, years	4.1 (2.0; 8.3)	3.9 (1.9; 8.7)	4.2 (2.2; 8.3)
Treatment with oral anti-diabetic drugs, years	2.5 (1.1; 6.7)	1.9 (0.9; 4.3)	3.2 (1.1; 7.1)
Daily dose of metformin, mg	1875 (519)	1746 (530)	1939 (504)
At baseline of the 12-week EASIE Extension trial			
Body weight, kg	84.6 (21.0)	86.0 (21.5)	83.9 (20.8)
Body mass index, kg/m^2	31.3 (5.2)	32.1 (5.8)	30.8 (4.8)
A1c, %	8.0 (1.0)	7.8 (0.9)	8.1 (1.1)
A1c, mmol/mol	64 (11)	62 (10)	65 (12)
Self monitored 7-point blood glucose, mmol/l	8.0 (2.1)	6.1 (1.2)	9.0 (1.8)
Self monitored fasting blood glucose, mmol/l	9.2 (1.8)	8.3 (1.4)	9.6 (1.8)

Data are expressed as mean (SD), median (interquartile range) or n (%).

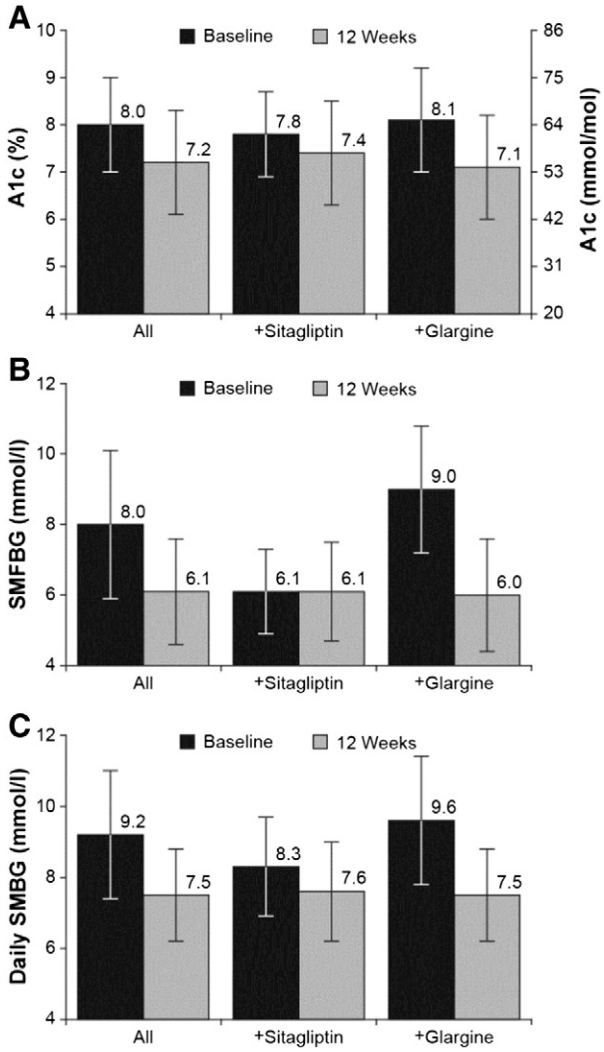

Fig. 2. Glycated haemoglobin (A1c, Panel A), self monitored fasting blood glucose (SMFBG Panel B) and daily SMBG (Panel C) in type 2 diabetic subjects after 24-week treatment with metformin–glargine or metformin–sitagliptin combination treatment (baseline) followed by addition of the other drug in the modified intention-to-treat (mITT) group and subgroups of subjects treated with additional sitagliptin or glargine for 12 weeks.

numerically greater reduction in the MS + G group than the MG + S group. Table 3 shows the rates of symptomatic hypoglycemia in the ITT population with a higher event rate of hypoglycemia in the MG + S group (6.5 per patient-year) compared to 3.2 per patient-year in the MS + G group. During the first 8 weeks of active insulin titration, there were 32 events in the MG + S group (n = 37) with a total exposure period of 4.47 patient-years, giving an event rate of 7.16 per patient-year. In the MS + G group (n = 75) with a total exposure period of 8.9 patient-years, there were 44 events with an event rate of 4.94 per patient-year. Between weeks 8 and 12, there were 29 events with a total exposure period of 2.69 patient-years and an event rate of 10.78 per patient-year in the MG + S group. In the MS + G group, there were 15 events with a total exposure period of 5.45 patient-years and 2.75 events per patient-year.

A total of 41 patients (36.6%) experienced ≥1 TEAE. The most frequent TEAEs reported were influenza, naso-pharyngitis and urinary tract infection reported by 4 persons (3.6%). Two subjects presented with serious TEAEs, one due to right ventricular failure, considered to be possibly related to sitagliptin and the other due to endometrial cancer which was not considered to be drug-related. There was no TEAE resulting in treatment discontinuation or deaths during the 12-week extension trial.

4. Discussion

The 24-week original EASIE trial has provided the first comparative data between glargine and sitagliptin, a DDP4-inhibitor, in type 2 diabetic subjects who failed metformin with 50% of them attaining A1c < 7% (Aschner et al., 2012). In this 12-week extension trial, 50% of subjects who failed MS or MG therapy attained A1c goal when given triple therapy (MS + G or MG + S), with a low risk of severe hypoglycemia.

Despite their different mechanisms of actions, all classes of anti-diabetic drugs including insulin are efficacious in reducing blood glucose (Tahrani, Bailey, Del Prato, & Barnett, 2011). In a recent meta-analysis, the magnitude of reduction in A1c across 10 classes of anti-diabetic drugs closely correlated with baseline A1c (DeFronzo, Stonehouse, Han, & Wintle, 2010). This might be in part due to the amelioration of glucotoxicity with possible restoration of beta cell function, thence the importance of optimizing glycemic control during early stage of disease to preserve beta cell function (Weng, Li, Xu, et al., 2008). In the original EASIE Trial which enrolled subjects with type 2 diabetes who failed metformin monotherapy, the mean disease duration was only 3 years. Less than 10% of the original cohort had cardiovascular complications in whom the risk–benefit ratio of intensive glycemic control was expected to be favorable (Del Prato, 2009; Gerstein, Miller, Byington, et al., 2008).

Since glargine predominantly lowers FBG by suppressing hepatic glucose production while sitagliptin tends to lower PPBG by augmenting meal-stimulated insulin secretion and suppressing glucagon production (DeFronzo et al., 2010), we explored the possible impacts of FBG and PPBG on treatment responses in the MS and MG groups. However, using regression analysis, only FBG was associated with A1c changes in the MG but not the MS group while PPBG did not bear any relationship with A1c changes in both groups. Given the potent effect of glargine in lowering FBG, more patients in the MG (68%) than the MS (42%) group attained A1c goal at the end of the 24-week original EASIE trial.

In our multivariable analysis, metformin-treated subjects with high baseline A1c, FBG and PPBG were not likely to attain A1c goal despite addition of glargine or sitagliptin. Although subjects with high FBG treated with glargine were more likely to respond than sitagliptin, we did not detect significant interaction between treatment and FBG/PPBG. Of note, older subjects with A1c ≥ 8.3% were 3.3-fold more likely to attain A1c goal than their young counterparts with poor control with significant age × A1c interaction. In observational surveys, young age was consistently associated with suboptimal glycemic control with high non-compliance rates (Yeung et al., 2014; Gregg, Karter, Gerzoff, et al., 2010). In these subjects who might have competing priorities or low motivation for long term therapy, individualized psychological–behavioral strategies in addition to medications may be needed for disease control.

Although subjects with high A1c generally had greater reduction in A1c (DeFronzo et al., 2010), given a mean reduction of 0.4%–0.8% in A1c with most oral anti-diabetic drugs (McIntosh, Cameron, Singh, et al., 2011), many type 2 diabetic persons required multiple drugs to attain A1c goal (Tong et al., 2008). Thus, during the design of the original EASIE trial protocol, we had built in an extension trial to explore the effects of triple therapy in those who failed MG or MS combination treatment. Over 50% of those eligible from the MS and MG groups participated in the extension trial, with the non-participants being younger and having better glycemic control than the participants. In this extension trial, we did not intend to compare efficacy between the MS + G and MG + S triple therapy but provided a descriptive analysis to inform readers regarding the effects of triple therapy in uncontrolled subjects on MS + G or MG + S dual therapy. Besides, it would not have been possible to re-randomize the entire group which was either redundant for those who had attained goal or unethical for those who had not reached goal. Given the fact that the non-participants had better glycemic control than the participants and that most centers did not participate in the extension trial due to administrative reasons, addition

Table 3
Changes in efficacy and safety measures in type 2 diabetic subjects uncontrolled after 24-week combination treatment with metformin–glargine or metformin–sitagliptin followed by addition of the other drug in the modified intention-to-treat (mITT) group and subgroups of subjects treated with additional Glargine (MS + G) or Sitagliptin (MG + S) for 12 weeks.

	m-ITT group (N = 111)	MG + S (n = 37)	MS + G (n = 74)
Efficacy measures			
A1c, %	−0.8 [−1.0; −0.6]	−0.4 [−0.8; 0.0]	−1.0 [−1.2; −0.8]
Self monitored fasting BG, mmol/l	−2.0 [−2.4; −1.5]	−0.0 [−0.3; 0.3]	−3.0 [−3.4; −2.5]
Mean daily SMBG, mmol/l	−1.6 [−2.0; −1.3]	−0.7 [−1.1; −0.2]	−2.1 [−2.5; −1.7]
7-Point SMBG, mmol/l			
Before breakfast	−1.9 [−2.3; −1.5]	−0.2 [−0.6; 0.2]	−2.7 [−3.2; −2.3]
After breakfast	−1.9 [−2.4; −1.4]	−0.7 [−1.5; 0.1]	−2.5 [−3.2; −1.9]
Before lunch	−1.5 [−2.0; −1.0]	−0.5 [−1.3; 0.3]	−2.0 [−2.6; −1.3]
After lunch	−1.5 [−1.9; −1.0]	−0.7 [−1.4; −0.0]	−1.9 [−2.5; −1.2]
Before dinner	−1.4 [−1.9; −0.9]	−1.0 [−1.9; −0.2]	−1.6 [−2.2; −1.0]
After dinner	−1.4 [−1.9; −0.9]	−0.7 [−1.4; −0.0]	−1.8 [−2.5; −1.1]
Bedtime	−2.0 [−2.6; −1.4]	−1.1 [−2.0; −0.2]	−2.4 [−3.1; −1.6]
Body weight, kg	1.2 [0.7, 1.6]	0.9 [0.1, 1.7]	1.3 [0.8, 1.8]
Total cholesterol, mmol/l	−0.15 [−0.34; 0.04]	−0.03 [−0.38; 0.32]	−0.21 [−0.43; 0.01]
LDL cholesterol, mmol/l	−0.02 [−0.12; 0.16]	−0.07 [−0.23; 0.38]	−0.01 [−0.16; 0.14]
HDL cholesterol, mmol/l	0.02 [−0.02; 0.06]	−0.06 [−0.13; 0.00]	0.06 [−0.01; 0.10]
Triglycerides, mmol/l	−0.49 [−0.80; −0.18]	0.08 [−0.17; 0.34]	−0.77 [−1.21; −0.33]
	All participants (N = 112)	MG + S (n = 37)	MS + G (n = 75)
Safety measures, Events per patient-year			
All symptomatic hypoglycemia	4.3 [3. 6; 5.1]	6.5 [4.9; 8.3]	3.2 [2.4; 4.1]
Symptomatic hypoglycemia with SMBG ≤3.9 mmol/l	3.4 [2.8; 4.2]	4.6 [3.3; 6.1]	2.8[2.1; 3.7]
Nocturnal symptomatic hypoglycemia	1.2 [0.8; 1.7]	1.9 [1.1; 3.0]	0.9 [0.5; 1.4]
Nocturnal symptomatic hypoglycemia with SMBG ≤3.9 mmol/l	1.1 [0.7; 1.6]	1.9 [1.1; 3.0]	0.7 [0.4; 1.2]
Severe symptomatic hypoglycemia	0 [0.0; 0.1]	0 [0.0; 0.4]	0 [0.0; 0.2]
Severe nocturnal symptomatic hypoglycemia	0 [0.0; 0.1]	0 [0.0; 0.4]	0 [0.0; 0.2]
Symptomatic hypoglycemia with SMBG ≤3.1 mmol/l	1.3 [0.9; 1.7]	1.4 [0.7; 2.4]	1.2 [0.7; 1.8]
Nocturnal symptomatic hypoglycemia with SMBG ≤3.1 mmol/l	0.4 [0.2; 0.7]	0.4 [0.1; 1.1]	0.4 [0.1; 0.8]

Data are mean [95% CI]. HDL, high density lipoprotein; LDL, low density lipoprotein; SMBG, self-monitored blood glucose. Mean daily SMBG based on 7-point blood glucose profile.

of the other drug based on the initial randomization was unlikely to introduce systematic bias.

At the end of the 24-week original EASIE trial, subjects in the MS group had higher A1c and lower body weight that those in the MG group. The addition of glargine to the MS group resulted in a 1% reduction in A1c accompanied by a reduction in SMFBG and mean SMBG during the 7-point SMBG profile. By week 12, A1c control had stabilized with a dosage of 0.46 U/kg. This was similar to the glargine dosage in the MG group at week 12 during the original EASIE trial with a 1.7% A1c reduction and a stable dosage thereafter. Despite similar dosages, the different A1c responses might be due to the higher A1c level in the MG group at randomization (8.5%) compared to 8.1% after 24 weeks of MS treatment followed by the addition of glargine in the extension trial.

In the MG group with an A1c of 7.8% at the end of the original EASIE trial, the addition of sitagliptin resulted in a 0.4% reduction in A1c. This degree of A1c reduction was within the range in most comparative trials of DPP4 inhibitors (Tahrani et al., 2011). In the SAVOR study, saxagliptin reduced A1c by 0.3% compared to placebo in subjects with a baseline A1c of 8% (Scirica et al., 2013). The latter was comparable to 7.8% in our subjects after 24 weeks of MG combination therapy. During this 12-week extension trial, the rate of hypoglycemia was considerably higher in the MG + S group which was not anticipated. This was likely to be due to multiple factors, such as the lower A1c of 7.8% in the MG group compared to 8.1% in the MS group at the end of 24-week and the possible recovery of insulin secretion with better glycemic control in the MG group (Weng et al., 2008), further augmented by the introduction of sitagliptin. Since we had not introduced a fixed dose reduction of glargine at the time when sitagliptin was introduced, the investigator could only down titrate the dosage of glargine when hypoglycemia occurred. Besides, the dosage of sitagliptin (100 mg daily) was fixed in the MG + S group compared to the dosage titration of glargine in the MS + G group. Although DPP4 inhibitors are associated with low risk of hypoglycemia (McIntosh et al., 2011), this side effect is not uncommon in those treated with insulin or sulphonylureas (Barnett et al., 2013), especially with a low A1c (Krobot, Ferrante, Davies, et al., 2012).

Given the considerable phenotypic heterogeneity of type 2 diabetes, many experts and professional bodies emphasized the need to individualize treatment goals and strategies (Pozzilli, Leslie, Chan, et al., 2010; Raz, Riddle, Rosenstock, et al., 2013). Long term trials using glargine (The ORIGIN Trial investigators, Gerstein, Bosch, et al., 2012) and DPP4 inhibitors (Scirica et al., 2013; White, Cannon, Heller, et al., 2013) have now confirmed their cardiovascular safety. Although obesity is often an accompanying feature, beta cell dysfunction remains a hallmark in type 2 diabetes (Kahn, 2004). Thus, despite the minor weight gain and hypoglycemic episodes, in metformin-treated subjects with short disease duration and few comorbidities, intensive glycemic control by adding glargine and/or DPP4 inhibitors, offers an additional option to control hyperglycemia.

In this post-hoc analysis of the original EASIE study, metformin-treated subjects over the age of 54 and those given additional glargine were most likely to reach A1c goal. Subjects with high FBG, PPBG and A1c were not likely to reach goal although those with high FBG (≥8.8 mmol/L) were more likely to respond to glargine than sitagliptin, while sitagliptin-treated patients with low FBG were more likely to respond than those with high FBG. In subjects who failed either the dual therapy of MS or MG, triple therapy of MSG or MGS would further improve glycemic control although in MG-treated patients, the dosage of glargine should be reduced by 20%–30% or a lower dosage of sitagliptin should be used with increased SMBG to avoid hypoglycemia.

5. Conclusion

In type 2 diabetic subjects uncontrolled on dual therapy of MS or MG, 50% attained A1c < 7% with triple therapy in 12 weeks. Together with 50% response rate with dual therapy of MS or MG, the majority of type 2 diabetic subjects with short disease duration, uncontrolled on metformin monotherapy, could attain A1c goal with additional

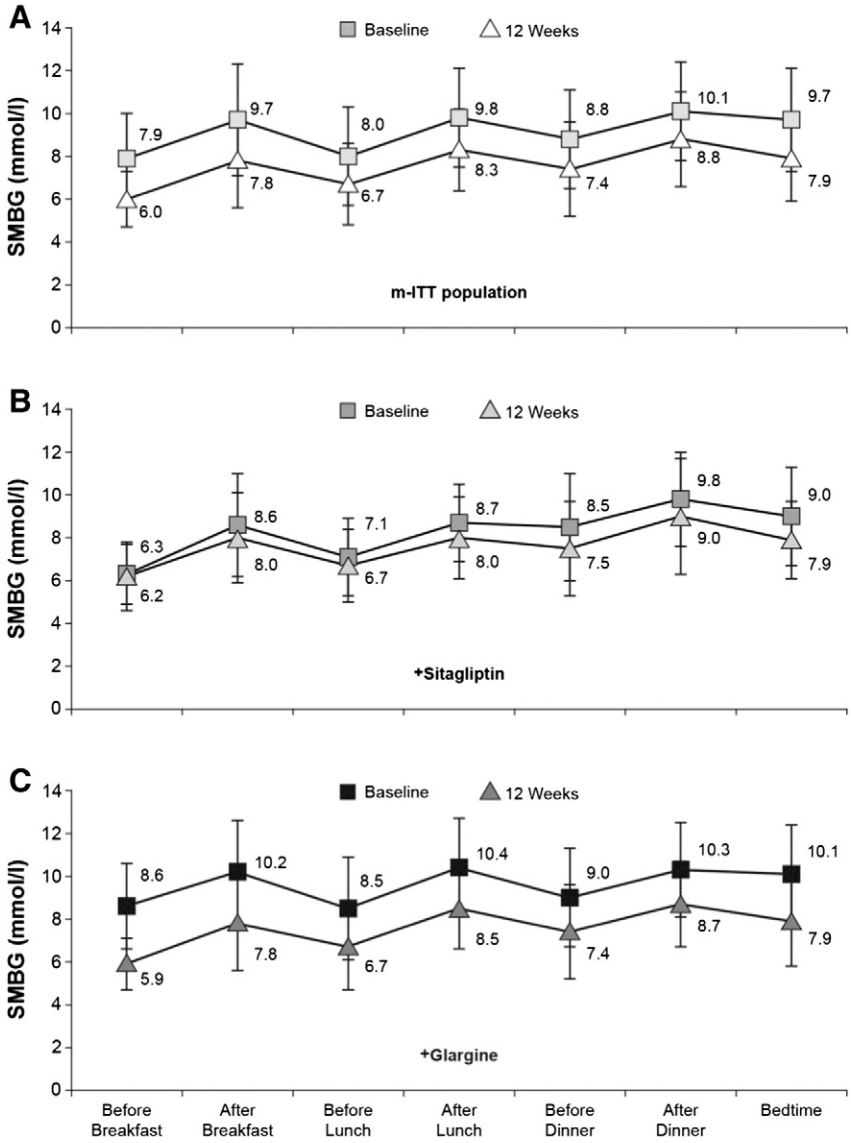

Fig. 3. Baseline and 12-week 7-point self-monitored blood glucose (SMBG) profile in type 2 diabetic subjects after 24-week combination treatment with metformin–glargine or metformin–sitagliptin followed by addition of the other drug in the modified intention-to-treat (mITT) group (panel A) and subgroup of subjects treated with additional sitagliptin or (panel B) glargine (panel C) for 12 weeks.

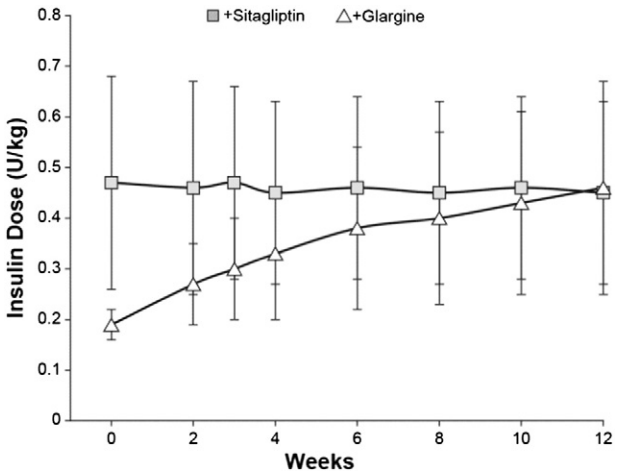

Fig. 4. Insulin dosage (U/kg) in type 2 diabetic subjects uncontrolled with metformin–glargine or metformin–sitagliptin combination treatment after 24 weeks with addition of sitaglipin or glargine respectively for 12 weeks.

DPP4 inhibitors and/or glargine with self-titration of insulin dosage and SMBG.

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