# Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial

*Pablo Aschner*, Juliana Chan*, David R Owens, Sylvie Picard, Edward Wang, Marie-Paule Dain, Valérie Pilorget, Akram Echtay, Vivian Fonseca, on behalf of the EASIE investigators*

*Lancet* 2012; 379: 2262–69
Published Online June 9, 2012
DOI:10.1016/S0140-6736(12)60439-5

See Comment page 2220

*Equal contributions

**Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogotá, Colombia** (Prof P Aschner MD); **The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong Special Administrative Region, China** (Prof J Chan FRCP); **Centre for Endocrine and Diabetes Science, Cardiff University, Cardiff, UK** (Prof D R Owens MD); **Point Medical Rond Point de la Nation, Dijon, France** (S Picard MD); **Sanofi, Bridgewater, NJ, USA** (E Wang PhD); **Sanofi, Paris, France** (M-P Dain MD, V Pilorget MD); **Rafic Hariri University Hospital, Beirut, Lebanon** (A Echtay MD); **and Tulane University Medical Center, New Orleans, LA, USA** (Prof V Fonseca MD)

Correspondence to:
Prof Pablo Aschner, Pontificia Universidad Javeriana, Hospital Universitario San Ignacio, Bogotá, Colombia
**paschner@cable.net.co**

See Online for appendix

## Summary

**Background** In people with type 2 diabetes, a dipeptidyl peptidase-4 (DPP-4) inhibitor is one choice as second-line treatment after metformin, with basal insulin recommended as an alternative. We aimed to compare the efficacy, tolerability, and safety of insulin glargine and sitagliptin, a DPP-4 inhibitor, in patients whose disease was uncontrolled with metformin.

**Methods** In this comparative, parallel, randomised, open-label trial, metformin-treated people aged 35–70 years with glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) of 7–11%, diagnosis of type 2 diabetes for at least 6 months, and body-mass index of 25–45 kg/m² were recruited from 17 countries. Participants were randomly assigned (1:1) to 24-week treatment with insulin glargine (titrated from an initial subcutaneous dose of 0·2 units per kg bodyweight to attain fasting plasma glucose of 4·0–5·5 mmol/L) or sitagliptin (oral dose of 100 mg daily). Randomisation (via a central interactive voice response system) was by random sequence generation and was stratified by centre. Patients and investigators were not masked to treatment assignment. The primary outcome was change in $HbA_{1c}$ from baseline to study end. Efficacy analysis included all randomly assigned participants who had received at least one dose of study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable. This trial is registered at ClinicalTrials.gov, NCT00751114.

**Findings** 732 people were screened and 515 were randomly assigned to insulin glargine (n=250) or sitagliptin (n=265). At study end, adjusted mean reduction in $HbA_{1c}$ was greater for patients on insulin glargine (n=227; –1·72%, SE 0·06) than for those on sitagliptin (n=253; –1·13%, SE 0·06) with a mean difference of –0·59% (95% CI –0·77 to –0·42, p<0·0001). The estimated rate of all symptomatic hypoglycaemic episodes was greater with insulin glargine than with sitagliptin (4·21 [SE 0·54] *vs* 0·50 [SE 0·09] events per patient-year; p<0·0001). Severe hypoglycaemia occurred in only three (1%) patients on insulin glargine and one (<1%) on sitagliptin. 15 (6%) of patients on insulin glargine versus eight (3%) on sitagliptin had at least one serious treatment-emergent adverse event.

**Interpretation** Our results support the option of addition of basal insulin in patients with type 2 diabetes inadequately controlled by metformin. Long-term benefits might be expected from the achievement of optimum glycaemic control early in the course of the disease.

**Funding** Sanofi.

## Introduction

In type 2 diabetes, large-scale randomised clinical trials have shown that early achievement of glycaemic control with glycated haemoglobin $A_{1c}$ ($HbA_{1c}$) less than 7% resulted in long-term benefits in reduction of microvascular complications and might reduce macrovascular problems.[1–3] With the exception of patients with substantial renal impairment or gastrointestinal intolerance, metformin is the mainstay of treatment in type 2 diabetes. However, most people eventually need additional treatment to achieve their glycaemic goal.[4–6] In view of the low associated risk of hypoglycaemia and neutral effect on bodyweight, dipeptidyl peptidase-4 (DPP-4) inhibitors are increasingly added to metformin as an alternative second agent to sulphonylureas.[7,8] Alternatively, randomised clinical trials[9,10] and meta-analysis[11] have suggested that the early addition of basal insulin to metformin treatment can lower $HbA_{1c}$ effectively with good tolerability. To date, no studies have compared the use of DPP-4 inhibitors versus basal insulin in people with type 2 diabetes who have not responded to metformin monotherapy. In the EASIE (Evaluation of insulin glargine versus Sitagliptin in Insulin-naive patients) trial, we aimed to compare the efficacy, safety, and tolerability of basal insulin (insulin glargine) versus a DPP-4 inhibitor (sitagliptin) in such a population during a 24-week period.

## Methods

### Study design

EASIE was a multicentre, 6-month, comparative, two-arm, parallel, randomised, open-label trial undertaken in 17 countries (appendix p 1) from Nov 12, 2008, to July 28, 2011. It included an initial 2-week screening

period followed by 6 months of treatment (insulin glargine or sitagliptin) and, finally, a 1–7 day follow-up to record any new adverse event or episode of symptomatic hypoglycaemia that occurred during the 24 h after the last study dose (figure 1). The study was undertaken in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Every centre obtained local research ethics committee approval after approval from a multicentre research ethics committee. All participants gave full informed written consent before entry into the study.

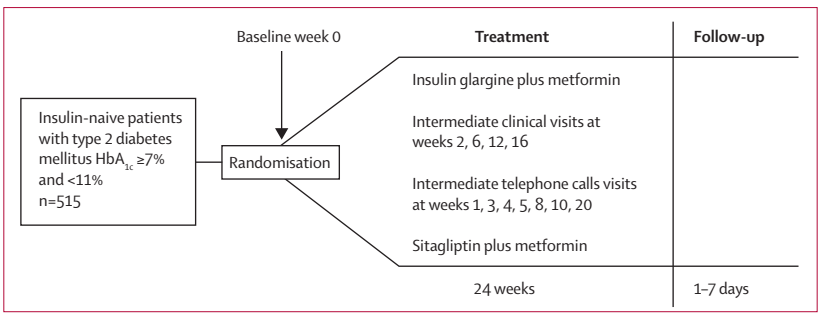


***Figure 1:*** **Study design**
$HbA_{1c}$=glycated haemoglobin $A_{1c}$.

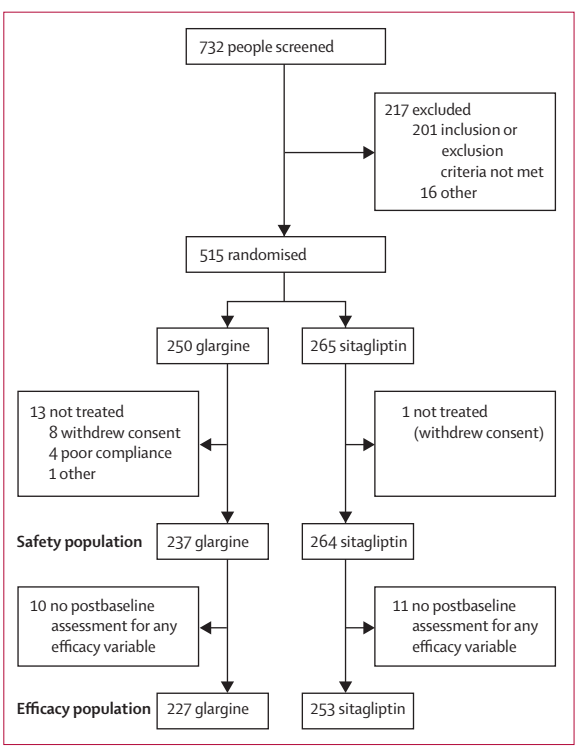


***Figure 2:*** **Study profile**

## Patients

People aged 35–70 years (inclusive) and diagnosed with type 2 diabetes for at least 6 months were eligible if they had $HbA_{1c}$ of 7% or greater and less than 11% and body-mass index (BMI) between 25 kg/m² and 45 kg/m² (inclusive). Furthermore, they had to be willing to take structured self-monitored blood glucose measurements and complete a monitoring diary. People were excluded if they had been treated with oral glucose-lowering drugs other than metformin within the past 3 months, had received combination treatment with metformin plus a sulphonylurea in the past year, or had previous treatment with glucagon-like peptide-1 agonists or DPP-4 inhibitors. Other exclusion criteria were fasting plasma glucose of 15·4 mmol/L or more, impaired renal function (serum creatinine ≥133 μmol/L in men or ≥124 μmol/L in women) or hepatic function (greater than three times the upper limit of the normal range for alanine aminotransferase or aspartate aminotransferase), or any disorder (present or expected) that the investigator felt would compromise the patient's safety or restrict the patient's successful participation in the study.

## Randomisation and masking

Eligible people were allocated a four-digit randomisation number through a central interactive voice response system in France. The randomisation list, generated centrally by a clinical research organisation (Cardinal Systems, Paris, France), linked sequential numbers to the treatment allocated at random. Stratification by centre was done to ensure a balanced number of participants in each treatment group at each centre (1:1 ratio). Participants were randomly assigned to treatment groups in the order in which they qualified for inclusion in the study. Participants and investigators were not masked to group assignment.

## Procedures

Clinic visits were scheduled for screening, randomisation (week 0), and weeks 2, 6, 12, 16, and 24 with telephone visits at weeks 1, 3, 4, 5, 8, 10, and 20. After week 24 and within a week, a follow-up phone call was done. All participants received a glucose meter (calibrated to read plasma glucose values) to record self-monitored glucose values. Individuals randomly assigned to insulin glargine implemented insulin titration to attain self-monitored fasting plasma glucose concentrations between 4·0 mmol/L and 5·5 mmol/L (inclusive). The initial subcutaneous dose was 0·2 units per kg of bodyweight injected at dinner or bedtime using a prefilled SoloSTAR pen (sanofi-aventis, Frankfurt, Germany). The dose was either decreased by two units if fasting plasma glucose concentration was less than 4·0 mmol/L with or without symptomatic hypoglycaemia, increased by two units if the concentration was 5·6–7·7 mmol/L, and increased by four units if the concentration was greater than 7·7 mmol/L. Participants monitored fasting plasma glucose daily and generally used the middle of the past three values to undertake the titration twice a week. Self-monitored glucose values and insulin doses were reviewed by an international titration committee on an ongoing basis via a website and the study investigators were

contacted by email if titration was inadequate. Minor departures from the algorithm were allowed, although the final decision rested with the investigator. Participants in the sitagliptin group received a fixed oral dose of 100 mg once daily taken in the morning either with or without food and no changes in dose were allowed during the trial.

| | Glargine (n=227) | Sitagliptin (n=253) | Total (n=480) |
|---|---|---|---|
| Age (years) | 53·9 (8·9) | 53·3 (8·7) | 53·6 (8·8) |
| Women | 113 (50%) | 121 (48%) | 234 (49%) |
| Bodyweight (kg) | 83·4 (18·2) | 84·2 (18·3) | 83·8 (18·2) |
| Body-mass index (kg/m²) | 31·1 (4·9) | 31·3 (4·9) | 31·1 (4·9) |
| Duration of diabetes (years) | 3·9 (1·9–8·2) | 4·8 (1·9–8·2) | 4·5 (1·9–8·2) |
| Systolic blood pressure (mm Hg) | 129·8 (13·3) | 131·7 (15·1) | 130·8 (14·3) |
| Diastolic blood pressure (mm Hg) | 79·5 (8·7) | 80·0 (8·3) | 79·7 (8·5) |
| Heart rate (beats per min) | 75·6 (8·7) | 76·3 (9·3) | 76·0 (9·0) |
| Duration of OADs (years) | 2·5 (1·0–5·3) | 3·1 (1·1–6·1) | 2·9 (1·0–6·0) |
| Antidiabetic treatments in previous 3 months | | | |
| α-glucosidase inhibitors | 1 (<1%) | 0 | 1 (<1%) |
| Metformin | 227 (100%) | 253 (100%) | 480 (100%) |
| Fast-acting insulin or insulin analogues | 1 (<1%) | 0 | 1 (<1%) |
| Dose of metformin (mg) | 1852 (535) | 1835 (486) | 1843 (509) |
| Any late diabetes complication | 65 (29%) | 67 (26%) | 132 (28%) |
| Myocardial infarction | 11 (5%) | 16 (6%) | 27 (6%) |
| Angina pectoris | 10 (4%) | 11 (4%) | 21 (4%) |
| Coronary artery disease | 26 (11%) | 20 (8%) | 46 (10%) |
| Heart failure | 4 (2%) | 0 | 4 (1%) |
| Stroke | 5 (2%) | 3 (1%) | 8 (2%) |
| Transient ischaemic attack | 2 (1%) | 2 (1%) | 4 (1%) |
| Peripheral vascular disease | 4 (2%) | 8 (3%) | 12 (3%) |
| Diabetic neuropathy | 24 (11%) | 28 (11%) | 52 (11%) |
| Diabetic nephropathy | 11 (5%) | 7 (3%) | 18 (4%) |
| Diabetic retinopathy | 12 (5%) | 9 (4%) | 21 (4%) |
| $HbA_{1c}$ (%) | 8·5% (1·0) | 8·5% (1·1) | 8·5% (1·1) |
| FPG (mmol/L) | 9·1 (2·2) | 9·5 (2·3) | 9·3 (2·3) |
| SMFPG (mmol/L) | 9·1 (2·1) | 9·3 (2·1) | 9·2 (2·1) |
| Total cholesterol (mmol/L) | 4·8 (1·1) | 4·8 (1·0) | 4·8 (1·0) |
| HDL cholesterol (mmol/L) | 1·2 (0·4) | 1·2 (0·3) | 1·2 (0·3) |
| LDL cholesterol (mmol/L) | 2·9 (0·9) | 3·0 (0·9) | 2·9 (0·9) |
| Triglycerides (mmol/L) | 2·2 (1·6) | 2·1 (1·3) | 2·1 (1·4) |
| Aspartate aminotransferase (UI/L) | 24·3 (10·8) | 23·8 (12·5) | 24·1 (11·7) |
| Alanine aminotransferase (UI/L) | 31·4 (17·4) | 29·7 (17·0) | 30·5 (17·2) |
| Serum creatinine (μmol/L) | 69·5 (17·1) | 70·0 (16·6) | 69·8 (16·8) |
| Concomitant treatments (other than OADs) | | | |
| Any | 198 (87%) | 217 (86%) | 415 (86%) |
| β blockers | 52 (23%) | 47 (19%) | 99 (21%) |
| Calcium-channel blockers | 33 (15%) | 39 (15%) | 72 (15%) |
| Diuretic agents | 41 (18%) | 35 (14%) | 76 (16%) |
| Agents acting on renin-angiotensin system | 131 (58%) | 134 (53%) | 265 (55%) |
| Lipid-modifying agents | 111 (49%) | 114 (45%) | 225 (47%) |
| Antithrombotic agents | 75 (33%) | 90 (36%) | 165 (34%) |

Data are n (%), mean (SD), or median (Q1–Q3). OADs=oral antidiabetes drugs. $HbA_{1c}$=glycated haemoglobin $A_{1c}$. FPG=fasting plasma glucose. SMFPG=self-monitored fasting plasma glucose. *All participants randomly assigned to treatment groups who had received at least one dose of study drug and had at least one on-treatment assessment of any primary or secondary efficacy variables.

***Table 1:*** **Baseline clinical characteristics of patients included in efficacy analysis***

$HbA_{1c}$ was recorded at baseline (week 0), week 12, and week 24, and seven-point plasma glucose profiles were recorded twice during the week before clinic visits at weeks 0, 12, and 24. Seven-point plasma glucose was measured immediately before and 2 h after breakfast, lunch, and dinner and at bedtime. Self-monitored fasting plasma glucose measurements were recorded over 6 consecutive days before the visits at weeks 0, 6, 12, 16, and 24 with bodyweight recorded at the same clinic visits. For the insulin glargine group, the last insulin dose given before the visits on weeks 2, 6, 12, 16, and 24 was recorded. $HbA_{1c}$ and other laboratory blood tests were analysed by a central laboratory.

The primary objective was to show the superiority of insulin glargine over sitagliptin in reduction of $HbA_{1c}$ from baseline to the end of the 6-month treatment period. The primary efficacy variable was change in $HbA_{1c}$ from baseline to study endpoint. We also assessed several secondary efficacy variables: $HbA_{1c}$ at baseline, week 12, week 24, and study end; proportion of participants achieving $HbA_{1c}$ less than 7% or less than 6·5% for the same timepoints; self-monitored fasting plasma glucose measured on 6 consecutive days at or before baseline (week 0) and weeks 6, 12, 16, and 24; seven-point plasma glucose profiles over 2 days in the week before baseline and weeks 12 and 24; insulin doses at weeks 0, 2, 6, 12, 16, and 24 and study end; and lipid profile at baseline and study end. Safety variables were adverse events reported by the patient or noted by the investigator, standard haematology and blood chemistry tests, bodyweight, vital signs, and hypoglycaemia. Symptomatic hypoglycaemia was defined as an event with typical symptoms (eg, sweating, palpitation, feeling of hunger) with or without confirmation by a plasma glucose less than 4·0 mmol/L. Severe symptomatic hypoglycaemia was defined as episodes necessitating assistance from another person and associated with a measured plasma glucose lower than 2·0 mmol/L or with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

## Statistical analysis

SAS version 9.2 was used for all analyses. Data are expressed as mean (SD), median (Q1–Q3), estimates (SE), or differences with 95% CI. Efficacy analysis included all participants randomly assigned to treatment groups who had received at least one dose of study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable, irrespective of compliance with the study protocol and procedures. This group was used to focus on patients who had available assessments under treatment; in particular, this method allowed evaluation of the change in $HbA_{1c}$ from baseline. All participants who were randomly assigned to treatment groups and who were treated were included in the safety population for analysis.

For the primary endpoint, we undertook ANCOVA with the change from baseline in $HbA_{1c}$ as the dependent variable, treatment group as fixed effect, and baseline $HbA_{1c}$ value as covariate. The corresponding 95% CIs were calculated for the adjusted difference (insulin glargine–sitagliptin) in means. On the assumption of a difference in the $HbA_{1c}$ change of 0·4% in favour of insulin glargine, a SD of 1·3%, a two-tailed α risk of 5%, 446 evaluable people were needed (223 per group) to ensure a statistical power of 90%. ANCOVA was used to describe the change from baseline in $HbA_{1c}$, fasting plasma glucose, and seven-point plasma glucose profile. For categorical variables, Pearson $\chi^2$ or Fisher's exact test were used. The rate of hypoglycaemia per patient-year was analysed with a generalised linear model based on a Poisson, negative binomial, zero-inflated Poisson, or zero-inflated negative binomial distribution. The best model was fitted according to likelihood ratio test and Vuong test.

This trial is registered at ClinicalTrials.gov, NCT00751114.

### Role of the funding source

The funding source participated in initial discussions about trial design, participated in the respective study steering committees, and undertook the data analysis and preparation of study reports. Company representatives are named as authors and contributed to development of the report as described in the authors' contributions. The authors had access to all data and participated in the analysis and interpretation of data. The authors vouch for the completeness and veracity of the data and analyses. PA, JC, DRO, EW, M-PD, VP, and VF served on the steering committee and had full access to the data. All authors jointly made the decision to submit for publication.

## Results

732 people were initially screened and 515 were randomly assigned to insulin glargine (n=250) or sitagliptin (n=265; figure 2). Most of the 217 people excluded after screening did not meet inclusion criteria; the most common cause was an $HbA_{1c}$ value out of range (n=146, 67%). 13 people randomly assigned to the insulin glargine group (mean $HbA_{1c}$ 8·4% [68 mmol/mol]) and one to the sitagliptin group ($HbA_{1c}$ 7·5% [58 mmol/mol]) were never treated, mostly because of withdrawal of consent, and ten (mean $HbA_{1c}$ 8·6% [70 mmol/mol]) and 11 ($HbA_{1c}$ 8·5% [69 mmol/mol]) people in the respective safety populations had no postbaseline assessment for any efficacy variables and were excluded from the efficacy analysis. The groups had similar baseline characteristics (table 1).

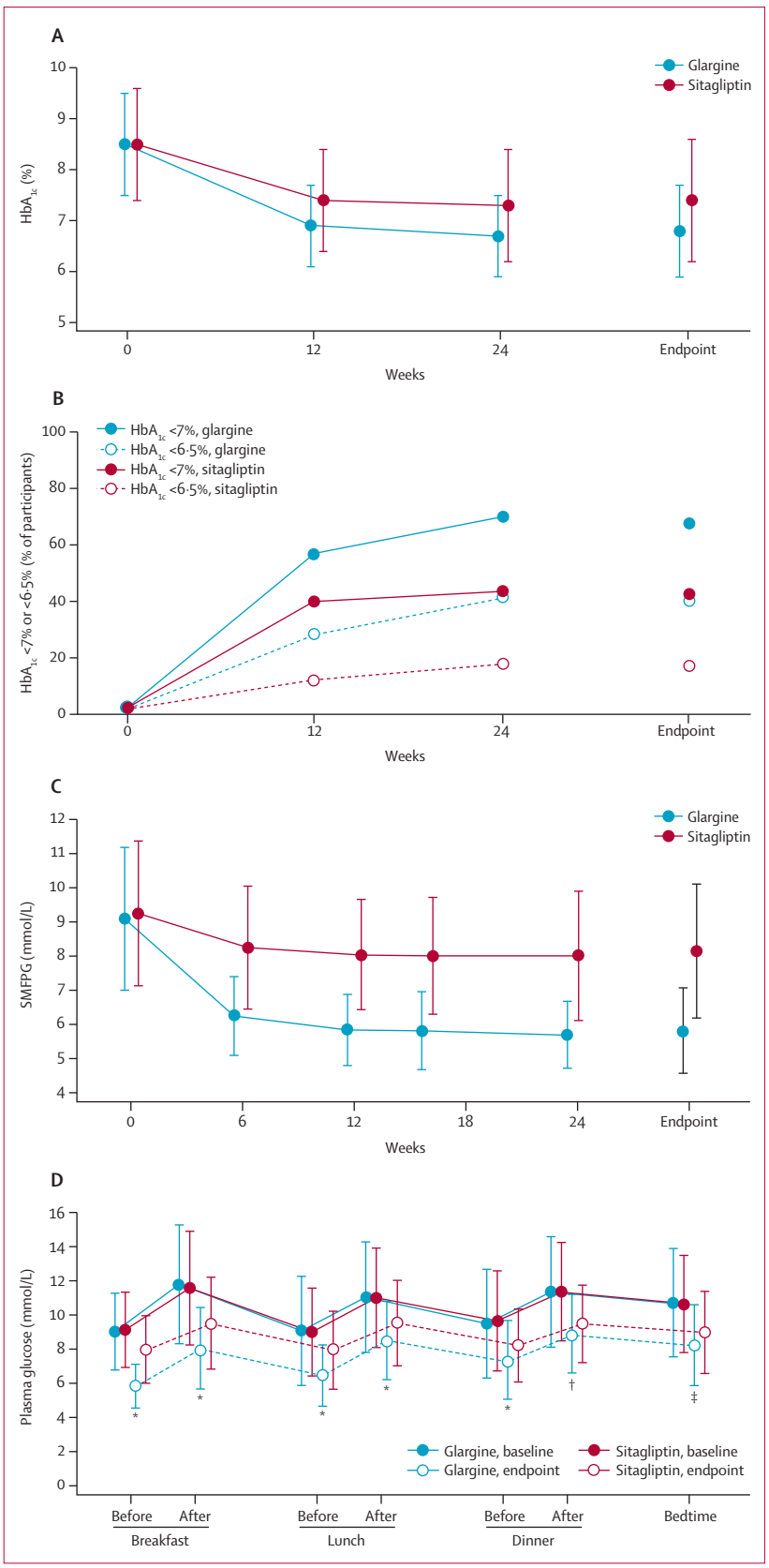


***Figure 3:*** **$HbA_{1c}$ (A), $HbA_{1c}$ less than 7% or 6·5% (B), self-monitored fasting plasma glucose (C) and seven-point self-monitored blood glucose profiles during a 24-h period (D) in a 24-week study comparing glargine versus sitagliptin in patients with type 2 diabetes who did not respond to metformin monotherapy**

$HbA_{1c}$=glycated haemoglobin $A_{1c}$. SMFPG=self-monitored fasting plasma glucose. *p<0·0001. †p=0·0012. ‡p=0·0008 versus sitagliptin (endpoint).

| | Insulin glargine (n=237) | | Sitagliptin (n=264) | | Insulin glargine/sitagliptin for events per patient-year | |
|---|---|---|---|---|---|---|
| | Patients with ≥1 event | Events per patient-year | Patients with ≥1 event | Events per patient-year | Ratio (95% CI) | p value |
| All symptomatic hypoglycaemia | 108 (46%) | 4·21 (0·54) | 35 (13%) | 0·50 (0·09) | 8·45 (5·55–12·87) | <0·0001 |
| Symptomatic hypoglycaemia with plasma glucose ≤3·9 mmol/L | 86 (36%) | 3·16 (0·47) | 28 (11%) | 0·38 (0·08) | 8·24 (5·07–13·40) | <0·0001 |
| Nocturnal symptomatic hypoglycaemia | 41 (17%) | 0·92 (0·18) | 8 (3%) | 0·07 (0·03) | 12·41 (5·43–28·35) | <0·0001 |
| Nocturnal symptomatic hypoglycaemia with plasma glucose ≤3·9 mmol/L | 36 (15%) | 0·76 (0·16) | 8 (3%) | 0·07 (0·03) | 10·34 (4·46–23·98) | <0·0001 |
| Severe symptomatic hypoglycaemia | 3 (1%) | 0·03 (0·02) | 1 (<1%) | 0·01 (0·01) | 3·40 (0·35–32·72)* | 0·29* |
| Severe nocturnal symptomatic hypoglycaemia | 1 (<1%) | 0·01 (0·01) | 1 (<1%) | 0·01 (0·01) | 1·13 (0·07–18·14)* | 0·93* |
| Symptomatic hypoglycaemia with plasma glucose ≤3·1 mmol/L | 56 (24%) | 0·90 (0·13) | 12 (5%) | 0·11 (0·03) | 8·42 (4·40–16·11) | <0·0001 |
| Nocturnal symptomatic hypoglycaemia with plasma glucose ≤3·1 mmol/L | 20 (8%) | 0·29 (0·08) | 2 (1%) | 0·02 (0·01) | 17·64 (3·87–80·34) | 0·0002 |

Data are n (%), estimated event rate (SE), estimated rate ratio (95% CI), or p value. The safety population consisted of all participants randomly assigned to treatment groups and treated. Estimated rate ratios and p values were derived from a binomial negative model with the exception of those denoted by *, which were from a Poisson model.

*Table 2:* **Rate of symptomatic, severe, and nocturnal hypoglycaemia during 24-week treatment with glargine or sitagliptin in the safety population**

$HbA_{1c}$ was reduced to a greater extent with insulin glargine than with sitagliptin throughout the study (figure 3), with the reduction at study end greater for patients on insulin glargine (adjusted mean –1·72% [SE 0·06] or –18·8 [0·7] mmol/mol) than for those on sitagliptin (–1·13% [0·06] or –12·4 [0·7] mmol/mol). The adjusted mean difference in $HbA_{1c}$ (insulin glargine–sitagliptin) at study end was –0·59% (95% CI –0·77 to –0·42) or –6·4 mmol/mol (–8·4 to –4·6) in favour of insulin glargine (p<0·0001). Throughout the study, more participants on insulin glargine than on sitagliptin achieved $HbA_{1c}$ less than 7% or less than 6·5% (figure 3). At study end, 152 (68%) of 224 participants on insulin glargine had $HbA_{1c}$ less than 7% compared with 104 (42%) of 248 on sitagliptin (p<0·0001); 90 (40%) on insulin glargine had $HbA_{1c}$ less than 6·5% compared with 42 (17%) on sitagliptin (p<0·0001). Participants in the insulin glargine group had greater reduction in self-monitored fasting plasma glucose and seven-point plasma glucose profile than did those in the sitagliptin group (figure 3). The adjusted mean difference in self-monitored fasting plasma glucose (insulin glargine–sitagliptin) was –2·3 mmol/L (95% CI –2·6 to –2·0) lower with insulin glargine than with sitagliptin (p<0·0001). The adjusted mean difference (insulin glargine–sitagliptin) also favoured insulin glargine at each timepoint of the seven-point plasma glucose profile (after dinner, p=0·0012; at bedtime, p=0·0008; all others, p<0·0001). Changes in vital signs and lipid profiles were similar for the two treatments (appendix p 2).

Dose of insulin glargine increased throughout the study, mainly during the first 12 weeks. At baseline, the mean daily dose was 0·19 (SD 0·3) units per kg (15·8 [4·2] units), which increased to 0·27 (0·08) units per kg at 2 weeks, 0·38 (0·16) units per kg at 6 weeks, 0·45 (0·2) units per kg at 12 weeks, 0·48 (0·23) units per kg at 16 weeks, and 0·5 (0·26) units per kg at 24 weeks. At study endpoint, the dose was 0·49 (SD 0·36) units per kg or 41·4 (25·8) units daily. Bodyweight increased in the insulin glargine group and decreased in the sitagliptin group. The adjusted mean change in bodyweight from baseline to endpoint was 0·44 (SE 0·22) kg in the insulin glargine group and –1·08 (0·2) kg in the sitagliptin group with an adjusted mean difference of 1·51 kg (95% CI 0·93–2·09; p<0·0001). More participants in the insulin glargine group had symptomatic hypoglycaemia than in the sitagliptin group; severe symptomatic and severe nocturnal hypoglycaemia were rare events in either group (table 2).

Treatment-emergent adverse events were reported by 108 (46%) of 237 participants in the insulin glargine and 143 (54%) of 264 participants in the sitagliptin group. The most frequently reported treatment-emergent events (reported in >3% of participants in at least one of the groups) were influenza (eight [3%] patients on insulin glargine and 15 [6%] on sitagliptin), nasopharyngitis (eight [3%] and 15 [6%]), headache (15 [6%] and 14 [5%]), dizziness (eight [3%] and eight [3%]), diarrhoea (five [2%] and ten [4%]), and nausea (four [2%] and 12 [5%]). Serious treatment-emergent adverse events were reported by 15 (6%) patients on insulin glargine and eight (3%) on sitagliptin (table 3). Most types of event were reported by only one individual, except for hypoglycaemia (three patients, including one with unconsciousness) and unstable angina (two events in the insulin glargine group). Two (1%) of 237 people in the insulin glargine group and four (2%) of 264 in the sitagliptin group withdrew from the study because of a treatment-emergent adverse event. Withdrawal in the insulin glargine group was due to malaise, injection-site inflammation, and nausea, whereas cellulitis, acute myocardial infarction, overdose, and pregnancy were causes of withdrawal in the sitagliptin group.

## Discussion

In this international, multicentre trial, 24-week treatment with either insulin glargine or sitagliptin was well tolerated with low discontinuation rates in individuals with type 2 diabetes inadequately controlled on metformin (panel). Treatment with insulin glargine lowered $HbA_{1c}$ by 0·59% more than did sitagliptin, and was 1·6-times more likely than was sitagliptin to achieve $HbA_{1c}$ less than 7% and 2·5-times more likely to achieve $HbA_{1c}$ less than 6·5% and with concurrently lower fasting and postprandial plasma glucose concentrations. Most guidelines agree on a glycaemic target of $HbA_{1c}$ 7% or less, although some now recommend a tighter glycaemic goal of 6·5% in specific groups of patients with a low cardiovascular risk in view of the adverse results of the ACCORD study in high-risk individuals.[4–6] Recent meta-analyses, however, including the ACCORD trial,[2,12,13] showed that more intensive control reduces non-fatal coronary heart disease events and has a neutral effect on mortality. Additionally, the UK Prospective Diabetes Study[14,15] showed that a low $HbA_{1c}$ reduced the risk of microvascular complications. Data are insufficient to prove or refute a relative risk reduction for cardiovascular mortality, non-fatal myocardial infarction, composite microvascular complications, or retinopathy with intensive glycaemic control.[16] The prevalence of diabetes-related complications in our study was similar to that in other similar trials or even in trials recruiting recently diagnosed patients.

In addition to a greater likelihood of reaching $HbA_{1c}$ less than 7% at study end, significantly more participants on insulin glargine than on sitagliptin achieved the goal by week 12. By week 24, there was a further increase in the number of participants in the insulin glargine group who reached the goal, whereas the number in the sitagliptin group increased only slightly. Although the duration of the study was fairly short, the results show that if people learn to titrate basal insulin and do not have episodes of severe hypoglycaemia, more of them might continue over time to reach their glycaemic goal with the combination of insulin glargine plus metformin.

The results of this study are in general agreement with previous results for both insulin glargine and sitagliptin. In previous clinical trials, insulin glargine added to metformin treatment reduced $HbA_{1c}$ by 1·7% or more,[9–11] an effect size similar to our findings. On the other hand, sitagliptin added to metformin reduced $HbA_{1c}$ by an average of 0·7% in earlier trials,[7,8,17] but in subgroups of participants with baseline $HbA_{1c}$ of 8–9% the reduction in $HbA_{1c}$ was nearly identical to the present study.[8] Weight loss with sitagliptin was greater than expected since DPP-4 inhibitors are usually weight-neutral,[17] but a similar weight loss has been reported in patients treated with the combination of sitagliptin and metformin.[18] The prevalence of diabetes-related complications in our study was similar to that in other similar trials and in trials recruiting recently diagnosed patients.

| | Insulin glargine (n=237) | Sitagliptin (n=264) |
|---|---|---|
| Any class | 15 (6%) | 8 (3%) |
| Infections and infestations | 1 (<1%) | 1 (<1%) |
| Anal abscess | 1 (<1%) | 0 |
| Cellulitis | 0 | 1 (<1%) |
| General disorders and administration site | 1 (<1%) | 0 |
| Non-cardiac chest pain | 1 (<1%) | 0 |
| Nervous system disorders | 3 (1%) | 0 |
| Carotid artery occlusion | 1 (<1%) | 0 |
| Epilepsy | 1 (<1%) | 0 |
| Loss of consciousness | 1 (<1%) | 0 |
| Nerve compression | 1 (<1%) | 0 |
| Muscular and connective tissue disorders | 0 | 1 (<1%) |
| Pain in leg | 0 | 1 (<1%) |
| Gastrointestinal disorders | 1 (<1%) | 1 (<1%) |
| Impaired gastric emptying | 1 (<1%) | 0 |
| Diverticulum intestinal | 0 | 1 (<1%) |
| Vascular disorders | 2 (1%) | 1 (<1%) |
| Hypertension | 0 | 1 (<1%) |
| Orthostatic hypotension | 1 (<1%) | 0 |
| Peripheral arterial occlusive disease | 1 (<1%) | 0 |
| Metabolism and nutrition disorders | 3 (1%) | 0 |
| Hypoglycaemia | 2 (1%) | 0 |
| Hypoglycaemic unconsciousness | 1 (<1%) | 0 |
| Cardiac disorders | 3 (1%) | 2 (1%) |
| Angina unstable | 2 (1%) | 0 |
| Angina pectoris | 1 (<1%) | 1 (<1%) |
| Acute myocardial infarction | 0 | 1 (<1%) |
| Injury, poisoning, and procedural complications | 1 (<1%) | 0 |
| Vascular pseudoaneurysm | 1 (<1%) | 0 |
| Renal and urinary disorders | 2 (1%) | 0 |
| Calculus ureteric | 1 (<1%) | 0 |
| Renal colic | 1 (<1%) | 0 |
| Blood and lymphatic system disorders | 1 (<1%) | 0 |
| Haemorrhagic anaemia | 1 (<1%) | 0 |
| Neoplasms (benign, malignant, and unspecified, including cysts and polyps) | 0 | 2 (1%) |
| Kaposi's sarcoma | 0 | 1 (<1%) |
| Prostate cancer | 0 | 1 (<1%) |

Data are number (%) of patients with at least one adverse event. The safety population consisted of all participants randomly assigned to treatment groups and treated. MedDRA version 14.0 was used for assessment.

***Table 3:*** **Serious treatment-emergent adverse events in the safety population**

During the seven-point plasma glucose monitoring, insulin glargine was more effective than was sitagliptin in reducing both fasting and postprandial plasma glucose. This finding could be accounted for by the effect of basal insulin on reduction of hepatic glucose production.[19] Amelioration of glucotoxicity that is often accompanied by improved endogenous insulin secretion might also play a part, but was not addressed in this

*Panel:* Research in context

**Systematic review**

We searched PubMed Clinical Queries up to Feb 28, 2012, with the search terms "type 2 diabetes", "insulin therapy", and "dipeptidyl peptidase-4 inhibitor". We reviewed randomised clinical trials and meta-analyses published in English. Both treatments effectively improve glycaemic control with clinically acceptable safety. However, we were unable to find a comparative effectiveness trial comparing the two strategies head to head.

**Interpretation**

This randomised trial is the first to compare two therapeutic approaches often considered as second-line add-on treatment to metformin, under conditions that are as close to real life as is possible in a randomised trial. In this study, insulin glargine when added to metformin reduced glycated haemoglobin $A_{1c}$ more than did sitagliptin added to metformin, with an effect size similar to previous clinical trials.[9–11] Hypoglycaemia overall, however, was less frequent with sitagliptin. There was a small weight loss with sitagliptin, by contrast with minimum weight gain with insulin glargine. The results of this comparative effectiveness trial might help physicians to choose between these two drugs for patients whose diabetes is uncontrolled on metformin and provide clinical experience to guide the design of future studies needed to assess the long-term efficacy of these two therapeutic strategies.

study. Intensive insulin treatment has been shown to improve insulin secretion.[20–22]

The estimated rate of hypoglycaemia per patient-year was eight-times higher with insulin glargine than with sitagliptin. However, not all episodes were confirmed by blood glucose testing and 13% of patients treated with sitagliptin (known to have low risk [<3%] of hypoglycaemia[17]) also reported hypoglycaemia. The risk of severe hypoglycaemia, although three-times higher with insulin glargine, was not significantly different from that with sitagliptin, and the risk of severe nocturnal hypoglycaemia was the same for the two groups. Lessons from recent megatrials have shown that intensive lowering of blood glucose should be accompanied by structured self-monitoring of blood glucose, especially in high-risk people with long disease duration, in an attempt to avoid hypoglycaemia-related adverse effects such as cardiovascular disease and related death.[23] In view of the possible long-term benefits of intensive lowering of blood glucose and the superior efficacy of insulin to optimise glycaemic control, strong arguments could be made to use insulin early when the dose is expected to be fairly low, with a reduced risk of hypoglycaemia.[24] As shown in the present study, glycaemic control can be achieved with an average supplementary dose of 0·5 units per kg of insulin glargine and a weight gain of less than 0·5 kg. Upcoming results from the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial[25] will further address this question and other aspects related to the benefit of early intensive glucose lowering with basal insulin.

Despite the large sample size and multinational nature of the study population, the present study is not without limitations. We recognise that the open-label nature of the study and the absence of placebo groups preclude determination of absolute $HbA_{1c}$ changes. We also acknowledge that initiation of insulin treatment is inevitably accompanied by increased frequency of monitoring and contacts with care teams, which might contribute to metabolic improvement. However, many randomised clinical trials have shown the benefits of early attainment of goals with intensive insulin treatment.[20] Our objective was to establish the relative effect of basal insulin glargine versus the DPP-4 inhibitor sitagliptin under conditions that were as close to real life as can be simulated in a randomised clinical trial. The results extend the earlier findings to show the feasibility of application of this knowledge in day-to-day practice. Although the increased reduction in $HbA_{1c}$ in the insulin glargine group might be partly attributable to the increased frequency of blood-glucose monitoring needed for insulin titration and thus a different level of interaction with the carers, otherwise, both groups had a similar number of clinic visits, telephone reminders, and seven-point plasma glucose monitoring. We also recognise the short-term nature of the study and realise that long-term studies will be needed to reaffirm our findings and to provide greater understanding about the differences between these two therapeutic options. Acceptance of insulin treatment is another consideration despite the likely benefits.

In conclusion, we have shown in this 24-week trial the feasibility of initiating basal insulin therapy early in individuals who have not achieved the desired glycaemic target with metformin monotherapy. Early introduction of basal insulin glargine was associated with lower $HbA_{1c}$ and fasting and postprandial blood glucose concentrations with a higher rate of attainment of $HbA_{1c}$ goals compared with sitagliptin. Minimum weight gain was noted with insulin glargine and a small weight loss with sitagliptin. The results of this study support the option of introduction of basal insulin in patients with type 2 diabetes inadequately controlled by metformin, with the potential for long-term benefits arising from the achievement of optimum glycaemic control early in the course of the disease.

**Contributors**

PA, JC, DRO, EW, M-PD, VP, and VF served on the steering committee. SP served on the international titration committee. VP undertook statistical analyses for the report. All authors contributed to the interpretation of the data and provided comments on the report at various stages in its development.

**EASIE Study Group**

*Austria* T Hermann, A Luger, G Schernthaner, G Fließer-Görzer, B Paulweber, S Pusnarig, J Föchterle, K Elcic-Mihaljevic, B Hölzl; *Brazil* J Gross, F Eliaschewitz, M Hissa, R Réa, R Kupfer; *Colombia* A Almanzar, P Aschner, A Orduz, E Maria; *Greece* V Klisiaris, N Tentolouris, A Melidonis, S Pappas, G Dimitriadis; *Hong Kong* R Osaki, C C Tsang, S C Siu, M W Tsang, V Yeung; *India* S Pendsey, S Trivedi, S Murthy; *Israel* T Zornitzki, J Wainstein, O Shemuel, I Harman Boehm; *Lebanon* S Azar, C Saab, A Echtay; *Mexico* L-G Mancillas-Adame, C-A Dominguez-Reyes, A Romero-Zazueta, N-A Caracas-Portilla, F de M C Mercado-Palacios; *Netherlands* J van de Walle, M van Vollevelde, S Jenniskens, B Sombekke, W van Kempen, L de Schipper, W Everts, A Kooy, I Agous; *Portugal* L Guerra, J Guimaraes, R Silva; *South Korea* D Kim, W Lee, S Baik,

H Jang, M Lee, K Won; *Spain* C Zapon Llópis, D Bellido Guerrero, M Rivas Fernández, F Botella Romero, F Tinahones Madueño, A Robles Iniesta, J A Paniagua González, L de Teresa Parreño, L Flores Meneses; *Turkey* H Sargin, B Efe, S Gonen, I Sahin, R Sari, S Shelbaya; *UK* D R Owens, J Litchfield, A Ellery, N Armstrong; *USA* M Wong, D Robbins, N Patel, L Fogelfeld, B Mirada-Palma, J McGill, L Chaykin, S Garg, C Lovell, R Lorraine, P Snell, S Rizvi, H Maheshwari, S Nakhle, S Ong, J Mitchell, K Roberts.

#### Conflicts of interest

PA has served on advisory boards for AstraZeneca, Eli Lilly & Co, GlaxoSmithKline, Janssen, Merck, Sharpe & Dohme, Novartis, and Sanofi and on speakers' bureaus for AstraZeneca, Eli Lilly & Co, Merck, Sharpe & Dohme, Novartis, and Sanofi. JC has served on advisory boards for Amylin, AstraZeneca, Bayer Healthcare, Eli Lilly & Co, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Pfizer, and Sanofi and on speakers' bureaus for AstraZeneca, Bayer Healthcare, Eli Lilly & Co, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Pfizer, Sanofi, and Takeda; she has received research support from Amylin, AstraZeneca, Bayer Healthcare, Eli Lilly & Co, GlaxoSmithKline, Merck-Serono, Merck, Sharpe & Dohme, Sanofi, and Takeda. DRO has served on advisory boards and speakers' bureaus for Roche and Sanofi and has received research support from Boehringer Ingelheim, Roche, and Sanofi. SP has served on advisory boards, as a board member, and as a consultant for Medtronics, Novo Nordisk, and Sanofi and on speakers' bureaus for Eli Lilly & Co, Lifescan, Medtronic, Merck-Serono, Novartis, Pierre Fabre, Novo Nordisk, Sanofi, and Solvay. EW, M-PD, and VP are employees of Sanofi. AE has served on an advisory board for Merck, Sharpe & Dohme and on speakers' bureaus for AstraZeneca, Eli Lilly & Co, Merck & Co, Merck, Sharpe & Dohme, Novartis, Novo Nordisk, and Sanofi. VF has served as a consultant and on speakers' bureaus for AstraZeneca, Daiichi Sankyo, Eli Lilly & Co, GlaxoSmithKline, Novo Nordisk, Pamlabs, Sanofi, Takeda, and Xoma.

#### Acknowledgments

The study was funded by Sanofi. Editorial support was provided by Tom Claus of PPSI (a PAREXEL Company; Hackensack, NJ, USA) and funded by Sanofi.

#### References

1 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.

2 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:** 1765–72.

3 Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009; **52:** 2288–98.

4 IDF Clinical Guidelines Task Force. Guideline for management of postmeal glucose. Brussels: International Diabetes Federation, 2007. http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf (accessed Jan 10, 2012).

5 Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2009; **52:** 17–30.

6 Rodbard HW, Blonde L, Braithwaite SS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007; **13** (suppl 1)**:** 1–68.

7 Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006; **29:** 2638–43.

8 Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab* 2007; **9:** 194–205.

9 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26:** 3080–86.

10 Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia* 2008; **51:** 408–16.

11 Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. *Diabetes Obes Metab* 2011; **13:** 814–22.

12 Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2011; **343:** d4169.

13 Mannucci E, Monami M, Lamanna C, Gori F, Marchionni N. Prevention of cardiovascular disease through glycemic control in type 2 diabetes: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 2009; **19:** 604–12.

14 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:** 837–53.

15 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:** 854–65.

16 Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011; **343:** d6898.

17 Ahren B. Use of DPP-4 inhibitors in type 2 diabetes: focus on sitagliptin. *Diabetes Metab Syndr Obes* 2010; **3:** 31–41.

18 Wainstein J, Katz L, Engel SS, et al. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; **14:** 409–18.

19 Triplitt C, Glass L, Miyazaki Y, et al. Comparison of glargine insulin versus rosiglitazone addition in poorly controlled type 2 diabetic patients on metformin plus sulfonylurea. *Diabetes Care* 2006; **29:** 2371–77.

20 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; **371:** 1753–60.

21 Noh YH, Lee SM, Kim EJ, et al. Improvement of cardiovascular risk factors in patients with type 2 diabetes after long-term continuous subcutaneous insulin infusion. *Diabetes Metab Res Rev* 2008; **24:** 384–91.

22 Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care* 2008; **31:** 1927–32.

23 Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care* 2010; **33:** 1389–94.

24 Pozzilli P, Leslie RD, Chan J, et al. The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach. *Diabetes Metab Res Rev* 2010; **26:** 239–44.

25 Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). *Am Heart J* 2008; **155:** 26–32.