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An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The A$_1$chieve study☆,☆☆

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ABSTRACT

Aim: The aim of A$_1$chieve was to remedy the deficit of data on the efficacy and safety of insulin analogues in routine clinical care in less well-resourced/newly developed countries.
Methods: A non-interventional, 6-month, observational study of 66,726 people with type 2 diabetes, both insulin users and non-insulin users, started on insulin detemir, insulin aspart or biphasic insulin aspart in 28 countries across four continents.
Results: Baseline HbA$_{1c}$ (±SD) was poor: 9.5 ± 1.8%. At 6 months, improvement was −2.1 ± 1.7% in the entire cohort, and −2.2 ± 1.7% and −1.8 ± 1.7% for prior non-insulin users and insulin users. All three analogue therapies gave similar results, again independently of prior insulin use, but also from seven pre-specified country groupings. Overall, hypoglycaemia did not increase in those new to insulin, and fell in those switching insulins. There was no change in body weight (−0.1 ± 3.7 kg), while lipid profile and systolic blood pressure (−6.3 ± 17.1 mmHg) were improved.
Conclusions: Beginning insulin analogue therapy in people with type 2 diabetes and poor blood glucose control is associated with marked improvements in diverse aspects of vascular risk factor profile without evidence of clinically significant safety or tolerability problems.

1. Introduction

The progressive nature of type 2 diabetes (T2D) over time results in the majority of people with diabetes being unable to maintain HbA$_{1c}$ targets on a management regimen of lifestyle changes with oral glucose-lowering drugs (OGLDs) [1,2]. Furthermore, suboptimal glycaemic control commonly persists even in insulin users [3]. What is sometimes described as ''clinical inertia'' or ''patient resistance'' further results in people remaining on inappropriate therapy regimens for too long [4–6]. It is known that when therapies are actively

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assessed, titrated and increased in number, glycaemic targets are more likely to be achieved [7]. Accordingly, the American Diabetes Association (ADA) and International Diabetes Federation (IDF) guidelines emphasise the importance of continually modifying therapy regimens when HbA_{1c} goals are no longer maintained. In practice, however, most people with T2D still experience significant periods when their HbA_{1c} levels are well above 53–64 mmol/mol (7.0–8.0%), increasing their risk of developing diabetes-related health complications [8–10].

Modern insulin analogues were designed to aid achievement of better glycaemic control while addressing concerns over tolerability, notably in regard of hypoglycaemia and body weight gain [11,12], and their clinical benefits have been assessed in randomised controlled trials (RCTs) and observational studies [6,13–19]. These studies have shown that a change of therapy from OGLDs or conventional insulin preparations to insulin analogues can be associated with clinically significant improvements in efficacy measures, while being well tolerated.

Well-designed RCTs are a rigorous way of assessing treatments in a restricted population sample. However, they focus on a selected patient group under intensive clinical supervision, and may not represent the reality of the people in everyday life, or when seen in normal clinical practice. Furthermore, these studies are often performed in restricted geographical areas, such that information from less well-resourced countries is relatively sparse. While there are limitations with observational studies with regard to potential bias, study effects and lack of a control group, they can have less stringent inclusion and exclusion criteria, and, being much less costly, can address larger numbers of people in more diverse environments [20–22].

The aim of the A_1chieve study was, therefore, to broaden the knowledge of the clinical safety and effectiveness of insulin analogues in a large and diverse population from a globally broad variety of clinical care. As the largest observational study ever conducted in insulin therapy, A_1chieve has explored both beginning insulin in non-insulin users and switching to these analogues in more than 65,000 people from 28 different countries across four continents. Part of the intention behind the study was to explore how the insulins performed in countries in which resource, practice and genetic differences might be expected (or not) to influence outcomes.

2. Methods

2.1. Study design

This was a 24-week, international, prospective, multicentre, non-interventional, observational study of people with T2D who had begun using basal insulin detemir (Levemir®, Novo Nordisk, Denmark), bolus insulin aspart (NovoRapid®, Novo Nordisk) and biphasic insulin aspart 30 (NovoMix® 30, Novo Nordisk), alone or in combination, to evaluate their clinical safety and effectiveness in routine clinical use outside the Western economies [23]. The study was carried out in 3166 centres in 28 countries across Asia, Africa, Latin America and Europe, grouped into seven geographical regions: China; South Asia (Bangladesh, India, Pakistan); East Asia (Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan); north Africa (Algeria, Morocco, Tunisia, Libya); Middle East/Gulf (Egypt, Iran, Jordan, Turkey, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, Yemen); Latin America (Argentina, Mexico) and Russia. Participants were recruited between January 2009 and June 2010.

The insulin therapies were prescribed by a physician in the course of normal clinical practice, were commercially available and were funded according to local practice in normal routine care. Thus, the participant and advising physician determined the choice of insulin, the starting dose, administration frequency and any later changes to either dose or frequency. In the study, insulin analogues were used in accordance with the licensed approval from the local regulatory authority. Changes to OGLDs at the time of starting the insulin analogue, or thereafter, were entirely at the discretion of the participant and advising physician.

There were no defined study-related procedures; measurements were made by the treating physician team only as determined by normal clinical care. Thus, safety and effectiveness of therapy were determined from measurements made at usual clinic visits. Trial visits were defined as baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visit. Data were collected from the physicians' clinical notes, and participants' recall and self-monitoring diary/meter at each visit, as available. This information was transferred to a standard case report form (CRF).

2.2. Participants

A total of 66,726 people were included in the study. Any current and prior medications were acceptable for participant inclusion other than the insulin analogues being evaluated. Women who were pregnant, breast-feeding or had the intention of becoming pregnant were excluded. Ethics committee approval was obtained for each country, and signed informed consent from all participants. Participants were free to withdraw at will at any time. If they withdrew, the data collected were used for analysis until the point when consent was withdrawn. Safety events were reported according to the protocol. All investigators underwent specific training on the study protocol, CRF completion, informed consent and safety reporting procedures.

2.3. Assessments and outcome measures

The primary objective of this study was to evaluate the clinical safety of the insulin analogues by the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, considered related to the study insulin between baseline and final visit. Secondary safety assessments were the change in number of hypoglycaemic events in the last 4 weeks before interim and final visits, compared with the last 4 weeks before baseline visit, the change in number of nocturnal hypoglycaemic events during these periods and the number of adverse drug reactions (ADRs) from baseline to final visit. Major hypoglycaemic events were defined as events with severe central nervous system symptoms, consistent with hypoglycaemia, for which the person was unable to self-treat,

and accompanied by plasma glucose <3.1 mmol/L or 56 mg/dL, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration. Minor hypoglycaemia was any event, with or without symptoms of hypoglycaemia, with a plasma glucose reading below 3.1 mmol/L or 56 mg/dL that the participant was able to self-treat. Nocturnal hypoglycaemia was defined as a symptomatic event consistent with hypoglycaemia that occurred during sleep between bedtime after the evening insulin injection and before getting up in the morning.

Efficacy assessments were change in HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and body weight between baseline and interim and final visits, and change in systolic blood pressure (SBP) and lipid profile at final visit. All laboratory measurements were made in local laboratories and were thus subject to local standardisation and quality control procedures. Quality-of-life assessments were made at baseline and final visit, and are communicated in a separate report. The rationale for choosing each study insulin regimen was recorded, with the aim of determining which factors influence the selection criteria of the specific regimen.

2.4. Statistical methods

Analyses were performed for the entire cohort (all participants), for the entire cohort divided as prior insulin-treated or insulin-naïve, for the insulin analogue regimen used and by geographical regions (as above). As this was not a randomised trial, and as the characteristics determining choice of insulin regimen, time of starting insulin and concomitant medical conditions were not fully known, comparison between regimens, prior insulin use or not and regions is reported as a matter of observation only. The insulin regimens were defined as biphasic insulin aspart (premix) alone, insulin detemir alone, insulin aspart alone or insulin aspart with a basal insulin (this could include insulin detemir), or other. In each instance, the use or non-use of concurrent OGLDs was allowed.

The sample size was based on the number of people (20,000) exposed for 6 months required to confirm at 95% confidence a frequency of any one ADR of ≥15 events/100,000 person-years. This rate, for example, would detect a rate of major hypoglycaemia as reported in any published clinical trial. Analysis of all variables, including safety and efficacy outcomes, was performed using any participant entered into the study who had the data relevant to that analysis. Continuous variables were summarised using descriptive statistics and discrete variables were summarised using frequency tables (*n*, %). All statistical analyses were two-sided, using a pre-specified 5% significance level, unless otherwise stated. For hypoglycaemia change from baseline, the percentage of people reporting at least one event was analysed using Fisher's exact test. Prevalence data rather than incidence rate were tested as low event rates, in the circumstances where some people had recurrent events, could not be modelled in a statistically sensitive way. Change from baseline HbA_{1c}, FPG, PPPG and blood lipids was analysed using an analysis of covariance (ANCOVA) model with baseline characteristics as covariates. The percentage of patients having HbA_{1c} <7.0% at 24 weeks was analysed using a logistic regression model using the factors and covariates of treatment, country, region, age, gender, ethnicity, body mass index (BMI), duration of diabetes, smoking status, total blood cholesterol, high-density lipoprotein (HDL) cholesterol, SBP and pre-study glucose-lowering therapy. Corresponding baseline HbA_{1c} was included as a fixed effect. All data were analysed by Novo Nordisk using SAS (Version 9.1.3).

3. Results

3.1. Study participants

Participant characteristics for the entire cohort and by pre-study therapy (insulin-naïve or insulin users) are given in Table 1. Use of OGLDs prior to beginning insulin analogues is given in Table 1. Prior to enrolment in the study, 58.2% of patients were being treated with OGLDs alone, 23.8% were receiving OGLD + insulin therapy, 8.1% insulin only and 9.0% no medication for diabetes.

The regional distribution of participants is given in Table 1. Notable regional differences in baseline characteristics compared with the global cohort were that the majority of study participants in Russia were female (70.9%), people from Latin America and north Africa reported the longest duration of diabetes (12.0 ± 8.3 and 11.5 ± 7.2 years, respectively), and BMI was highest in the Middle East/Gulf region (30.4 ± 5.5 kg/m^2) and in Russia (31.1 ± 5.3 kg/m^2). Baseline HbA_{1c} was similar in all regions, whether prior insulin-treated or not (data not shown), being highest in Latin America (85 ± 24 mmol/mol [9.9 ± 2.2%]) and lowest in south Asia (78 ± 16 mmol/mol [9.3 ± 1.4%]).

Participant characteristics were comparable between the different types of insulin analogues started (data not shown). By prior insulin therapy, insulin-experienced people were older than the insulin-naïve cohort (55.6 years vs. 53.2 years) and had a higher BMI (27.9 kg/m^2 vs. 26.7 kg/m^2). Baseline HbA_{1c} was similar (79 mmol/mol vs. 80 mmol/mol [9.4% vs. 9.5%]), while diabetes duration was 10.8 years vs. 6.6 years.

The reasons given for change in therapy by treating physicians were similar across all subgroups, with the most common reasons being to improve glycaemic control (96%), reduce the risk of hypoglycaemia (31%) and reduce plasma glucose variability (30%).

Of the 66,726 patients enrolled, all 66,726 (100%) were exposed and constituted the full analysis set and the safety analysis set, while 53,002 (79.4%) constituted the efficacy analysis set (definitions above). A total of 9335 (14.0%) withdrew from the study, the most common reason being failure to maintain contact with their physician, 6170 (9.2%); 64 (0.1%) withdrew due to an ADR; and the remaining 3101 (4.6%) for a variety of other reasons. As a result, 57,391 (86.0%) people completed the study.

3.2. Entire cohort and by prior insulin usage

3.2.1. Blood glucose lowering and insulin dose

In the insulin-naïve cohort, total daily insulin dose at 24 weeks had been titrated up to 36.4 ± 20.9 U/day. In prior insulin users,

Table 1 – Participant numbers and characteristics for the entire cohort and by pre-study therapy.

	Entire cohort	Insulin-naïve	Prior insulin users
n (%)	66,726 (100)	44,872 (67.2)	21,854 (32.8)
Sex, M/F (%)	55.6/44.4	57.3/42.7	51.9/48.1
Age (years)	54.0 (12.0)	53.2 (11.6)	55.6 (12.5)
Body weight (kg)	72.9 (15.0)	71.7 (14.4)	75.3 (15.9)
BMI (kg/m^2)	27.1 (5.0)	26.7 (4.7)	27.9 (5.5)
Diabetes duration (years)	8.0 (6.2)	6.6 (5.4)	10.8 (6.8)
HbA_{1c} (mmol/mol)	80 (19)	80 (19)	79 (20)
HbA_{1c} (%)	9.5 (1.7)	9.5 (1.7)	9.4 (1.8)
Prior OGLDs, *n* (%)			
Metformin	44,801 (82.0)	32,006 (82.4)	12,795 (81.1)
Sulfonylureas	37,086 (67.9)	29,645 (76.3)	7441 (47.2)
Thiazolidinediones	10,578 (19.4)	8087 (20.8)	2491 (15.8)
One/two/>two	16,193 (29.6)/27,466 (50.3)/10,981 (20.1)	8519 (21.9)/21,372 (55.0)/8971 (23.1)	7674 (48.6)/6094 (38.6)/2010 (12.7)
Geographic region, *n* (%)			
China	11,020 (100)	8206 (74.4)	2814 (25.6)
East Asia	10,032 (100)	6594 (65.7)	3438 (34.3)
Latin America	1138 (100)	636 (55.9)	502 (44.1)
Middle East + Gulf	14,976 (100)	7501 (50.1)	7475 (49.9)
North Africa	4039 (100)	1969 (48.7)	2070 (51.3)
Russia	3074 (100)	1899 (61.8)	1175 (38.2)
South Asia	22,447 (100)	18,067 (80.5)	4380 (19.5)

Data are *n* (%), %, or mean (SD).

pre-analogue insulin dose was 41.0 ± 22.9 U/day, total starting insulin dose was 41.0 ± 21.4 U/day and, at 24 weeks, was 46.7 ± 24.5 U/day.

Blood glucose control improved markedly and statistically significantly between baseline and 6 months in the whole cohort (Table 2: HbA_{1c} −23 mmol/mol [−2.1%], FPG −3.8 mmol/L, PPPG −5.4 mmol/L), and was clinically similar in the insulin-naïve and prior insulin use groups, although numerically larger in the insulin-naïve group (Table 2). Overall, the percentage of participants achieving an HbA_{1c} level of <53 mmol/mol (<7.0%) increased from 3.9% at baseline to 31.8% at week 24.

OGLD usage while starting people on insulin showed that metformin was continued in around 78% of people, for all insulin regimens. While most people starting basal insulin continued using sulfonylureas (79%), 55% or less continued using sulfonylureas with other regimens. Approximately 50% of those using a thiazolidinedione discontinued this on all regimens. Metformin use remained unchanged in people transferring insulin regimen at the start of the study. Sulfonylurea use was continued by 90% of people changing to basal insulin therapy use but discontinued by 40% of the cohort transferring to other regimens. Thiazolidinedione use continued in 70% of prior insulin users. Overall, the percentage of people who were being treated with more than two OGLDs before starting any insulin regimen was reduced by 68% (23.1% pre-study, 7.3% baseline, 7.1% end of study) and by 50% in people changing insulin therapy (12.7, 6.3 and 6.6% respectively).

3.2.2. *Hypoglycaemia*

The reported rate of all hypoglycaemic episodes in the 4 weeks before study visits differed for the insulin-naïve and prior insulin use cohorts (Table 2). In the insulin-naïve population reported rates of overall hypoglycaemia increased marginally from 1.07 to 1.19 events/person-year, with no statistical difference in the proportion of people having an event. In the prior insulin users, the reported rate decreased from 7.31 to 2.48 events/person-year before the end of the study, associated with a statistically significant fall ($p < 0.0001$) in the number of people affected. The rate of minor hypoglycaemic events increased in the insulin-naïve cohort, from 0.98 to 1.18 events/person-year (people affected $p = 0.0056$), but the rate of nocturnal hypoglycaemia was clinically unchanged (0.28 vs. 0.26 events/person-year). In the prior insulin use cohort, the incidence of minor and nocturnal events decreased from 6.50 to 2.47 and 2.24 to 0.58 events/person-year (people affected both $p < 0.0001$), respectively, during the study period.

On pre-study therapy, major hypoglycaemic episodes were more frequent in the prior insulin use population (0.81 events/person-year) than in the insulin-naïve population (0.09 events/person-year at baseline), and reported incidence in the prior insulin users reduced to <0.01 events/person-year after 24 weeks (Table 2, people affected $p < 0.0001$).

3.2.3. *Body weight, blood lipids and blood pressure control*

For both the entire cohort and the insulin-naïve population, mean body weight change over 24 weeks was statistically but not clinically significant (Table 2, mean +0.1 kg, $p < 0.001$). No change in weight occurred in the prior insulin users.

Total cholesterol levels were reduced in the entire cohort from a mean of 5.3 mmol/L to 4.8 mmol/L after 24 weeks (Table 2, −0.5 mmol/L, $p < 0.001$). Low-density lipoprotein (LDL) cholesterol levels fell from a mean of 3.1 mmol/L to 2.8 mmol/L after 24 weeks (−0.4 mmol/L, $p < 0.001$), and a significant reduction was also seen in triglyceride levels (−0.3 mmol/L, $p < 0.001$). There was a small increase in HDL

Table 2 – Glucose control and body weight for the entire cohort and by pre-study therapy at baseline and after 24 weeks of insulin analogue therapy.

		Entire cohort		Insulin-naïve		Prior insulin users	
		Baseline	24 weeks	Baseline	24 weeks	Baseline	24 weeks
HbA_{1c}, mmol/mol/%	*n*	44,661		30,369		14,292	
	Baseline/24 weeks	80 (19)/9.5 (1.7)	57 (12)/7.4 (1.1)	80 (19)/9.5 (1.7)	57 (11)/7.4 (1.0)	79 (20)/9.4 (1.8)	60 (13)/7.6 (1.2)
	Change, *p*	−23 (19)/−2.1 (1.7), <0.001		−23 (19)/−2.2 (1.7), <0.001		−19 (19)/−1.8 (1.7), <0.001	
FPG, mmol/L	*n*	48,191		33,087		15,104	
	Baseline/24 weeks	10.9 (3.5)	7.1 (1.9)	11.2 (3.4)	7.1 (1.8)	10.5 (3.7)	7.2 (2.2)
	Change, *p*	−3.8 (3.5), <0.001		−4.1 (3.3), <0.001		−3.2 (3.8), <0.001	
PPPG, mmol/L	*n*	33,742		23,334		10,408	
	Baseline/24 weeks	15.1 (4.4)	9.7 (2.9)	15.5 (4.3)	9.8 (2.9)	14.2 (4.5)	9.7 (3.0)
	Change, *p*	−5.4 (4.5), <0.001		−5.8 (4.4), <0.001		−4.5 (4.6), <0.001	
Weight, kg	*n*	50,059		33,716		16,343	
	Baseline/24 weeks	73.3 (14.8)	73.3 (14.1)	72.1 (14.3)	72.2 (13.5)	75.7 (15.7)	75.7 (15.1)
	Change, *p*	0.1 (3.7), <0.001		0.1 (3.7), <0.001		−0.0 (3.6), 0.081	
SBP, mmHg	*n*	45,285		29,595		15,690	
	Baseline/24 weeks	134.2 (17.8)	127.9 (13.5)	134.0 (17.7)	127.3 (13.3)	134.7 (18.0)	129.0 (13.7)
	Change, *p*	−6.3 (17.1), <0.001		−6.6 (17.4), <0.001		−5.7 (16.6), <0.001	
Total cholesterol, mmol/L	*n*	20,293		11,994		8299	
	Baseline/24 weeks	5.3 (1.3)	4.8 (1.0)	5.4 (1.3)	4.8 (1.0)	5.2 (1.3)	4.8 (1.0)
	Change, *p*	−0.5 (1.2), <0.001		−0.6 (1.2), <0.001		−0.4 (1.2), <0.001	
Triglycerides, mmol/L	*n*	19,856		11,672		8184	
	Baseline/24 weeks	2.1 (1.1)	1.8 (0.7)	2.1 (1.1)	1.7 (0.7)	2.0 (1.1)	1.8 (0.7)
	Change, *p*	−0.3 (0.9), <0.001		−0.4 (1.0), <0.001		−0.3 (0.9), <0.001	
HDL cholesterol, mmol/L	*n*	17,306		10,189		7117	
	Baseline/24 weeks	1.1 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.1 (0.4)	1.2 (0.4)
	Change, *p*	0.1 (0.4), <0.001		0.1 (0.4), <0.001		0.0 (0.4), <0.001	
LDL cholesterol, mmol/L	*n*	17,494		10,304		7190	
	Baseline/24 weeks	3.1 (1.0)	2.8 (0.9)	3.2 (1.0)	2.7 (0.9)	3.1 (1.1)	2.8 (0.9)
	Change, *p*	−0.4 (1.0), <0.001		−0.4 (1.0), <0.001		−0.3 (1.1), <0.001	
Hypoglycaemia (event per person-year/percent with event)							
Overall	Baseline/24 weeks	3.11/8.9	1.61/5.9	1.07/4.2	1.19/4.4	7.31/18.4	2.48/8.9
	[a]*p*	<0.0001		0.1713		<0.0001	
Minor	Baseline/24 weeks	2.79/8.5	1.60/5.8	0.98/4.0	1.18/4.4	6.50/17.6	2.47/8.9
	[a]*p*	<0.0001		0.0056		<0.0001	
Nocturnal	Baseline/24 weeks	0.93/4.0	0.36/1.8	0.28/1.6	0.26/1.3	2.24/9.0	0.58/2.9
	[a]*p*	<0.0001		0.0012		<0.0001	
Major	Baseline/24 weeks	0.33/1.5	0.01/0.03	0.09/0.5	0.00/0.02	0.81/3.5	0.01/0.07
	[a]*p*	<0.0001		<0.0001		<0.0001	

Data are mean (SD), *n* or incidence.

[a] *p*-value is for difference in percent of people with at least one event.

cholesterol levels during the study (+0.1 mmol/L, $p < 0.001$). Results were similar for the insulin-naïve and prior insulin use populations (Table 2).

SBP fell significantly in the entire cohort, from a mean of 134 to 128 mmHg after 24 weeks of treatment (−6.3 mmHg; $p < 0.001$). The absolute levels at baseline and 24 weeks, and the change between these times, were very similar for the prior insulin use and insulin-naïve populations.

3.2.4. *SADRs and serious adverse events*

In total, 39 SADRs were reported by 36 participants after beginning insulin analogues (0.13 events/100 patient-years). Of these, 28 people suffered a hypoglycaemic SADR. Four participants were reported to have had a serious hyperglycaemic event, one inadequate control, and ketoacidosis was observed in two people.

During the study, 214 participants had 259 serious adverse events (SAEs; 0.84 events/100 patient-years). The largest class reported was of metabolism and nutrition disorders (51 events in 50 people), of which hypoglycaemia accounted for the majority (31 events in 30 patients). The incidence of cardiac disorders was second highest with 44 events in 40 patients. Out of the total 259 SAEs, 63 events had fatal outcomes.

3.3. *Insulin regimens*

3.3.1. *Insulin dose*

In the insulin-naïve populations, starting insulin dose (0 weeks) was lowest when insulin detemir was begun (18.0 U/day), and increased to 26.7 U/day at 24 weeks (Table 3). However, even smaller increases in insulin dose (none at all for aspart alone) were seen for the other insulin regimens, although from higher baseline doses. Overall insulin use was higher in those started on insulin aspart plus basal insulin. In the insulin-experienced population, pre-study insulin dose appeared to be lower in the population starting insulin detemir, which seemingly accounts for this group having the lowest daily dose at 24 weeks (Table 3). In all groups, however, the insulin doses were 10–20% higher at 24 weeks than prior or starting insulin doses. Pre-study insulin dose was highest in patients switching to an aspart + basal insulin regimen (51.8 U/day). After 24 weeks treated with an insulin analogue, the dose was 63.3 U/day.

3.3.2. *Blood glucose control including hypoglycaemia*

Clinically meaningful improvements in overall blood glucose control were found with all insulin regimens in both the insulin-naïve and insulin-experienced populations, but were larger for all insulin analogues in the insulin-naïve population (Table 3). For both populations, the regimen giving the biggest improvements was insulin aspart + basal insulin (as above, the groups with the highest insulin doses). This pattern was echoed for both FPG and PPPG control, where, again, there was no obvious differential effect of insulin type between these pre- and post-meal measures, although, again, the biggest improvements were in the insulin-naïve populations (Table 3).

When HbA_{1c} change from baseline was analysed using ANCOVA with regimen, region, sex, smoking status and pre-study therapy as factors, and age, BMI, duration of diabetes and baseline HbA_{1c} as covariates, significant differences in HbA_{1c} reduction were found between insulin aspart + basal insulin compared with all other regimens ($p < 0.001$).

In the insulin-naïve cohort, reported overall hypoglycaemia moved erratically by insulin regimen, increasing most with the combined insulin regimen (people affected $p < 0.0001$), and not at all with insulin aspart alone (Table 3). For prior insulin users, reported hypoglycaemia fell markedly from the 4 weeks before baseline to the same period before 24 weeks (people affected all $p < 0.0001$), an effect greatest for those using insulin detemir. Major hypoglycaemia was reported too infrequently towards the end of study to do further analyses. In general, the changes in nocturnal hypoglycaemia tended to echo those of the overall change (Table 3).

3.3.3. *Body weight, lipid profile and blood pressure*

Changes in body weight in the study (small reductions in all groups and with all insulin regimens, Table 3) were very consistent between insulins. The same was true for the reduction in SBP, which echoed that of the entire cohort for all insulins (Table 3). Reductions in serum triglycerides were also very similar between insulin regimens, although slightly different between insulin-naïve and non-naïve populations. The same was true of LDL cholesterol, while HDL cholesterol was unchanged with all regimens in both populations (Table 3).

3.4. *Regional differences*

3.4.1. *Insulin doses*

There were differences in starter insulin doses between regions, with the Middle East/Gulf being highest at around 42 U/day and South and East Asia being lowest (26 and 27 U/day, respectively) (Table 4). This pattern was exaggerated at 24 weeks, when the Middle East/Gulf region had increased to a mean of 53 U/day but there was little change in South Asia (26 U/day) or in China (increasing only from 31 to 32 U/day).

3.4.2. *Blood glucose control including hypoglycaemia*

Although baseline measure of blood glucose control were very similar between regions, the largest reductions in HbA_{1c} were seen in China (−28 mmol/mol [−2.5%]), and smallest in north Africa (−18 mmol/mol [−1.6%]), but most clustered closely around the reduction for the entire cohort (Table 4). While north Africa also tended to have the lowest changes in FPG and PPPG, no particular pattern emerged in other regions and, in particular, there was no suggestion that fasting and postprandial improvements in control moved independently between regions.

Reductions in overall hypoglycaemia rates were reported from all regions, but reported baseline rates varied considerably by region (Table 4). Furthermore, in Russia the proportions of people affected (15.4% at baseline and 15.3% at 24 weeks, NS) did not reflect the event rate (Table 4). In other regions, the proportion of people affected fell significantly ($p < 0.001$, except China $p = 0.018$). In general, the falls in event

Table 3 – Baseline and 24-week data for effectiveness and safety outcomes by insulin analogue regimen started.

		Insulin-naïve				Prior insulin users			
		Biphasic aspart	Insulin detemir	Insulin aspart alone	Insulin aspart + basal	Biphasic aspart	Insulin detemir	Insulin aspart alone	Insulin aspart + basal
Insulin dose, U/day	*n*	27,591	12,078	2751	1593	13,318	3467	1145	2512
	Pre-study	–	–	–	–	40.5 (21.3)	31.8 (19.7)	35.1 (18.9)	51.8 (26.1)
	Baseline	28.9 (12.4)	18.0 (9.9)	27.7 (12.0)	43.0 (17.7)	40.6 (18.7)	26.7 (15.1)	30.0 (15.9)	56.6 (22.9)
	Week 24	32.6 (16.1)	26.7 (15.1)	27.7 (12.7)	47.0 (23.0)	45.6 (21.8)	34.4 (20.1)	36.9 (19.9)	63.3 (27.9)
HbA_{1c}, mmol/mol/%	*n*	18,459	8459	1764	1127	8574	2122	709	1869
	Baseline	80 (19)/9.5 (1.7)	80 (18)/9.5 (1.6)	81 (20)/9.6 (1.8)	87 (23)/10.1 (2.1)	79 (20)/9.4 (1.8)	78 (19)/9.3 (1.7)	77 (21)/9.2 (1.9)	79 (20)/9.4 (1.8)
	Week 24	56 (11)/7.3 (1.0)	57 (12)/7.4 (1.1)	56 (11)/7.3 (1.0)	56 (13)/7.3 (1.2)	58 (13)/7.5 (1.2)	60 (14)/7.6 (1.3)	58 (13)/7.5 (1.2)	58 (13)/7.5 (1.2)
	Change, *p*	−24 (19)/−2.2 (1.7) <0.001	−23 (18)/−2.1 (1.6) <0.001	−25 (20)/−2.3 (1.8) <0.001	−51 (22)/−2.8 (2.0) <0.001	−20 (19)/−1.8 (1.7) <0.001	− 38 (19)/−1.6 (1.7) <0.001	− 19 (21)/−1.7 (1.9) <0.001	−22 (19)/−2.0 (1.7) <0.001
FPG, mmol/L	*n*	20,678	8560	2029	1221	9206	2182	774	1905
	Baseline	11.1 (3.4)	11.2 (3.2)	11.4 (4.0)	11.9 (4.1)	10.6 (3.8)	9.9 (3.3)	10.1 (3.6)	10.3 (3.5)
	Week 24	7.1 (1.8)	7.0 (1.9)	7.6 (2.2)	7.0 (1.7)	7.3 (2.2)	7.3 (2.3)	7.3 (2.2)	7.0 (1.9)
	Change, *p*	−4.0 (3.3) <0.001	−4.2 (3.2) <0.001	−3.8 (3.3) <0.001	−4.9 (4.2) <0.001	−3.3 (3.9) <0.001	−2.6 (3.5) <0.001	−2.7 (3.6) <0.001	−3.3 (3.6) <0.001
PPPG, mmol/L	*n*	14,642	5757	1559	917	6169	1391	599	1447
	Baseline	15.6 (4.2)	15.0 (4.2)	16.5 (5.0)	15.7 (5.0)	14.3 (4.5)	13.8 (4.3)	13.9 (4.6)	13.8 (4.5)
	Week 24	9.8 (2.8)	9.5 (2.8)	10.6 (3.6)	9.0 (2.3)	9.8 (3.0)	9.9 (3.2)	10.3 (3.2)	8.8 (2.3)
	Change, *p*	−5.8 (4.4) <0.001	−5.5 (4.2) <0.001	−5.8 (4.3) <0.001	−6.7 (5.0) <0.001	−4.5 (4.5) <0.001	−3.8 (4.3) <0.001	−3.6 (4.3) <0.001	−4.9 (4.5) <0.001
Body weight, kg	*n*	20,446	9336	2052	1273	9748	2598	862	2030
	Baseline	70.2 (12.6)	76.5 (16.3)	68.2 (12.0)	74.7 (16.9)	74.7 (14.9)	76.7 (16.3)	70.1 (14.0)	79.7 (17.1)
	Week 24	70.5 (12.0)	76.2 (15.4)	68.4 (11.4)	74.6 (15.5)	74.9 (14.5)	76.0 (15.7)	70.2 (13.4)	79.4 (16.0)
	Change, *p*	0.3 (3.5) <0.001	−0.3 (4.0) <0.001	0.2 (2.8) 0.007	−0.0 (4.2) 0.687	0.2 (3.6) <0.001	−0.7 (3.6) <0.001	−0.0 (4.2) 0.687	−0.3 (3.7) <0.001
SBP, mmHg	*n*	17,025	9077	1660	1268	9222	2543	765	2062
	Baseline	134.1 (17.8)	133.3 (16.7)	135.8 (20.9)	133.7 (18.1)	135.4 (18.2)	133.0 (16.9)	133.6 (17.4)	133.7 (17.9)
	Week 24	126.9 (12.2)	127.9 (15.2)	127.1 (12.5)	127.6 (12.6)	129.3 (13.8)	128.4 (13.7)	127.6 (14.8)	129.0 (13.1)
	Change, *p*	−7.1 (17.0) <0.001	−5.4 (17.7) <0.001	−8.7 (19.6) <0.001	−6.1 (15.7) <0.001	−6.1 (17.0) <0.001	−4.5 (15.6) <0.001	−6.0 (16.1) <0.001	−4.8 (15.3) <0.001
Total cholesterol, mmol/L	*n*	6111	4529	457	618	4900	1262	301	1239
	Baseline	5.4 (1.2)	5.3 (1.2)	5.1 (1.3)	5.6 (1.5)	5.2 (1.3)	5.2 (1.4)	5.2 (1.3)	5.3 (1.3)
	Week 24	4.8 (1.0)	4.8 (0.9)	4.6 (1.0)	4.9 (1.0)	4.8 (1.0)	4.8 (1.0)	4.7 (1.0)	4.9 (1.0)
	Change, *p*	−0.6 (1.2) <0.001	−0.6 (1.1) <0.001	−0.5 (1.3) <0.001	−0.7 (1.3) <0.001	−0.4 (1.2) <0.001	−0.4 (1.1) <0.001	−0.5 (1.1) <0.001	−0.4 (1.1) <0.001
Trigylceride, mmol/L	*n*	6086	4251	471	582	4910	1162	303	1190
	Baseline	2.1 (1.1)	2.1 (1.0)	2.0 (1.1)	2.2 (1.2)	2.1 (1.1)	1.9 (1.0)	2.0 (1.0)	2.0 (1.0)
	Week 24	1.8 (0.7)	1.7 (0.7)	1.8 (0.8)	1.7 (0.7)	1.8 (0.7)	1.7 (0.8)	1.8 (0.7)	1.8 (0.7)
	Change, *p*	−0.4 (1.0) <0.001	−0.4 (0.9) <0.001	−0.3 (1.0) <0.001	−0.5 (1.0) <0.001	−0.3 (1.0) <0.001	−0.2 (0.9) <0.001	−0.2 (0.7) <0.001	−0.3 (0.9) <0.001
HDL cholesterol, mmol/L	*n*	5589	3418	439	488	4373	970	264	936
	Baseline	1.2 (0.4)	1.1 (0.4)	1.1 (0.3)	1.2 (0.5)	1.1 (0.4)	1.1 (0.4)	1.2 (0.4)	1.1 (0.5)
	Week 24	1.3 (0.4)	1.2 (0.3)	1.2 (0.4)	1.3 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)
	Change, *p*	0.1 (0.4) <0.001	0.0 (0.3) <0.001	0.1 (0.4) <0.001	0.1 (0.4) <0.001	0.0 (0.4) <0.001	0.0 (0.4) 0.012	0.0 (0.3) 0.826	0.1 (0.4) <0.001
LDL cholesterol, mmol/L	*n*	5648	3459	447	495	4437	969	272	927
	Baseline	3.2 (1.0)	3.1 (1.0)	3.0 (1.0)	3.3 (1.1)	3.1 (1.1)	3.0 (1.0)	3.1 (1.0)	3.0 (1.0)
	Week 24	2.8 (0.9)	2.7 (0.8)	2.8 (1.0)	2.8 (0.8)	2.8 (0.9)	2.7 (0.9)	2.8 (0.9)	2.7 (0.9)
	Change, *p*	−0.4 (1.0) <0.001	−0.4 (1.0) <0.001	−0.3 (1.0) <0.001	−0.5 (1.0) <0.001	−0.3 (1.1) <0.001	−0.3 (0.9) <0.001	−0.3 (1.1) <0.001	−0.3 (1.0) <0.001

Hypoglycaemia (event per person-year/percent with event)									
Overall	Baseline	0.95/4.0	1.14/4.1	1.59/5.9	1.66/5.4	5.49/15.4	8.30/20.7	6.95/18.1	14.50/29.0
	Week 24	1.04/4.2	1.33/4.4	0.88/3.0	2.95/8.7	2.35/8.8	1.83/6.4	1.82/7.4	4.08/12.9
	[a]*p*	0.1886	0.1982	<0.0001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001
Minor	Baseline	0.86/3.8	1.06/3.9	1.46/5.6	1.50/5.4	4.96/14.9	7.42/19.7	6.02/16.8	13.10/27.9
	Week 24	1.04/4.2	1.33/4.4	0.88/3.0	2.95/8.7	2.34/8.7	1.83/6.4	1.82/7.4	4.08/12.8
	[a]*p*	0.0113	0.0669	<0.0001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001
Nocturnal	Baseline	0.27/1.4	0.27/1.5	0.46/2.8	0.37/1.8	1.60/6.9	2.79/11.2	2.00/8.7	4.54/15.1
	Week 24	0.20/1.1	0.38/1.7	0.15/0.9	0.42/2.4	0.55/2.9	0.47/1.9	0.33/1.8	0.95/5.0
	[a]*p*	0.0007	0.3078	<0.0001	0.3083	<0.0001	<0.0001	<0.0001	<0.0001
Major	Baseline	0.09/0.5	0.07/0.4	0.13/0.08	0.16/0.6	0.53/2.6	0.88/3.6	0.93/4.0	1.42/6.2
	Week 24	0.00/0.02	0.00/0.01	0.00/0.0	0.00/0.0	0.02/0.07	0.01/0.07	0.00/0.0	0.001/0.05
	[a]*p*	<0.0001	<0.0001	<0.0001	0.0022	<0.0001	<0.0001	<0.0001	<0.0001

Data are mean (SD) unless otherwise stated. A small number of people using other insulin regimens ($n = 2146$) could not be included in the above classifications.
[a] *p*-value is for difference in percent of people with at least one event.

rate were greatest in those regions with the highest baseline reported rates (north Africa and Russia).

3.4.3. *Body weight, blood pressure and blood lipids*

Mean body weight change was not clinically significant in any region, including China, with the greatest improvement in HbA_{1c} (−28 mmol/mol [−2.5%]). There was no suggestion that regions with greater improvements in glucose control by any measure had greater weight gain. Indeed, the region with the highest overall weight gain (north Africa, +0.9 kg) was the region with the poorest improvement in HbA_{1c} (−18 mmol/mol [−1.6%]). In the regional groups, reduction in SBP varied widely, although always statistically significantly, from 2 mmHg in north Africa to 9 mmHg in Russia. In Russia, at baseline SBP was 142 mmHg, the highest of all the regions. Total cholesterol levels were significantly reduced across all regions over 24 weeks. North Africa reported the smallest reduction (0.2 mmol/L) and the lowest value at baseline (4.7 mmol/L) (Table 4). Latin America had the highest total cholesterol at baseline (5.6 mmol/L) but a similar reduction, as in the other regions (0.5 mmol/L). The results for serum triglycerides and LDL cholesterol followed a similar regional pattern. HDL cholesterol values remained largely unchanged during the study and were similar across all regions (Table 4).

4. Discussion

The overall results from the A_1chieve non-interventional observational study find that beginning therapy with the insulin analogues detemir, aspart and biphasic aspart 30 under routine clinical practice was associated with marked improvements in average blood glucose levels (as measured by HbA_{1c}), without evident tolerability or safety issues in the short term. Indeed, given that increase in hypoglycaemia was not a problem, and body weight was essentially unchanged, improvements in HbA_{1c} of 22 mmol/mol (2.0%) or more are remarkable, and larger than would be expected from data from most RCTs [13–17,24,25]. Furthermore, these findings were reproduced in people from all the seven global regions studied, and were irrespective of the insulin regimen started, or indeed, for the most part, of whether the participants were insulin-treated at the time of starting the analogues or insulin-naïve. Although the reductions in HbA_{1c} were large, the proportion of people then achieving a target level of <53 mmol/mol (<7.0%) was disappointing, reflecting the very poor blood glucose control at baseline, the short duration of follow-up and the limited titration of insulin doses over the 6 months of study.

That the HbA_{1c} data are real is supported by the large and consistent reductions in FPG and PPPG control. Although people previously managed on lifestyle therapy alone or with OGLDs seemingly experienced greater improvements in glucose control than prior insulin users (Table 2), their baseline levels tended to be higher. This result is not unexpected, similar findings with regard to pre-study treatment regimen having been reported in the IMPROVE observational study of 52,419 people from 11 countries with T2D starting or switching to biphasic insulin aspart as part of routine clinical care [6]. Also consistent with the glucose-lowering findings are the

Table 4 – Glucose control and body weight by global region at baseline and after 24 weeks of insulin analogue therapy.

		China	South Asia	East Asia	North Africa	Middle East + Gulf	Latin America	Russia
Dose, U/day	*n*	11,013	22,415	10,031	4033	14,896	1136	3074
	Baseline	31.0 (12.5)	26.4 (11.5)	27.1 (16.6)	32.2 (21.0)	42.3 (23.4)	31.8 (20.9)	29.5 (18.5)
	Week 24	32.0 (12.8)	26.1 (11.5)	33.3 (18.0)	41.8 (23.4)	52.7 (25.0)	41.3 (24.1)	44.4 (21.7)
HbA_{1c}, mmol/mol/%	*n*	5784	17,111	4167	2601	11,618	573	2807
	Baseline	80 (25)/9.5 (2.3)	78 (16)/9.3 (1.4)	83 (21)/9.7 (1.9)	80 (20)/9.5 (1.8)	81 (19)/9.6 (1.7)	85 (24)/9.9 (2.2)	81 (19)/9.6 (1.7)
	Week 24	53 (11)/7.0 (1.0)	57 (10)/7.4 (0.9)	62 (16)/7.8 (1.4)	63 (16)/7.9 (1.4)	57 (12)/7.4 (1.1)	62 (16)/7.8 (1.4)	57 (11)/7.4 (1.0)
	Change	−28 (24)/−2.5 (2.2)	−21 (16)/−1.9 (1.4)	−22 (22)/−2.0 (2.0)	−18 (21)/−1.6 (1.9)	−24 (18)/−2.2 (1.6)	− 24 (24)/−2.2 (2.2)	−24 (17)/−2.2 (1.5)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
FPG, mmol/L	*n*	8281	17,287	5225	2904	10,737	738	3019
	Baseline	10.3 (3.6)	10.9 (3.0)	11.5 (4.3)	11.4 (4.2)	11.3 (3.7)	11.6 (4.6)	10.4 (2.7)
	Week 24	6.8 (1.3)	7.3 (1.9)	7.3 (2.4)	7.9 (2.8)	7.0 (1.9)	7.2 (2.4)	6.6 (1.3)
	Change	−3.5 (3.7)	−3.6 (2.7)	−4.2 (4.5)	−3.5 (4.7)	−4.3 (3.6)	−4.4 (4.7)	−3.8 (2.7)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PPPG, mmol/L	*n*	6251	12,570	2987	1683	7588	146	2517
	Baseline	14.2 (4.9)	15.9 (3.7)	15.8 (5.0)	14.8 (4.7)	15.4 (4.6)	15.3 (5.7)	12.1 (3.1)
	Week 24	8.8 (1.9)	10.8 (3.2)	9.6 (3.3)	10.4 (3.5)	9.2 (2.4)	9.0 (2.5)	8.0 (1.4)
	Change	−5.4 (5.0)	−5.1 (3.8)	−6.1 (5.5)	−4.4 (5.5)	−6.2 (4.5)	−6.3 (5.7)	−4.2 (3.0)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Body weight, kg	*n*	7815	16,869	6831	3202	11,357	964	3021
	Baseline	68.6 (11.5)	68.9 (10.2)	64.0 (12.3)	75.4 (13.3)	84.4 (15.4)	77.9 (16.9)	85.2 (15.6)
	Week 24	68.9 (11.0)	68.9 (9.7)	64.7 (11.7)	76.2 (12.8)	84.0 (14.4)	78.1 (16.4)	84.4 (14.9)
	Change	0.3 (3.1)	0.0 (3.2)	0.7 (3.8)	0.9 (3.9)	−0.4 (4.4)	0.2 (4.1)	−0.8 (3.3)
	p	<0.001	0.569	<0.001	<0.001	<0.001	0.083	<0.001
SBP, mmHg	*n*	6414	12,739	6784	3070	12,295	954	3029
	Baseline	132.4 (16.8)	135.3 (18.4)	130.1 (17.3)	133.1 (18.2)	134.9 (17.3)	130.0 (16.9)	142.4 (17.1)
	Week 24	128.2 (12.4)	126.5 (11.1)	125.5 (14.9)	131.0 (19.2)	128.5 (13.2)	127.5 (14.0)	133.4 (12.3)
	Change, *p*	−4.2 (15.8) <0.001	−8.8 (16.9) <0.001	−4.6 (18.0) <0.001	−2.1 (20.9) <0.001	−6.4 (16.5) <0.001	−2.6 (17.7) <0.001	−9.0 (14.1) <0.001
Total cholesterol, mmol/L	*n*	3589	1417	2180	1532	8213	500	2862
	Baseline	5.1 (1.2)	5.1 (0.9)	5.2 (1.5)	4.7 (1.2)	5.3 (1.2)	5.6 (1.6)	6.0 (1.3)
	Week 24	4.6 (1.1)	4.7 (0.8)	4.6 (1.0)	4.5 (1.0)	4.7 (0.8)	5.1 (1.0)	5.5 (1.0)
	Change, *p*	−0.5 (1.3) <0.001	−0.4 (0.6) <0.001	−0.6 (1.4) <0.001	−0.2 (1.2) <0.001	−0.6 (1.1) <0.001	−0.5 (1.5) <0.001	−0.5 (1.0) <0.001
Triglycerides, mmol/L	*n*	3532	2264	1809	1586	8171	420	2074
	Baseline	2.1 (1.3)	2.1 (0.8)	2.0 (1.1)	1.7 (0.9)	2.2 (1.0)	2.4 (1.3)	2.1 (1.0)
	Week 24	1.7 (0.8)	1.8 (0.6)	1.6 (0.8)	1.5 (0.7)	1.8 (0.7)	1.9 (0.9)	1.7 (0.8)
	Change, *p*	−0.3 (1.2) <0.001	−0.3 (0.6) <0.001	−0.3 (1.0) <0.001	−0.1 (0.9) <0.001	−0.4 (0.9) <0.001	−0.5 (1.3) <0.001	−0.3 (0.8) <0.001
HDL cholesterol, mmol/L	*n*	3255	2327	1565	1044	7447	344	1324
	Baseline	1.2 (0.5)	1.0 (0.2)	1.2 (0.4)	1.1 (0.4)	1.1 (0.3)	1.1 (0.4)	1.4 (0.6)
	Week 24	1.4 (0.5)	1.0 (0.3)	1.3 (0.3)	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)	1.5 (0.5)
	Change, *p*	0.1 (0.5) <0.001	−0.0 (0.3) 0.783	0.1 (0.4) <0.001	0.0 (0.5) 0.046	0.0 (0.3) <0.001	0.1 (0.3) <0.001	0.1 (0.5) <0.001
LDL cholesterol, mmol/L	*n*	3313	2309	1567	1007	7630	322	1346
	Baseline	3.1 (1.1)	3.1 (0.9)	3.2 (1.2)	2.9 (1.2)	3.2 (1.0)	3.1 (1.1)	3.3 (1.1)
	Week 24	2.7 (1.0)	2.8 (0.7)	2.8 (0.9)	2.7 (1.1)	2.7 (0.8)	2.9 (0.8)	2.9 (1.0)
	Change, *p*	−0.4 (1.1) <0.001	−0.3 (0.7) <0.001	−0.4 (1.2) <0.001	−0.1 (1.5) 0.003	−0.4 (1.0) <0.001	−0.2 (1.1) <0.001	−0.4 (1.0) <0.001

Hypoglycaemia (event per person-year/percent with event)								
Overall	Baseline	2.67/8.3	1.47/6.6	2.06/6.4	8.14/18.6	3.94/10.1	4.86/11.4	8.83/15.4
	Week 24	1.75/7.4	0.26/1.4	1.37/5.0	4.09/13.6	2.1/7.6	1.17/5.0	5.44/15.3
	[a]*p*	0.018	<0.001	<0.001	<0.001	<0.001	<0.001	0.943
Minor	Baseline	2.49/8.0	1.31/6.3	1.92/6.2	6.96/18.0	3.36/9.5	4.33/10.9	8.57/15.3
	Week 24	1.75/7.4	0.26/1.4	1.37/5.0	4.03/13.4	2.09/7.6	1.17/5.0	5.44/15.3
	[a]*p*	0.012	<0.001	<0.001	<0.001	<0.001	<0.001	0.7159
Nocturnal	Baseline	0.64/2.7	0.46/2.9	0.64/2.6	3.23/11.4	1.07/4.6	1.58/5.4	2.33/7.8
	Week 24	0.3/1.7	0.05/0.3	0.28/1.3	1.26/5.3	0.57/2.9	0.19/1.1	0.89/4.3
	[a]*p*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Major	Baseline	0.18/0.9	0.16/1.0	0.14/0.6	1.18/5.3	0.58/2.5	0.53/1.7	0.26/1.0
	Week 24	0.00/0.0	0.00/0.0	0.00/0.0	0.06/0.2	0.01/0.1	0.00/0.0	0.00/0.0
	[a]*p*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are mean (SD) except for hypoglycaemia.
[a] *p*-value is for difference in percent of people with at least one event.

reductions in LDL cholesterol and triglycerides, but, surprisingly, SBP was also lower, which, together with the lack of body weight gain, suggests that factors other than insulin therapy itself are contributors to the improvements in metabolic status.

The most likely factor here is improvement in lifestyle and, in particular, in nutritional intake. Body weight gain in 6 months with an HbA_{1c} improvement of around 22 mmol/mol (2.0%) or more would be expected to be around 4 kg [26], due to amelioration of urinary glycosuria and glucose concentration-driven glucose metabolism [27]; that this did not occur would suggest that participants and advising healthcare teams took advantage of the starting of insulin analogues to enhance self-care behaviours. This, in turn, is consistent with the improvement in blood pressure control and in the lipid profile, but the possibility remains that specific therapy changes (not recorded) could also have influenced the findings. Interestingly, the region with the numerically smallest fall in HbA_{1c} (north Africa) was that with the numerically largest gain in weight, suggesting perhaps that, in this region, changes in self-management were less marked than elsewhere.

Overall, the large reduction in the HbA_{1c}, FPG and PPPG levels following 24 weeks of use of these insulin analogues was associated with a low incidence of reported drug reactions (SADRs) and hypoglycaemia. While improvements in glycaemic control are usually associated with an increased risk of hypoglycaemia [28], the global cohort from this study reported a decrease in the rate of all hypoglycaemic episodes from 3.1 events/person-year at baseline to 1.6 events/person-year in the 4 weeks before the end of the study. The reduction in reported relative event rate was even more marked for major hypoglycaemic episodes. Although the percentage reduction in event rate appears high, in absolute terms it is low, consistent with other reports of hypoglycaemia in people with T2D [6,14,29]. Explanations for these findings might again be better self-management behaviours, including more consistent eating patterns as a result of patient education given at the time of starting insulin analogues, although the possibility that investigator recording of hypoglycaemia events differed in some way at 24 weeks from that at baseline cannot be excluded.

Unsurprisingly, differences in hypoglycaemia rate for the study insulin regimens were, however, influenced by pre-study therapy type. Thus, prior insulin users reported a marked decrease in incidence of events in all therapy subgroups, with the greatest numerical reductions being in those transferring to insulin detemir. Insulin-naïve patients generally experienced a slight increase in the rate of overall hypoglycaemia, with the exception of the insulin aspart group. This is not consistent with reports from RCTs. Regional baseline rates of hypoglycaemia varied considerably, but all reported reductions in overall hypoglycaemia (Table 4). The greatest reductions in rate were evident from north Africa and Russia, explained by the baseline rates being highest.

Even though the large body of data generated by this study offers the opportunity to explore other important disease and therapy-related questions, there were limitations inherent in the study design. In particular, concomitant medication and dietary intake were not controlled, and the latter remains largely unmeasurable. The study was non-randomised and

lacked a standardised treatment protocol and a control arm, with most safety and efficacy parameters based on participant recall, diverse diaries or self-reported information. The circumstances under which participants came under the care of the investigators are not known, and these could have been a trigger for starting modern insulin therapy while at the same time improving other aspects of diabetes care. Additionally, the findings could have been influenced by a study effect as, although entry was retrospective, further data collection was prospective following informed consent. Against that view, insulin dose titration after baseline was small.

Another limitation of the study is the heterogeneity of global healthcare systems involved, although this was part of the design, with the intention of trying to identify how cultural, resource and perhaps genetic influences might have different effects on the safety and efficacy profile of the different analogues. This proved not to be the case because, for the most part, the patterns of improvement in glucose control (including postprandial), blood lipid control and hypoglycaemia, and without weight gain, were consistent between regions.

In summary, in people whose HbA_{1c} suggested diabetes management neglect, starting an insulin analogue, whether in a current insulin user or not, appears to provide a valuable opportunity for broad improvements in self-management and metabolic control, independently of the type of insulin begun. With both lipids and blood pressure improving, cardiovascular risk will clearly be usefully reduced. Furthermore, starting these insulins was not associated in these circumstances with any tolerability or safety problem, notably of hypoglycaemia or body weight. Further analysis of this large database will seek to define the factors predicting changes in metabolic profile, and to build guidelines for diabetes management in the individual.

Conflict of interest

Philip Home or institutions with which he is associated receive funding from Novo Nordisk and other insulin manufacturers for his research, advisory and educational activities. Mohammed Khamseh is a speaker for Novo Nordisk. Guillermo Gonzalez-Galvez is a board member and speaker for Novo Nordisk. Praful Chakkarwar and Chunduo Shen are employed by Novo Nordisk. This study was sponsored by Novo Nordisk A/S Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies including insulin, or continuing clinical management of the participants.

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