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DOI:10.4158/EP12269.OR

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Original Article

EP12269.OR

**EFFECT OF BASELINE HBA1C ON GLYCEMIC CONTROL AND DIABETES
MANAGEMENT FOLLOWING INITIATION OF ONCE-DAILY INSULIN DETEMIR
IN REAL-LIFE CLINICAL PRACTICE**

Running title: Basal insulin and OAD treatment

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DOI:10.4158/EP12269.OR

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ABSTRACT

Objective: The SOLVE study investigated the initiation of basal insulin in patients with type 2 diabetes on oral antidiabetic (OAD) treatment and outcomes in patients with varying levels of glycemic control at baseline.

Methods: This was an observational cohort study conducted in 10 countries, using insulin detemir. Data were collected at three clinic visits (baseline, 12-week interim and 24-week final visit).

Results: A total of n=13,526 (77.9%) patients were included in the HbA1c subset analysis. Patients were grouped according to pre-insulin HbA1c values as follows: HbA1c <7.6% (n=2,797); HbA1c 7.6-9% (n=5,366) and HbA1c >9% (n=5,363). A total of 27 patients experienced SADR and/or severe hypoglycemia: n=3, n=10 and n=11 in patients with pre-insulin HbA1c <7.6%, 7.6-9.0%, and >9.0%, respectively. All patient sub-groups realized improvements in HbA1c, with the pre-insulin HbA1c >9% sub-group having the largest HbA1c reduction (-2.4% versus -0.9% and -0.2% for HbA1c subgroups 7.6-9% and <7.6%, respectively) during the study. In the total cohort (n=17,374), the incidence of severe hypoglycemia decreased from 4 events per 100 person years to <1 event per 100 person years by final visit; whereas the incidence of minor hypoglycemia increased from 1.6 to 1.8 events per person year.

Conclusions: In this study, insulin initiation was delayed until late in the course of the disease, and overall concordance with internationally recognized guidelines was low. The initiation of once-daily insulin detemir was associated with substantial improvements in glycemic control, and was not associated with an increase in severe hypoglycemia or weight gain.

Key words: type 2 diabetes mellitus, insulin therapy, glycemic control, hypoglycemia

Abbreviations:

AACE= American Association of Clinical Endocrinologists; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACE** = American College of Endocrinology; **ADA** =American Diabetes Association; **ADVANCE** = Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; **BMI** = Body mass index; **EASD** = European Association for the Study of Diabetes; **FBG** = Fasting blood glucose; **HbA1c** = Glycosylated hemoglobin A1c; **OAD** = Oral antidiabetic; **SAS** = Statistical Analysis Software; **SMBG** = Self-monitored blood glucose; **SOLVE** = Study of Once-daily Levemir; **T2DM** = Type 2 diabetes mellitus; **VADT** = Veterans Affairs Diabetes Trial

INTRODUCTION

Oral antidiabetic (OAD) treatment intensification remains the most commonly employed approach to managing persistent hyperglycemia in type 2 diabetes mellitus (T2DM), even though additional oral therapies may still leave patients in poor glycemic control.(1) Insulin is regarded as the most efficacious treatment for achieving glycemic control in T2DM (2), with reported reductions in glycosylated hemoglobin A1c (HbA1c) of up to 3.5%.(3) Despite a wide range of metabolic benefits(4), there are acknowledged barriers in insulin initiation such as misconceptions regarding insulin risk and negative impact on quality of life. Fears about hypoglycemia and weight gain often contribute as a barrier to insulin initiation.(5) Insulin is currently recommended as a second line agent for sub-optimally controlled T2DM patients in the most recently published American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus statement.(6) However, a large proportion of patients do not receive appropriate treatment intensification with either oral or insulin therapy.(7)

Despite many examples of well-intentioned and comprehensive guidelines aimed at improving glycemic control (8-12), up to 93% of patients with T2DM have an HbA1c above 7.0% and 57% have HbA1c above 9.0% at the time insulin treatment is commenced(1;7;13). Although there has been reasonable agreement concerning specified glycemic targets, results from studies such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation), ACCORD (Action to Control Cardiovascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial) have cast doubt on the goal of low glycemic targets for all population subgroups.(14;15) As a consequence of these trial results, there has been more emphasis on the need to individualize targets. (6;9;16)

Meta-analyses have examined the effect of pre-treatment HbA1c on treatment response with consistent results: higher initial HbA1c levels predict a greater magnitude of HbA1c change with therapy, regardless of therapeutic class. (17-20) This concept of baseline HbA1c as a determinant of glycemic response has also been confirmed in the real-world setting. (21) In addition to recognizing the need to individualize treatment goals, the (American College of Endocrinology/American Association of Clinical Endocrinologists) ACE/AACE treatment algorithm proposes treatments based on an initial HbA1c, stratified into three categories: (1) HbA1c <7.6%, (2) HbA1c 7.6-9% and (3) HbA1c >9%. (10) However, the evidence base for many of these suggested treatment combinations are lacking, and the extent to which these approaches are implemented in clinical practice is unknown.

The SOLVE (Study of Once-Daily Levemir) study, investigated the effect of initiating basal insulin to existing OAD therapy in a large heterogeneous cohort of patients with type 2 diabetes from 10 different countries. This sub-analysis explores the real-world approach to diabetes management in patients with different levels of baseline glycemic control.

METHODS

The SOLVE study was a 24-week, multinational, multicenter observational study of insulin initiation. The study centers included primary and secondary care practices, and involved family, general medical and specialist physicians from 10 countries (Canada, China, Germany, Israel, Italy, Poland, Portugal, Spain, Turkey and the United Kingdom). The study has been described previously (22), and is summarized below.

Patient Selection

Following the decision by the health care provider to initiate basal insulin treatment with once-daily insulin detemir, patients with type 2 diabetes receiving treatment with one or more

OADs were eligible for enrollment into the study. There were some variations between countries with respect to age and insulin exposure at the time of enrollment (22). Female patients were excluded if they were pregnant, breast feeding or intending to be pregnant. Withdrawal criteria were as follows: becoming pregnant during the study, discontinuation of the study drug and/or all OADs, and the use of insulin detemir more than once-daily or with other insulin preparations/regimens.

Study Endpoints

Demographic variables and primary and secondary study outcomes were monitored at 3 time points: insulin initiation, interim (12-week) and final (24-week) visits. Since no visit schedule was imposed by the study design, visits occurring closest to the relevant time points were used for analytical purposes. The primary study endpoint was the incidence of serious ADRs including severe hypoglycemia. Other secondary points included: glycemic control [HbA1c, fasting blood glucose (FBG), and self-monitored blood glucose (SMBG)], hypoglycemia (severe, minor and nocturnal), and weight; as well as treatment related endpoints such as OAD regimen and insulin dose.

Severe hypoglycemia was defined as any symptomatic episode requiring third party assistance occurring in the 12 weeks prior to the scheduled visit. Minor hypoglycemia was defined as any symptomatic episode or any episode with a blood glucose measurement <56 mg/dl (3.1 mmol/l), occurring in the 4 weeks prior to the scheduled visit. Any episode occurring between bedtime and waking the next morning were considered as nocturnal episodes.

Statistical Analysis

All patients receiving insulin detemir at any time during the study were included in the full analysis set. Subgroup analyses according to the level of pre-insulin glycemic control were

performed in accordance with a pre-planned statistical analysis plan. The three subgroups comprised patients with (1) HbA1c <7.6%, (2) HbA1c 7.6-9% and (3) HbA1c >9% (10).

Descriptive data are presented as mean \pm standard deviation (continuous data) or as percentages (categorical data), unless otherwise described. Statistical comparisons of data before and after the initiation of basal insulin therapy were performed using the paired t-test for continuous variables, or the Wilcoxon test for ordinal categorical variables. The McNemar test was used to test for changes in discrete variables such as the incidence of hypoglycemia.

The evaluation of demographic and study treatment parameters as predictors of end of study HbA1c was performed using a general linear model. The model was comprised of the parameters: patient age, gender, duration of diabetes, body mass index (BMI), and the number and type of prescribed OADs pre-insulin. Parameters were selected using a process of backward elimination (selection criteria $p < 0.05$). The effect of country was included as a random effect.

All testing employed two-sided tests at $\alpha = 0.05$ level of significance. All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.01. No adjustments were made for multiple comparisons.

RESULTS

The total SOLVE study cohort assessed $n = 17,374$ patients. Of these, $n = 13,526$ (77.8%) patients had recorded pre-insulin HbA1c measurements as follows: HbA1c <7.6% ($n = 2,797$); HbA1c 7.6-9% ($n = 5,366$) and HbA1c >9% ($n = 5,363$). Amongst these patients included in the efficacy analysis, $n = 11,023$ (63.4% of the total cohort) patients were included in the sub-analysis, with HbA1c values as follows: HbA1c <7.6% ($n = 2,351$); HbA1c 7.6-9% ($n = 4,476$) and HbA1c >9% ($n = 4,196$). The reasons for excluding subjects from the sub-analysis were as follows: no measurement at baseline and final visit ($n = 1538$), a final visit outside the 16-32 week

range (n=636), study insulin prescribed more than once daily (n=85), addition of a short-acting insulin (n=9), or a first dose of insulin prescribed at a date outside the allowed range (n=235).

Patient Demographics

The characteristics of participants according to pre-insulin HbA1c subgroup are shown in Table 1. There were no apparent trends between an increasing pre-insulin HbA1c with respect to age, duration of diabetes or duration of OAD treatment, or gender. The proportion of ‘other’ ethnicity (predominantly made up of Asian participants) was higher in the subgroup with pre-insulin HbA1c <7.6% relative to the other HbA1c subgroups. Conversely, the proportion of black participants seemed to increase with ascending pre-insulin HbA1c; however, absolute numbers of black participants in the study were low. There also seemed to be a trend to increasing weight and BMI in the subgroups with higher pre-insulin HbA1c.

Hypoglycemia

A total of 27 patients experienced SADR and/or severe hypoglycemic. The distribution of these patients between the subgroups based on pre-insulin HbA1c were n=3 (13%) in the group with pre-insulin HbA1c <7.6%, n=10 (42%) with pre-insulin HbA1c 7.6-9.0%, and n=11 (46%) in patients with pre-insulin HbA1c > 9.0%. Pre-insulin HbA1c values were missing for the 3 remaining events.

In the total cohort, the incidence of severe hypoglycemia decreased from 4 events per 100 person years prior to the study to <1 event per 100 person years by final visit; whereas the incidence of minor hypoglycemia increased from 1.6 to 1.8 events per person year.

The incidence and period prevalence of hypoglycemia according to the level of pre-insulin HbA1c is shown in Table 2. The incidence of severe hypoglycemia decreased during the study irrespective of the level of pre-insulin glycemic control. There was a non-significant trend

toward a decreased incidence of minor hypoglycemia in the group with the lowest pre-insulin HbA1c; but a statistically significant increase in the other two HbA1c subgroups, with the largest increase in minor hypoglycemia occurring in the group with the highest level of HbA1c prior to the start of the study. The proportion of patients experiencing at least one episode of minor hypoglycemia was similar in all three subgroups by the final.

Risk factors for poor glycemic control prior to insulin initiation

The results of a multivariate analysis of pre-insulin demographic and treatment parameters as predictors of HbA1c prior to insulin initiation are shown in Figure 1. The analysis identified statistically significant independent associations between pre-insulin HbA1c and patient age, BMI, a previous history of hypoglycemia or microvascular disease, the number of OADs, and the use of metformin or sulphonylureas. The parameters associated with the largest reductions in pre-insulin HbA1c were age ≥ 65 years (compared with patients < 50 years), and a previous history of hypoglycemia (-0.40% [95% CI -0.52, -0.29%]). There was a dose-response relationship between the number of OADs and reduction in pre-insulin HbA1c (-0.22% and -0.10% for patients treated with >2 and 2 OADs compared to 1 OAD, respectively). After adjusting for the number of oral agents, the specific use of metformin (+0.13% [95% CI +0.06, +0.21%]) or sulphonylureas (+0.22% [95% CI +0.16, +0.29%]) was associated with increased pre-insulin HbA1c. The presence of microvascular disease was also associated with an increased pre-insulin HbA1c, after adjusting for other model parameters.

Glycemic control

In the total sub-analysis cohort, the HbA1c decreased from $8.9 \pm 1.6\%$ to $7.5 \pm 1.2\%$ at the end of the 24-week study (change -1.3%, $p < 0.001$). Corresponding improvements in FBG were also seen: from 183 ± 54 mg/dl (10.1 ± 3.0 mmol/l) to 128 ± 32 mg/dl (7.1 ± 1.8 mmol/l)

[change -55 ± 53 mg/dl (-3.1 ± 3.0 mmol/l), $p < 0.001$). The changes in HbA1c and FBG by pre-insulin HbA1c are shown in Figure 2. Significant reductions in HbA1c and FBG were observed in all three groups ($p < 0.001$). Participants with HbA1c $> 9\%$ prior to insulin initiation had the largest reduction in HbA1c, -2.4% [95% CI $-2.5, -2.4\%$], $p < 0.001$; and FBG, -83 mg/dl [95% CI $-86, -79$ mg/dl] (-4.6 mmol/l [95% CI $-4.8, -4.4$ mmol/l]), $p < 0.001$ during the study. Patients with HbA1c $7.6\text{--}9\%$ prior to insulin initiation had change in HbA1c of -0.9% [95% CI $-0.93, -0.87$], $p < 0.001$, while patients with HbA1c $< 7.6\%$ prior to insulin initiation had change in HbA1c of -0.17% [95% CI $-0.20, -0.13$], $p < 0.001$. The proportion of patients reaching an HbA1c target of $< 6.5\%$ at the end of the study was 31.3% ; 9.6% and 17.1% for HbA1c subgroups $< 7.6\%$; $7.6\text{--}9\%$ and $> 9\%$, respectively.

Figure 3 shows the SMBG measurements at baseline and end of study for the three HbA1c subgroups. Following treatment with insulin detemir, there was a consistent reduction in all SMBG measurements, with the largest changes seen in the pre- and post-breakfast measurements.

Body Weight

There was an overall decrease in body weight (-0.6 kg, $p < 0.001$) and BMI (-0.17 kg/m², $p < 0.001$) in the total cohort, by the end of the study. Both weight and BMI decreased in all three HbA1c subgroups by final visit. The mean weight changes were -0.6 kg [95% CI $-0.8, -0.5$], -0.6 kg [95% CI $-0.8, -0.5$ kg], -0.3 kg [95% CI $-0.4, -0.1$ kg] in the group with $< 7.6\%$, $7.6\text{--}9\%$ and $> 9\%$ pre-insulin HbA1c, respectively. Similarly, BMI values at the final visit were also reduced for all three groups at final visit. The mean changes in BMI values were -0.19 kg/m² [$-0.24, -0.14$ kg/m²], -0.20 kg/m² [$-0.24, -0.17$ kg/m²] and -0.08 kg/m² [95% CI $-0.12, -0.03$ kg/m²] for subjects in HbA1c groups $< 7.6\%$, $7.6\text{--}9\%$ and $> 9\%$, respectively.

Insulin Treatment

Total daily doses of insulin were 12.6 ± 6.3 IU (0.16 ± 0.09 IU/kg) at therapy initiation. At the final visit, insulin doses had increased to 21.6 ± 15.6 IU (0.27 ± 0.17 IU/kg). The insulin doses used according to HbA1c subgroups are shown in Figure 4. Larger initial unit per kilogram doses of insulin were administered to patients with higher pre-insulin HbA1c. The change in insulin dose was larger in patients with higher pre-insulin HbA1c. The corresponding unit doses of insulin at final visit were 17 IU (0.22 IU/kg), 21 IU (0.26 IU/kg) and 25 IU (0.30 IU/kg) in HbA1c subgroups of <7.6%, 7.6-9% and >9%, respectively.

OAD Treatment

Pre-insulin OAD regimens were considerably more consistent with ACE roadmap recommendations in patients with lower pre-insulin values (69.0%, 57.7% and 11.8% in HbA1c sub-groups <7.6%; 7.6-9% and >9%, respectively).

Prior to the addition of insulin, metformin was used by 56.6% of patients on monotherapy. Sulphonylurea or glinides accounted for 36.0% of patients using a single oral agent prior to insulin initiation. The most commonly used regimen was the combination of metformin with sulphonylurea (35.4%), with 58.2% of the cohort using either one of these alone or a combination. Glinides and dipeptidyl peptidase-4 (DPP-IV) inhibitors were most commonly used in combination with metformin (6.9% and 3.1%, respectively); whereas TZD were most commonly used in a triple OAD regimen in combination with metformin and sulphonylurea (4.9% of patients). Prior to insulin initiation, 1.4% of the participants were prescribed 4 or more agents, and 49% of these patients were taking the combination of metformin, sulphonylurea, TZD and α -glucosidase inhibitor. Other oral regimens prescribed to at least 1.0% of the patients with pre-insulin HbA1c values $\leq 7.5\%$ were the combination of a glinide and α -glucosidase

inhibitor with (1.1%) or without the addition of metformin (1.3%). In patients with pre-insulin HbA1c values $\geq 9.0\%$, other more common OAD regimens included the 4 OAD combinations of metformin, sulphonylurea, TZD and α -glucosidase inhibitor (1.0%), and the dual agent combination of sulphonylurea and TZD (1.0%). OAD usage consistent with ACE roadmap recommendations decreased from 69.0% in patients with pre-insulin values of $\leq 7.5\%$, to 11.8% in patients with HbA1c values $\geq 9.0\%$ (10).

At the time of insulin initiation, metformin and a secretagogue (used alone or in combination) were the most commonly used OAD regimens with basal insulin therapy, accounting for 76.3% of the total cohort. In patients starting basal insulin therapy, α -glucosidase inhibitors were most commonly used alone (3.1%) or with metformin, a sulphonylurea, or both (5.8%). In contrast, thiazolidinediones and DPP-IV inhibitors were rarely used as the only OAD treatment with insulin (0.3% and 0.4% of the total cohort, respectively). Other more common regimens were the combination of insulin with a glinide and α -glucosidase inhibitor in the subgroup with pre-insulin HbA1c $\leq 7.5\%$ (1.5%); and the triple combination of metformin, sulphonylurea and a DPP-IV inhibitor with insulin in the subgroups with intermediate and high pre-insulin HbA1c values (1.1% and 1.1%, respectively).

DISCUSSION

The SOLVE study represents the largest study of insulin initiation in type 2 diabetes mellitus to date, and reflects real-life clinical practice involving primary and secondary care from 10 countries.(23) The study highlights the low overall concordance with international guidelines endorsed by specialist diabetes bodies concerning the initiation of insulin and use of other oral therapies. In this analysis, all patient subgroups realized improvements in HbA1c without an increased risk of severe hypoglycemia or weight gain. As expected, patients with the highest

values of pre-insulin HbA1c experienced the most clinically significant improvements in glycemic control.

Data regarding how long SOLVE study patients had endured high levels of HbA1c were not collected. However, it is likely that poor glycemic control had been prevalent for some years in a substantial proportion of patients.(1;24) The UKPDS demonstrated reduced rates of microvascular (and to a lesser degree, macrovascular) complications with each 1% reduction in HbA1c; however, this relationship was curvilinear, suggesting greater risk reduction in association with improvements at higher HbA1c levels (e.g. from 9.0% to 8.0% versus 8.0% to 7.0%). (25) More recent studies investigating the effects of glycemic control on cardiovascular risk show that early glycemic control is advantageous, but that intensive treatment in patients with a long history of poor glycemic control and established vascular complications can increase the risk of all-cause mortality (14;26). This may reflect the increase in co-morbidity,(27) which may also be the result of previous episodes of poor glycemic control. Thus, delaying appropriate diabetes treatment intensification carries with it the increased risk of micro- and macrovascular complications, as well as a limit on the effectiveness of future diabetes management.(9;15) Such concerns may have been expected to influence the treatment approach to participants with high pre-insulin HbA1c levels in this study – the reality was that these patients received the highest insulin doses and experienced the largest reductions in HbA1c (mean 2.4%). Although the magnitude of these observed changes in glycaemic control and the levels of pre-insulin HbA1c appear to be relevant to microvascular (and probably macrovascular) risk reduction, it is not clear for how long these glycaemic improvements would have to be maintained in order to modify micro- and macrovascular risk. This study of only 6 months duration was not designed to address these issues. It is important to bear in mind, however, that critical to risk reduction

strategy, is a holistic approach to treatment, with the targeting of other cardiovascular risk factors such as hyperlipidaemia and hypertension (28) which may contribute more to cardiovascular risk than glycemic control per se.

The group of patients with the highest levels of HbA1c prior to the initiation of insulin, and greatest improvement in HbA1c during the study, also experienced the largest increase in the incidence of minor hypoglycemia, and completed the study with the same or higher rate of minor hypoglycemia relative to the other two subgroups despite the fact that both other subgroups had lower end of study HbA1c values (0.1 and 0.2% lower, respectively). However, the absolute incidence of minor hypoglycemia was low, irrespective of the patient subgroup. In addition, patients with high pre-insulin HbA1c showed the greatest decrease in the incidence of severe hypoglycemia during the study period (5% greater than both other groups; data not shown), despite receiving the highest doses of insulin. These findings corroborate those of the ACCORD study, which identified a higher incidence of severe hypoglycemia in patients with the highest levels of HbA1c and the smallest improvements in HbA1c (29;30).

Interestingly, larger BMI ≥ 30 was not associated with worse pre-insulin glycemic control (Figure 1). Concerns about weight gain are known barriers to insulin initiation, and this may have been more apparent in patients weighing more to begin with. Greater weight may also predispose to a more rapid progression to the need for insulin supplementation and replacement (i.e. more rapid beta cell failure); and/or may be compounded by specific treatments such as thiazolidinediones and sulphonylureas.(31) In this study, however, insulin treatment did not appear to be delayed on account of patient weight; and in general, weight gain was not observed during treatment with insulin detemir. The weight-sparing property of insulin detemir is well

documented and may occur as a result of a number of pharmacodynamics and pharmacokinetic mechanisms.(31-33)

The decision to initiate treatment should be considered on an individual patient basis. Importantly, however, individualization of therapy should not be used as an excuse not to appropriately intensify diabetes treatment. Despite the recent increased focus on individualization of therapy (6), insulin doses prescribed in this study were similar irrespective of pre-insulin (and during study) glycemic control. With respect of OAD regimen, there was a great deal of heterogeneity in terms of the number and combination of OAD classes, many of which do not fall within current recommendations (10) - 42% of SOLVE participants were on pre-insulin OAD regimens that were inconsistent with these guidelines and their degree of glycemic control. There was a general trend to reduce the number of OAD classes following the initiation of insulin. The largest overall percentage reductions in OAD prescribing were seen for sulphonylureas, and thiazolidinediones. Since all management decisions were performed at the discretion of the investigator, decisions to discontinue therapy were most probably restricted to patients that were deemed either to have not benefited from combination treatment or where risks of hypoglycemia, weight gain, treatment complexity or cost, and/or fluid retention, might have been perceived as higher.

In this study, delays to appropriate treatment intensification resulted in a large number of patients exceeding HbA1c of >9.0% before being considered for insulin initiation. Whilst insulin initiation in these patients was associated with significant improvements in HbA1c, it should be noted that achieving and maintaining good glycemic control requires continued insulin titration and patient support⁽³⁴⁾. Pre-insulin HbA1c has been identified as a key predictor of glycemic control. In a recently published study, multivariate analysis of patients with type 2 diabetes who

had initiated insulin therapy found that pre-insulin HbA1c was responsible for nearly all the explained variance in HbA1c change (35).. Each percentage point increase in pre-insulin HbA1c, reduced the probability of attaining end of study HbA1c <7% by 26% [95% CI 0.68-0.80], prompting the authors of the study to conclude that insulin initiation at lower levels of HbA1c improves goal attainment and independently increases glycemic response.

As this is an observational study, it is not possible to draw firm conclusions concerning the role of individual demographic and treatment variables in determining specific outcomes; additionally, treatment effects may also be exaggerated. Hypoglycemia was recorded retrospectively at each scheduled time point and may, therefore, be subject to recall bias. As such, the reported incidence of hypoglycemia is likely to be an underestimate. Although physicians would have had the opportunity to recommend the use of advanced glucose meters for the purposes of monitoring treatment and reporting hypoglycemia in this study, this practice was not enforced during the study. Despite these weaknesses, the relative risks of hypoglycemia at different time points remain valid. In addition, the large number of patients enrolled and managed by both primary and specialist care would be expected to provide a realistic overview of the process of basal insulin initiation in the treatment of type 2 diabetes management, which is often seen as challenging. However, the inclusion of ethnic minorities was low. No attempt was made specifically to recruit such patients into the study. Minority ethnic groups may be particularly vulnerable to experiencing poor glycemic control and earlier development of complications (36). Although the reason for the non-inclusion of such patients cannot be known, it is possible that their conspicuous absence may reflect inequalities in access to healthcare.

CONCLUSION

Insulin initiation is delayed until late in the course of the disease, in spite of internationally recognized guidelines. The initiation of once-daily insulin detemir by primary and hospital health care providers was associated with substantial improvements in glycemic control, particularly in patients with higher levels of HbA1c at baseline despite a relatively small increase in the unit dose of insulin. Insulin initiation was not associated with weight gain and the incidence of minor hypoglycemic events was low, irrespective of the level of pre-insulin glycemic control.

ACKNOWLEDGEMENT

The SOLVE Study Group comprises: Dr Jean-François Yale and Dr Stuart Ross (Canada), Dr Qiuhe Ji and Dr Chang Yu Pan (China), Dr Marcel Kaiser and Dr Andreas Liebl (Germany), Dr Eddy Karnieli (Israel), Dr Salvatore Caputo and Dr Alberto Maran (Italy), Dr Robert Ligthelm (The Netherlands), Dr Grzegorz Dzida (Poland), Dr Luisa Raimundo (Portugal), Dr Sara Artola and Dr Domingo Orozco-Beltran (Spain), Dr Taner Damçi and Dr Sazi Imamoglu (Turkey), Dr Jiten Vora and Dr Kamlesh Khunti (UK), and Dr Luigi Meneghini (US).

The authors thank Christopher Burton from Point Of Care Medical Consulting for medical writing assistance (supported by Novo Nordisk).

DISCLOSURE

Authors HA and ALS are employees at Novo Nordisk. All other authors have received financial support from Novo Nordisk to attend meetings to discuss the design, analysis and interpretation of the results of the SOLVE study. Authors SC, MK, EK, and LM have also received funding for membership on Novo Nordisk Advisory Boards and/or

consulting services. EK has received institutional research grants from Novo Nordisk. Each of the authors has submitted a completed ICMJE Form for Disclosure of Potential Conflicts of Interest; these are available from the lead author on request.

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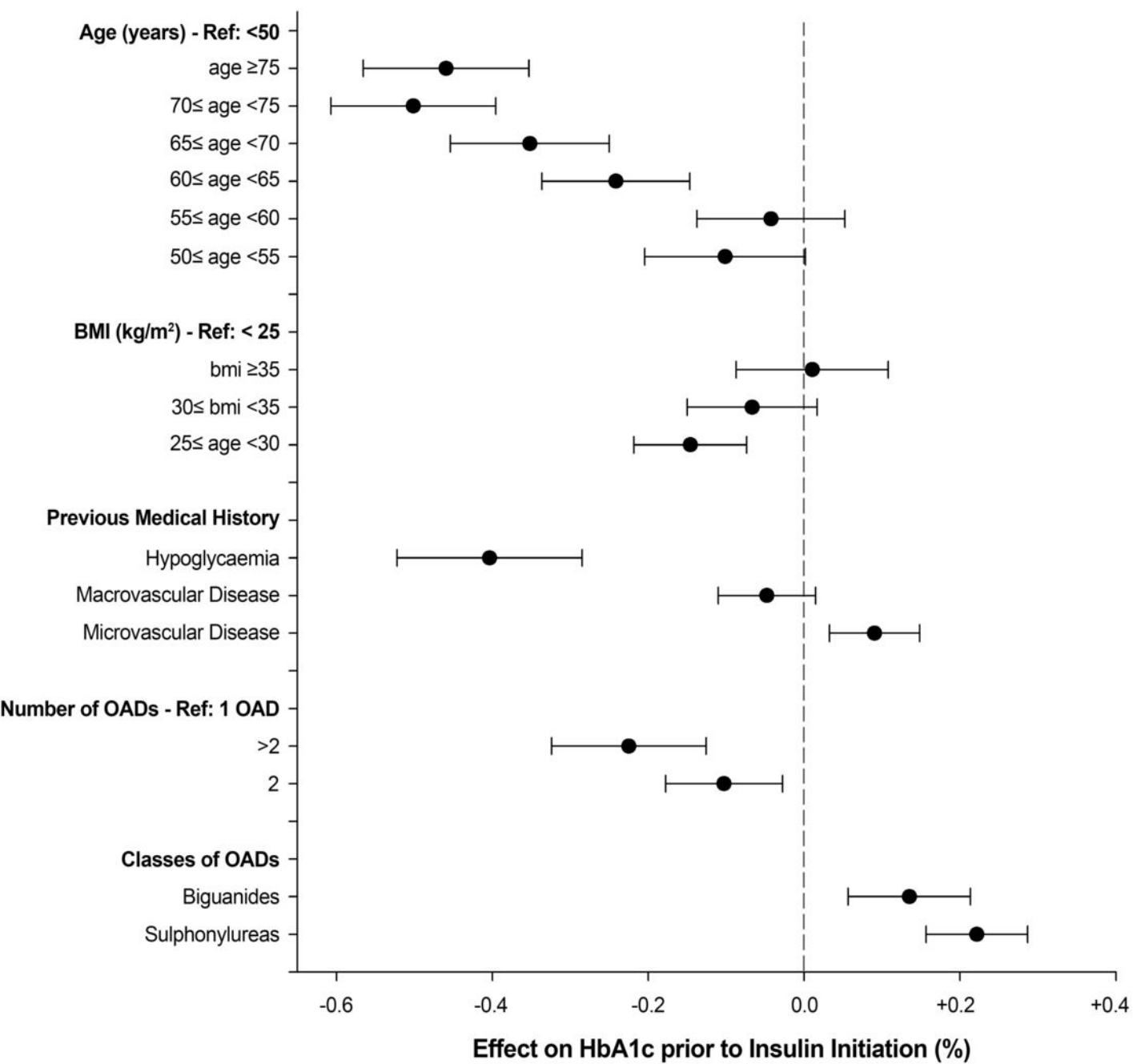
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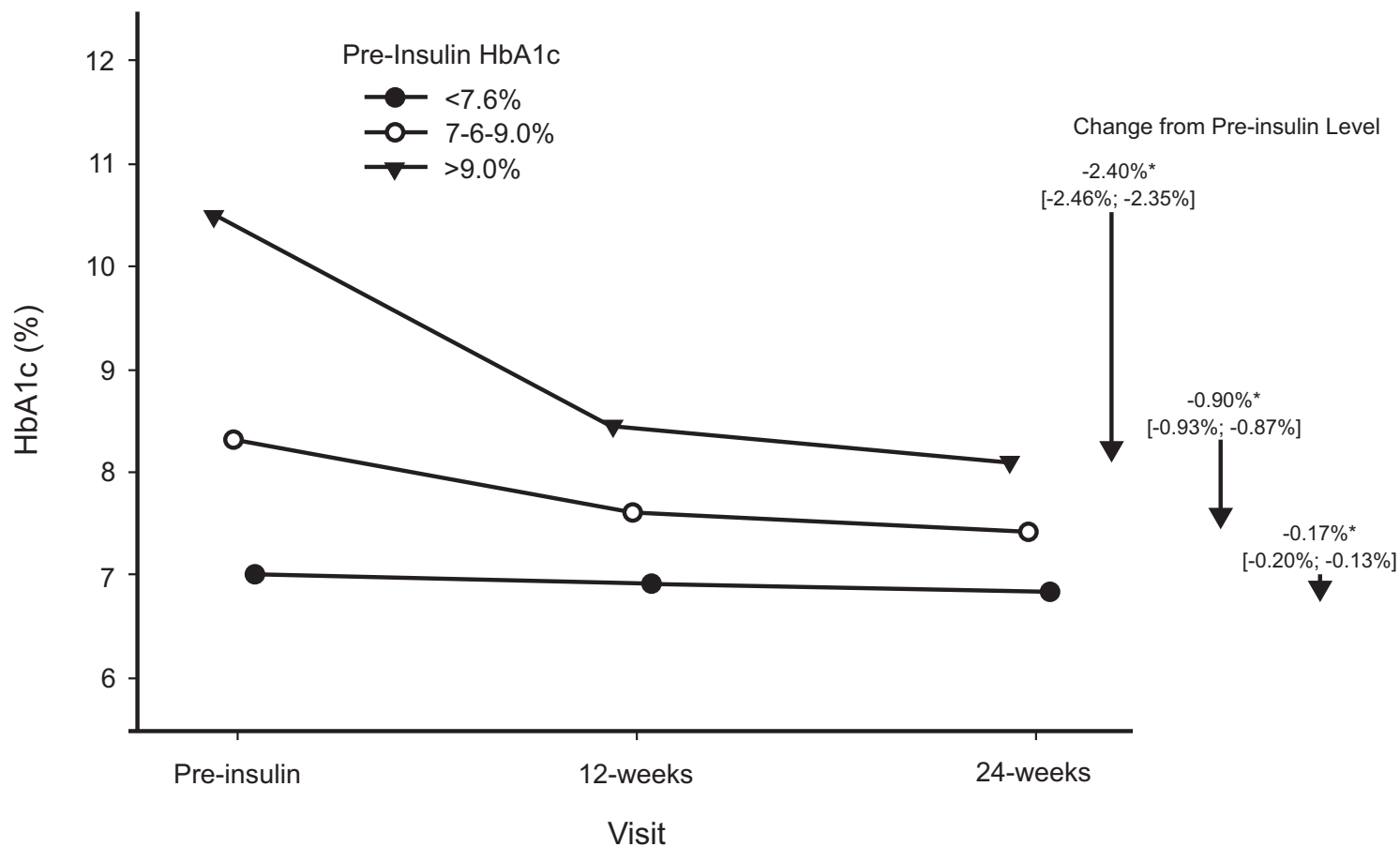
Fig. 1. Predictors of glycemic control prior to insulin initiation

Fig. 2. Changes in (a) HbA1c and (b) FBG by pre-insulin HbA1c

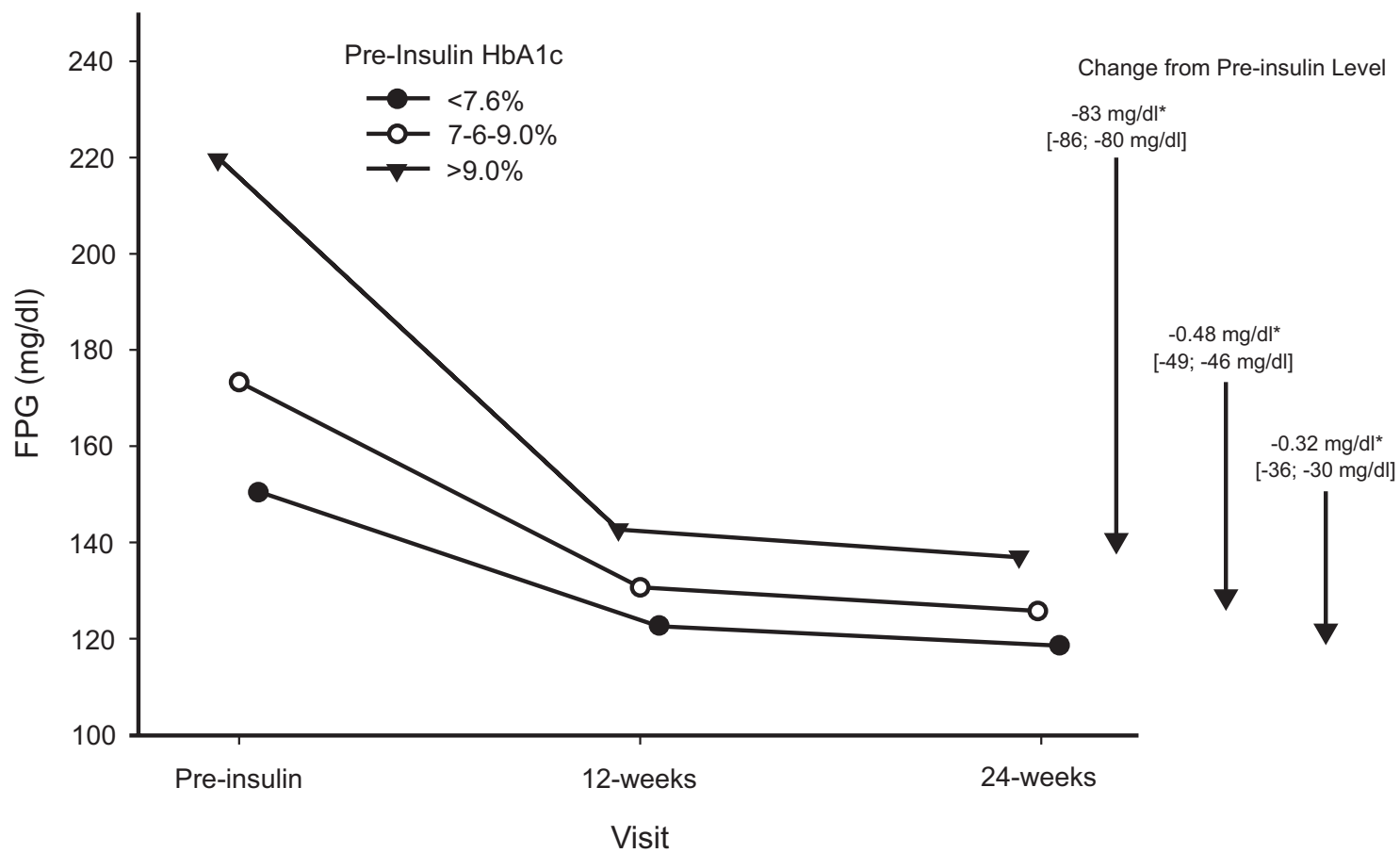
Fig. 3. Self-monitored blood glucose at baseline and end of study by HbA1c subgroup

Fig.4. Insulin dose by HbA1c subgroup

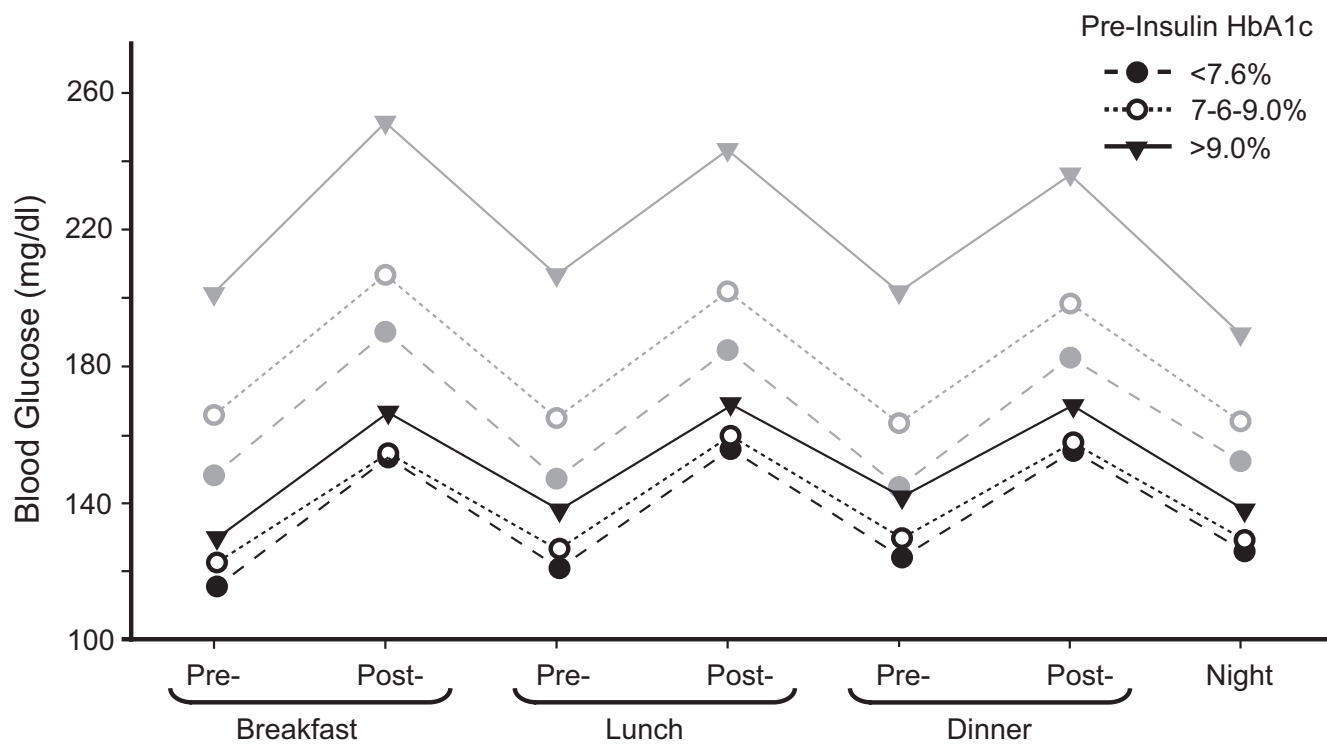




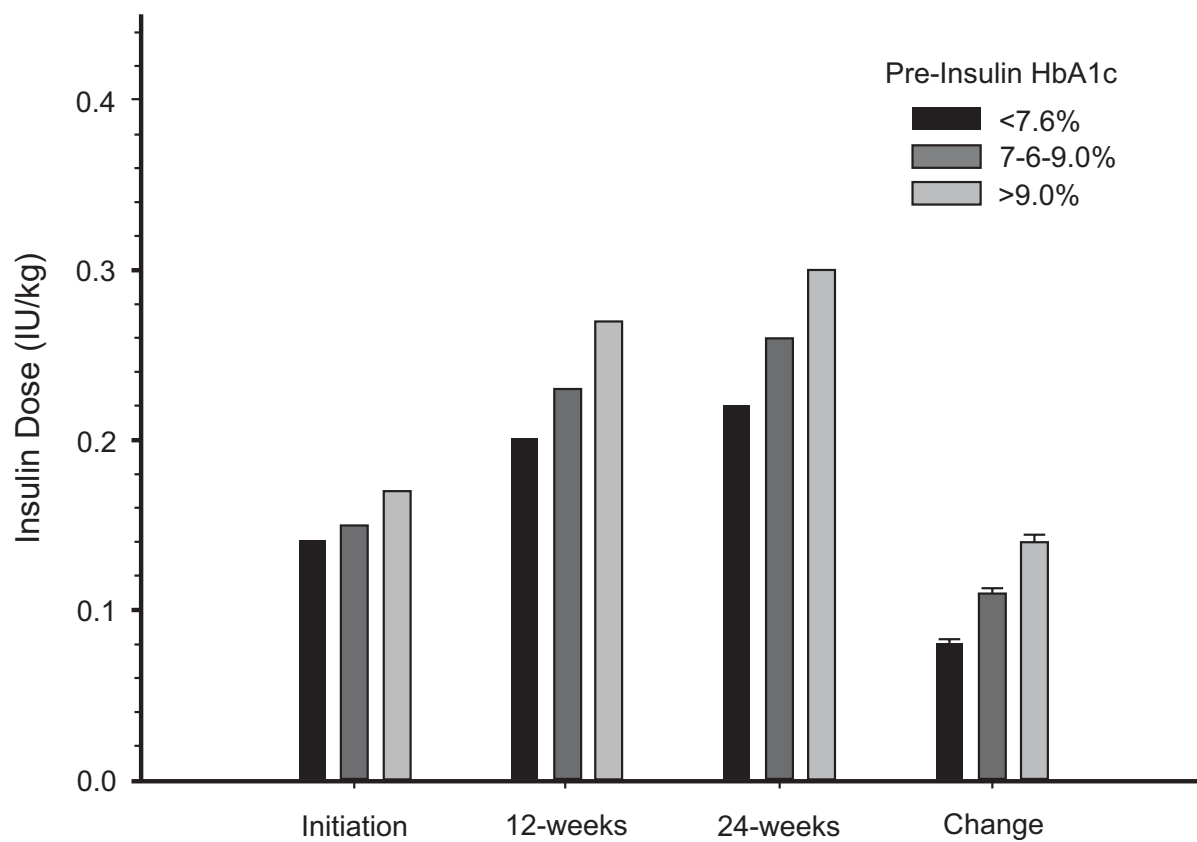
Change from pre-insulin value to 24-weeks provided with 95% confidence intervals and p value
*p<0.001 relative to pre-insulin HbA1c



Change from pre-insulin value to 24-weeks provided with 95% confidence intervals and p value
*p<0.001 relative to pre-insulin FPG



p<0.001 for all changes from pre-insulin values



Error bars indicate 95% confidence interval

Table 1: Patient demography: Total cohort and pre-insulin HbA1c subgroups.

	Pre-Insulin HbA1c			
	<7.6%	7.6-9.0%	>9.0%	Total Cohort
Patients <i>n</i> (%)	2,797 (20.7%)	5,366 (39.7%)	5,363 (39.6%)	17,374
Male (%)	54.6%	53.5%	53.6%	52.9%
Ethnicity				
White	51.1%	73.9%	77.4%	74.2%
Black	0.4%	0.7%	1.1%	0.7%
Other	48.4%	25.4%	21.4%	25.1%
Age (years)	61.1 ± 11.8	63.0 ± 11.1	60.6 ± 11.7	61.6 ± 11.5
Country				
Canada	6.8%	6.9%	7.3%	6.1%
China	41.0%	17.6%	15.5%	18.8%
Germany	16.1%	18.2%	9.4%	12.0%
Israel	2.2%	4.8%	6.9%	4.2%
Italy	14.1%	26.2%	29.9%	26.6%
Poland	9.6%	8.4%	3.4%	6.7%
Portugal	2.0%	1.7%	2.1%	1.7%
Spain	3.1%	5.7%	4.5%	5.6%
Turkey	3.8%	5.9%	12.7%	13.8%
UK	1.4%	4.5%	8.2%	4.4%
Duration of Diabetes (years)	9.0 ± 7.1	10.2 ± 6.9	9.6 ± 6.9	9.8 ± 7.0
Duration of OAD therapy (years)	7.6 ± 6.3	8.8 ± 6.4	8.4 ± 6.7	8.5 ± 6.6
Weight (kg)	77.9 ± 17.1	81.5 ± 17.2	82.2 ± 18.6	80.9 ± 17.7
BMI (kg/m ²)	27.9 ± 5.1	29.3 ± 5.1	29.7 ± 5.6	29.3 ± 5.4
Previous Medical History				
Macrovascular disease	26.9%	28.4%	25.8%	26.6%
Microvascular disease	30.4%	34.6%	33.5%	33.0%
Hypoglycemia	7.5%	5.2%	3.7%	4.9%
HbA1c (%)	7.0 ± 0.6	8.3 ± 0.4	10.5 ± 1.3	8.9 ± 1.6
FBG				

(mg/dl)	151 ± 31	173 ± 38	220 ± 63	185 ± 56
(mmol/l)	8.4 ± 1.7	9.6 ± 2.1	12.2 ± 3.5	10.3 ± 3.1
OAD Treatment				
A-glucosidase inhibitors	17.8%	10.7%	10.6%	12.2%
DPP-IV inhibitor	5.9%	8.6%	7.2%	6.5%
Glinide	17.6%	16.3%	14.5%	16.1%
Metformin	75.6%	82.6%	83.1%	81.3%
Sulphonylurea	49.8%	59.0%	64.0%	59.3%
Thiazolidinedione	10.8%	11.5%	13.1%	12.1%
Number of OADs				
1 x OAD	37.0%	28.3%	26.8%	29.9%
2 x OAD	49.7%	55.9%	55.7%	54.2%
3 x OAD	12.2%	14.6%	15.7%	14.5%
4 x OAD	1.1%	1.2%	1.8%	1.5%

HbA1c – glycosylated hemoglobin A1c; BMI – body mass index; FBG – fasting blood glucose; OAD – oral antidiabetic; DPP-IV - dipeptidyl peptidase-4

Table 2: Incidence and proportion of patients with minor and severe hypoglycemia, according to pre-insulin HbA1c

	Pre-insulin	Interim	Final	Change	p value
Minor hypoglycemia (events per patient year)					
<7.6%	2.913	2.211	2.160	-0.753	0.8
7.6-9.0%	1.701	1.875	1.887	0.186	0.004
>9.0%	1.225	1.920	2.033	0.809	<0.001
Severe hypoglycemia* (events per patient year)					
<7.6%	0.069	0	0.014	-0.055	0.02
7.6-9.0%	0.037	0.003	0.005	-0.032	<0.001
>9.0%	0.038	0.005	0.004	-0.034	<0.001
Any minor hypoglycemic events within the preceding 4 weeks of visit (N (%))					
<7.6%	159 (6.3%)	165 (6.6%)	159 (6.3%)		
7.6-9.0%	190 (4.0%)	291 (6.2%)	297 (6.3%)		
>9.0%	142 (3.2%)	292 (6.7%)	269 (6.0%)		
Any severe hypoglycemic events* within the preceding 12 weeks of visit (N (%))					
<7.6%	12 (0.5%)	0 (0.0%)	2 (0.1%)		
7.6-9.0%	24 (0.5%)	3 (0.1%)	5 (0.1%)		
>9.0%	16 (0.4%)	6 (0.1%)	4 (0.1%)		

*Severe hypoglycemia was recorded as events recalled within the preceding 12 weeks in all countries (with the exception of the United Kingdom where this timeframe was within the preceding 4 weeks).