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ORIGINAL RESEARCH

Safety and Effectiveness of Bolus Insulin Aspart in People with Type 2 Diabetes: A_1chieve Sub-Analysis

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ABSTRACT

Introduction: This sub-analysis evaluated clinical safety and effectiveness of bolus insulin aspart [with/without oral glucose-lowering drugs (OGLDs)] as the only insulin therapy.

Methods: A_1chieve was an international, multicenter, prospective, open-label, non-interventional, observational, 24-week study in people with type 2 diabetes mellitus starting/switching to biphasic insulin aspart 30, insulin detemir or insulin aspart treatment (alone/in combination) in routine clinical practice. This sub-analysis evaluated clinical safety and effectiveness of bolus insulin aspart (±OGLDs) as the only insulin therapy. Data were analyzed for all patients, insulin-experienced and insulin-naive sub-groups, and sub-groups defined by the number of OGLDs prescribed at baseline (no OGLDs, one OGLD or ≥two OGLDs). Safety and effectiveness endpoints were assessed at baseline and following 24 weeks' therapy.

The A_1chieve trial was registered with ClinicalTrials.gov (NCT00869908).

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Results: In total, 2,026 patients were included (insulin-experienced, $n = 561$; insulin-naive, $n = 1{,}465$) in this sub-analysis. Significant improvements from baseline after 24 weeks' treatment with insulin aspart ± OGLDs were observed across all sub-groups for: glycated hemoglobin (range of means across sub-groups −1.6 to −2.4%; $p < 0.001$ for all comparisons), fasting plasma glucose (−2.5 to −3.8 mmol/l; $p < 0.001$ for all comparisons), post-breakfast post-prandial glucose (−3.4 to −5.8 mmol/l; $p < 0.001$ for all comparisons), and health-related quality of life (HRQoL; $p < 0.001$ for all comparisons). The proportion of patients reporting hypoglycemia events was significantly reduced from baseline after 24 weeks (insulin-naive cohort: 7.9–2.8%; $p < 0.001$; insulin-experienced cohort: 23.2–7.8%; $p < 0.001$). There were no reports of major hypoglycemia events at 24 weeks; risk of nocturnal hypoglycemia was <0.6 events/person-year. No serious adverse drug reactions were reported.

Conclusion: Insulin aspart ± OGLDs is associated with significant improvements in glycemic control and HRQoL, without increased risk of hypoglycemia, in people with type 2 diabetes and sub-optimal glucose control.

Keywords: A_1chieve study; Bolus only; Insulin aspart; Oral glucose-lowering drugs; Type 2 diabetes

INTRODUCTION

Increased life expectancy and high global prevalence of type 2 diabetes mellitus [1, 2] render treatment of this condition a lifelong personal and social burden [3–5]. Post-prandial hyperglycemia is a common phenomenon in people with type 1 and 2 diabetes, and incurs a significant risk of diabetes-related complications [6]. Therefore, achieving control of post-prandial glucose (PPG) level and fasting plasma glucose (FPG) level is important to maintain glycated hemoglobin (HbA_{1c}) levels below target [6]. Despite the need to control PPG, the number of available drugs able to accomplish this is limited. Conventional oral glucose-lowering drugs (OGLDs) and lifestyle modifications, while fundamental to early management of the disease, are unable to maintain good glycemic control in the longer term, and there is a consequent additional requirement for exogenous insulin [7, 8].

Compared with exogenous human insulin, the rapid-acting analog insulin aspart (NovoRapid®; Novo Nordisk A/S, Bagsvaerd, Denmark) is associated with rapid absorption and early onset of action, which facilitates administration immediately before or shortly after a meal [9]. Subcutaneous administration of rapid-acting insulin analogs results in a physiologic profile that bears a closer resemblance to endogenous insulin than is achieved with subcutaneous administration of human insulin. By virtue of this action, insulin analogs, such as insulin aspart, offer advantages over human insulin (e.g., greater convenience [10]) and have the potential to reduce PPG excursions, thereby improving overall glycemic control [11, 12]. Clinical research shows that insulin aspart is also associated with reduced hypoglycemia risk and greater treatment satisfaction versus human insulin when administered in a basal-bolus regimen among people with type 1 and 2 diabetes mellitus [13–18]. Guidelines generally recommend initiating insulin therapy when OGLDs fail to provide adequate glycemic control [19]; in this context, some healthcare professionals start patients on prandial insulin as the only insulin therapy [20, 21]. While few studies have examined the safety

and effectiveness of bolus-only insulin aspart, particularly as add-on to OGLDs, available evidence suggests beneficial effects on glycemic control when OGLD therapy is insufficient [22].

While well-designed randomized controlled trials provide a stringent way of assessing insulin regimens, they focus on a selected patient group under intensive clinical supervision. Therefore, results obtained from such studies may not be truly representative of routine clinical practice. In addition, randomized controlled trials are often performed in restricted geographical regions, with less focus on those countries that are less well resourced. While observational studies are associated with limitations, such as lack of a control group, they are capable of enrolling a larger cohort of people from diverse geographic locations and environments, and may better represent everyday clinical practice than randomized controlled trials.

A_1chieve was an international observational study evaluating the safety and effectiveness of insulin analogs in people with type 2 diabetes mellitus receiving routine clinical care in 28 countries across four continents [20]. This subgroup analysis of participants from the A_1chieve study aimed to investigate the clinical safety and effectiveness of insulin aspart alone or as add-on to OGLDs for the management of type 2 diabetes mellitus in routine clinical practice.

MATERIALS AND METHODS

Study Design

A_1chieve was a 24-week, international, prospective, multicenter, non-interventional, observational study examining the safety and effectiveness of insulin analogs in 66,276 people with type 2 diabetes mellitus undergoing treatment in routine clinical practice between January 2009 and June 2010 [20]. The study was conducted across 3,166 centers in 28 countries, representing 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 (Egypt, Iran, Jordan, Turkey, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, UAE, Yemen), Latin America (Argentina, Mexico), and Russia.

Insulin analogs (manufactured by Novo Nordisk A/S, Bagsvaerd, Denmark) were used in accordance with the label approved by the regulatory authority, and all local requirements for Health Authorities or Ethics Committee approvals were obtained, if applicable. Physicians were able to adjust treatment during the 24 weeks. Details on inclusion and exclusion criteria, and study design have been reported elsewhere [20]. In every country, participants gave informed consent and were free to withdraw from the study at any time. The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2008 [23], and Guidelines for Good Pharmacoepidemiology Practice [24].

Results presented here are from a subanalysis of patients treated with insulin aspart alone or in combination with OGLDs (excluding those who received basal-bolus insulin regimens).

Assessments

Assessments were at baseline (time when the treating physician prescribed insulin aspart), approximately 12 weeks after baseline (results not reported here), and study end (approximately 24 weeks after baseline).

The primary objective of the study was to evaluate the safety profile of insulin analogs by measuring the incidence of serious adverse drug reactions (SADRs), including major hypoglycemia events. Other safety assessments included change in the number of hypoglycemia events between baseline and 24 weeks (reported as the percentage of patients reporting an event and events/person year). These were based on patient recall of events within the preceding 4 weeks of the study visit.

Effectiveness of therapy was determined from measurements made by the treating physician team at each assessment visit; data were collated into a standard case report form using information from the physicians' clinical notes and the participants' recall and self-monitoring diary/meter. Effectiveness outcomes included change from baseline after 24 weeks in glucose control measures [HbA_{1c}; FPG (pre-breakfast), and PPG (90–120 min after beginning breakfast)], body weight, and health-related quality of life (HRQoL). HRQoL was measured at baseline and after 24 weeks by self-report using the EQ-5D questionnaire [25], which evaluates five domains of patient health/lifestyle (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The questionnaire also includes a rating for an individual's current HRQoL on a visual analog scale [VAS; ranging from 0 (worst imaginable health) to 100 (best imaginable health)]. Scores in the five domains were converted to a single utility value (UK VAS set), with '1.00' indicating 'full health' and '0.00' indicating 'deceased' [26, 27].

Due to the non-interventional design of the analysis and lack of protocol enforcement to report all outcomes, data are described here as per available reports.

Statistical Analyses

Analyses were performed on data from all patients with a baseline visit who were treated with insulin aspart at least once during the study. For those patients who withdrew from the study, data collected until the date of withdrawal were used for analysis. Patients were split into two cohorts according to whether they had received insulin before the study (insulin-experienced and insulin-naive) or not. Sub-group analyses were then conducted in each cohort according to the number of OGLDs received at baseline (none, one, or ≥two).

Changes from baseline in effectiveness measures were assessed using Student's paired *t* test. For hypoglycemia, the percentage of patients reporting at least one event was analyzed using McNemar's test. All statistical analyses were two-sided, using a pre-specified 5% significance level, and were performed by Novo Nordisk A/S using SAS® Version 9.1.3 (SAS® Institute Inc., Cary, NC, USA).

RESULTS

Study Participants

In total, 3,898 patients from the A_1chieve study received treatment with insulin aspart alone or in combination with OGLDs at baseline (insulin aspart alone, $n = 1{,}560$; insulin aspart + one OGLD, $n = 1{,}514$; and insulin aspart + ≥two OGLDs, $n = 824$) [20]. Of these, 1,872 patients subsequently switched to insulin analog basal-bolus regimens, basal insulin analog regimens, or biphasic insulin analog regimens before completing the study. Thus, 2026 people who received insulin aspart alone or in combination with OGLDs at baseline and after 24 weeks (or last follow-up visit) were included in this analysis (Table 1).

Table 1 Baseline patient and disease characteristics

Measurement	Insulin-experienced				Insulin-naive			
	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline
n (% of cohort)	561 (100)	270 (48.1)	187 (33.3)	104 (18.5)	1,465 (100)	514 (35.1)	568 (38.8)	383 (26.1)
Mean (SD) age (years)[a]	55.8 (13.4)	55.2 (14.6)	55.9 (12.6)	57.6 (11.1)	51.5 (13.3)	53.3 (15.4)	51.0 (12.3)	49.8 (11.2)
Male gender (%)	56.9	59.3	54.5	54.8	59.0	57.0	60.6	59.3
Mean (SD) body weight (kg)[b]	68.7 (14.6)	67.2 (15.2)	69.6 (14.9)	71.1 (11.7)	67.3 (12.9)	65.7 (13.6)	67.3 (12.6)	69.4 (12.3)
Mean (SD) BMI (kg/m^2)[c]	25.2 (4.4)	24.6 (4.4)	25.6 (4.6)	26.3 (3.8)	25.2 (3.9)	24.2 (3.8)	25.4 (4.0)	25.9 (3.7)
Mean (SD) diabetes duration (years)[d]	11.2 (7.0)	10.6 (6.9)	12.0 (7.5)	11.2 (6.0)	5.8 (5.2)	5.2 (5.7)	6.3 (5.2)	5.9 (4.6)
Mean (SD) time since insulin initiation (years)[e]	3.5 (3.8)	3.7 (4.1)	3.2 (3.6)	3.4 (3.2)	n/a	n/a	n/a	n/a
Mean (SD) time since OGLD initiation (years)[f]	8.3 (6.4)	6.7 (6.0)	9.8 (7.1)	9.5 (5.4)	4.8 (4.6)	3.9 (4.9)	5.3 (4.5)	5.3 (4.1)

Due to the observational nature of the study not all measures were reported/collected

BMI body mass index, *OGLDs* oral glucose-lowering drugs

[a] In the total, no OGLD, one OGLD and ≥two OGLD groups: insulin-experienced, $n = 548$, $n = 267$, $n = 184$ and $n = 97$, respectively; insulin-naive, $n = 1{,}418$, $n = 506$, $n = 540$ and $n = 372$, respectively

[b] In the total, no OGLD, one OGLD and ≥two OGLD groups: insulin-experienced, $n = 526$, $n = 258$, $n = 182$ and $n = 86$, respectively; insulin-naive, $n = 1{,}388$, $n = 477$, $n = 538$ and $n = 373$, respectively

[c] In the total, no OGLD, one OGLD and ≥two OGLD groups: insulin-experienced, $n = 489$, $n = 246$, $n = 167$ and $n = 76$, respectively; insulin-naive, $n = 1{,}312$, $n = 452$, $n = 506$ and $n = 354$, respectively

[d] In the total, no OGLD, one OGLD and ≥two OGLD groups: insulin-experienced, $n = 556$, $n = 267$, $n = 185$ and $n = 104$, respectively; insulin-naive, $n = 1{,}447$, $n = 505$, $n = 561$ and $n = 381$, respectively

[e] In the total, no OGLD, one OGLD and ≥two OGLD groups $n = 500$, $n = 242$, $n = 160$ and $n = 98$, respectively

[f] In the total, no OGLD, one OGLD and ≥two OGLD groups: insulin-experienced, $n = 530$, $n = 254$, $n = 174$ and $n = 102$, respectively; insulin-naive, $n = 1{,}341$, $n = 467$, $n = 520$ and $n = 354$, respectively

Among treating physicians, the need to improve glycemic control (93.0%) represented the predominant reason for changing/switching to insulin aspart therapy followed by the need to reduce the risk of hypoglycemia (44.9%) and reduce variability of plasma glucose levels (27.8%). Among insulin-experienced patients ($n = 561$), previous insulin therapies included premix human insulin (42.1% of patients), human soluble insulin (20.7%), insulin glargine (15.9%), neutral protamine Hagedorn (NPH, 7.0%), NPH plus human soluble insulin (3.6%), and others such as premixed insulin lispro (10.9%). Baseline characteristics were generally similar between patient sub-groups, although insulin-experienced patients appeared to have had longer mean diabetes duration and longer time since OGLD initiation than insulin-naive patients (Table 1). In both insulin-experienced and insulin-naive patients, metformin was the most frequently prescribed OGLD pre-study (71% and 80% of patients, respectively), and sulfonylurea was the second most frequently prescribed (44% and 64% of patients, respectively).

Insulin Dose

Insulin-experienced patients received a mean (standard deviation; SD) insulin dose of 0.50

(0.29) U (or IU)/kg before entering the study. When patients switched to insulin aspart ± OGLDs at baseline the dose ranged from 0.45 to 0.47 U/kg in the different sub-groups (Fig. 1). In the insulin-naive cohort, mean (SD) insulin aspart dose was 0.40 (0.20) U/kg at baseline (Fig. 1). Following 24 weeks' therapy with insulin aspart, there were no obvious changes from baseline in mean insulin dose in either cohort (Fig. 1).

The proportion of insulin-experienced patients receiving once daily (qd), twice daily (bid), or ≥three times daily (tid) insulin aspart injections at baseline was 7.1%, 27.3%, and 65.5%, respectively. Insulin injection frequency was similar to baseline following 24 weeks of therapy with insulin aspart (7.8%, 32.5%, and 59.7% of patients, respectively). The proportion of insulin-naive patients receiving qd, bid, or ≥tid insulin injections at baseline was 5.5%, 40.2%, and 54.3%, respectively. Insulin injection frequency was similar to baseline following 24 weeks of insulin aspart therapy (5.4%, 44.9%, and 49.6% of patients, respectively).

Number of OGLDs

Most insulin-experienced and insulin-naive patients were receiving the same number of OGLDs at baseline and following 24 weeks of treatment with insulin aspart (Table 2). Most

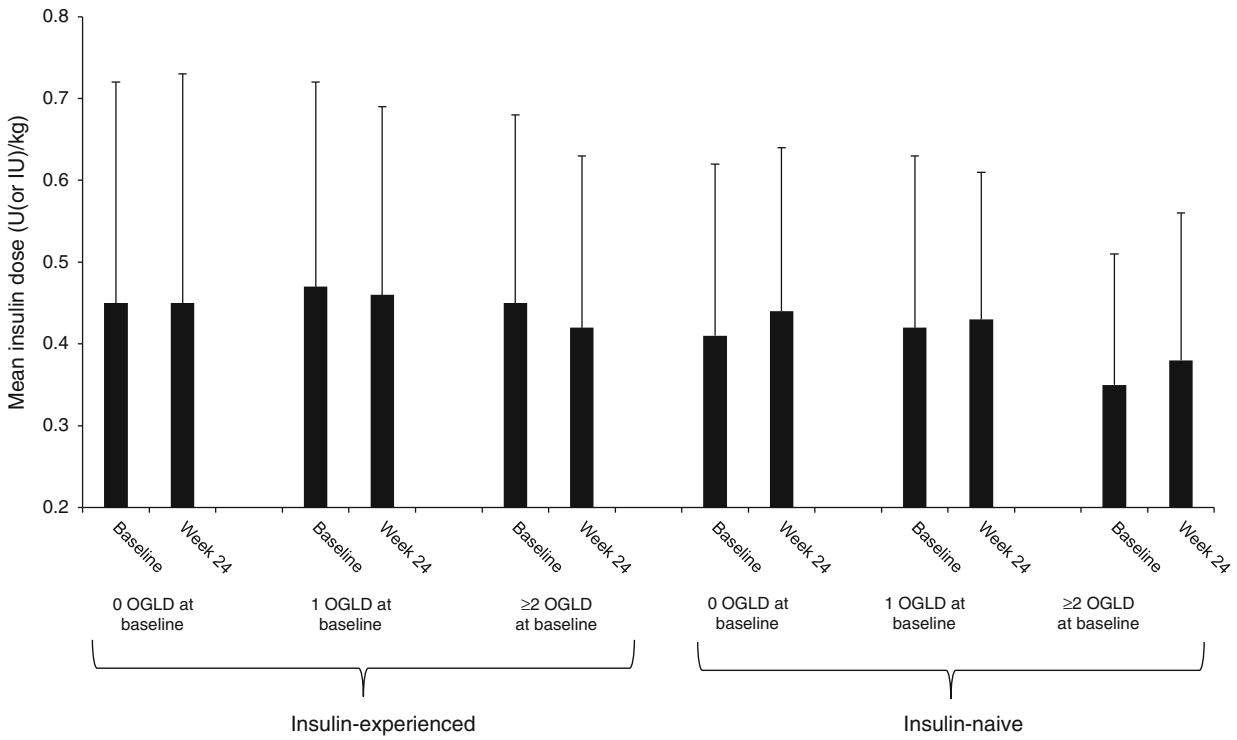

Fig. 1 Mean (SD) insulin dose received by patients at baseline and after 24 weeks on insulin aspart therapy in the A_1chieve study. Due to the observational nature of the study not all measures were reported/collected. At baseline: insulin-experienced: $n = 257$ in 0 OGLD sub-group; $n = 182$ in 1 OGLD sub-group; $n = 86$ in ≥2 OGLDs sub-group. Insulin-naive: $n = 477$ in 0 OGLD sub-group; $n = 536$ in 1 OGLD sub-group; $n = 373$ in ≥2 OGLDs sub-group. After 24 weeks: insulin-experienced: $n = 178$ in 0 OGLD sub-group; $n = 138$ in 1 OGLD sub-group; $n = 64$ in ≥2 OGLDs sub-group. Insulin-naive: $n = 326$ in 0 OGLD sub-group; $n = 422$ in 1 OGLD sub-group; $n = 274$ in ≥2 OGLDs sub-group. *OGLD* oral glucose-lowering drug

Table 2 Number of OGLDs taken at baseline and following 24 weeks of therapy with insulin aspart alone or with OGLDs

Number of OGLDs at 24 weeks	Insulin-experienced			Insulin-naive		
	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline
All, *n*	191	151	83	376	457	298
No OGLDs, *n* (% of cohort)	157 (82.2)	24 (15.9)	1 (1.2)	291 (77.4)	49 (10.7)	22 (7.4)
One OGLD, *n* (% of cohort)	27 (14.1)	111 (73.5)	15 (18.1)	68 (18.1)	286 (62.6)	55 (18.5)
≥Two OGLDs, *n* (% of cohort)	7 (3.7)	16 (10.6)	67 (80.7)	17 (4.5)	122 (26.7)	221 (74.2)

Due to the observational nature of the study not all measures were reported/collected
OGLDs oral glucose-lowering drugs

insulin-experienced (209/367, 56.9%) and insulin-naive (408/795, 51.3%) patients receiving insulin aspart injections ≥tid at baseline were not taking OGLDs. However, most insulin-experienced (22/40, 55.0%) and insulin-naive (43/82, 52.4%) patients taking qd insulin aspart injections at baseline were receiving ≥two OGLDs at baseline. In insulin-experienced patients receiving bid insulin aspart injections at baseline, the proportion of patients taking no OGLDs, one OGLD, or ≥two OGLDs at baseline was similar (52/154, 33.8%; 60/154, 39.0%; and 42/154, 27.3%, respectively). Most insulin-naive patients receiving bid insulin aspart injections were receiving one OGLD or ≥two OGLDs at baseline (270/588, 45.9% and 221/588, 37.6%, respectively).

Metformin and/or sulfonylureas were the predominant OGLDs administered in all subgroups of patients; >60% of patients in all subgroups were receiving metformin after 24 weeks.

Serious Adverse Events

Following 24 weeks of insulin aspart therapy, six serious adverse events (SAEs) were reported, which were considered unlikely to be related to the study treatment. In the insulin-naive cohort, three SAEs (one incident of acute cardiac failure, one malignant lung neoplasm, and one case of chronic renal failure) were reported in the group receiving no OGLDs at baseline and one SAE (vascular stenosis) was reported in the group receiving one OGLD at baseline; two deaths (one acute cardiac failure and the other malignant lung neoplasm) were reported in the insulin-naive cohort. In the insulin-experienced cohort, two SAEs were reported in the group receiving no OGLDs at baseline: upper gastrointestinal hemorrhage and hepatic coma. No other SAEs were reported.

Hypoglycemia Events

The proportion of insulin-experienced and insulin-naive patients reporting at least one hypoglycemia event was significantly decreased from baseline following 24 weeks of treatment with insulin aspart in patients receiving bid or tid insulin injections (Table 3). The proportion of patients reporting at least one hypoglycemia event did not significantly change between baseline and 24 weeks in patients receiving qd or four times daily (qid) insulin injections

(Table 3). There was no obvious effect of insulin injection frequency on the proportion of patients experiencing nocturnal hypoglycemia events at 24 weeks in insulin-experienced and insulin-naive patients (Table 3).

The proportion of patients reporting at least one hypoglycemia event was significantly decreased from baseline following 24 weeks of treatment with insulin aspart, irrespective of prior insulin experience and the number of OGLDs received at baseline (Table 4); the exception was no significant change between baseline and 24 weeks in insulin-naive patients who were receiving no OGLDs at baseline. The proportion of patients reporting at least one nocturnal hypoglycemia event was significantly decreased from baseline to 24 weeks irrespective of prior insulin experience and the number of OGLDs received at baseline; the exceptions were no change between baseline and 24 weeks in insulin-experienced patients taking ≥two OGLDs at baseline, and insulin-naive patients taking no OGLDs at baseline (Table 4).

At 24 weeks, no major hypoglycemia events were reported in the insulin-experienced or insulin-naive cohorts and the risk of nocturnal hypoglycemia was reduced to <0.6 events/person-year, irrespective of baseline insulin

Table 3 Safety outcomes before and after 24 weeks of treatment with insulin aspart alone or with OGLDs according to baseline insulin injection frequency

Measurement	% Patients with at least one event (event/person-year)							
	Insulin-experienced				Insulin-naive			
	Once daily	Twice daily	Three times daily	Four times daily	Once daily	Twice daily	Three times daily	Four times daily
Hypoglycemia (overall)								
Baseline	10.0 (2.3)	16.2 (4.5)	28.1 (10.8)	22.5 (19.2)	2.4 (0.5)	12.8 (3.3)	5.1 (1.7)	2.3 (0.3)
n	40	154	327	40	82	588	751	44
24 weeks	0 (0)	7.8 (1.3)*	8.1 (1.9)***	14.3 (2.3)	1.5 (0.6)	2.1 (0.5)***	3.5 (1.2)*	4.0 (0.5)
n	33	128	236	28	66	466	574	25
Hypoglycemia (major)[a]								
Baseline	2.5 (0.3)	5.2 (1.0)	5.8 (1.7)	7.5 (1.0)	0 (0)	1.7 (0.2)	0.7 (0.1)	0 (0)
24 weeks	0 (0)[b]	0 (0)**	0 (0)***	0 (0)	0 (0)[c]	0 (0)	0 (0)*	0 (0)[c]
Hypoglycemia (nocturnal)[a]								
Baseline	2.5 (0.3)	7.1 (1.4)	14.7 (3.0)	15.0 (8.5)	0 (0)	8.3 (1.3)	1.3 (0.3)	0 (0)
24 weeks	0 (0)	2.3 (0.3)	0 (0)***	3.6 (0.5)	1.5 (0.2)	0.6 (0.1)***	0.3 (0.1)	0 (0)[c]

Due to the observational nature of the study not all measures were reported/collected

*** $p < 0.001$ vs. baseline

** $p < 0.01$ vs. baseline

* $p < 0.05$ vs. baseline

[a] *n* for each cohort same as for hypoglycemia (overall) data

[b] Statistical analysis could not be performed with McNemar's test as patients reporting hypoglycemia at baseline were missing hypoglycemia data for 24 weeks

[c] No hypoglycemia events were reported at baseline and 24 weeks; therefore statistical analysis could not be conducted

Table 4 Safety outcomes before and after 24 weeks of treatment with insulin aspart alone or with OGLDs according to OGLDs taken at baseline

Measurement	% Patients with at least one event (event/person-year)							
	Insulin-experienced				Insulin-naive			
	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline
Hypoglycemia (overall)								
Baseline	23.2 (9.1)	26.3 (11.4)	20.3 (6.8)	20.2 (7.1)	7.9 (2.2)	4.9 (1.8)	7.7 (1.8)	12.3 (3.5)
n	561	270	187	104	1,465	514	568	383
24 weeks	7.8 (1.6)***	9.4 (2.2)***	6.6 (1.4)***	6.0 (0.8)*	2.8 (0.9)***	4.3 (1.4)	2.6 (0.8)***	1.3 (0.4)***
n	425	191	151	83	1,131	376	457	298
Hypoglycemia (major)[a]								
Baseline	5.5 (1.3)	6.3 (1.8)	3.2 (0.6)	7.7 (1.4)	1.0 (0.2)	0.4 (0.1)	0.7 (0.1)	2.3 (0.3)
24 weeks	0 (0)***	0 (0)***	0 (0)*	0 (0)*	0 (0)**	0 (0)	0 (0)*	0 (0)
Hypoglycemia (nocturnal)[a]								
Baseline	11.8 (2.8)	14.4 (3.2)	10.2 (2.4)	7.7 (2.1)	4.0 (0.7)	1.0 (0.3)	4.9 (0.6)	6.8 (1.2)
24 weeks	0.9 (0.1)***	0.5 (0.1)***	1.3 (0.2)**	1.2 (0.2)	0.5 (0.1)***	1.1 (0.2)	0.4 (0.1)***	0 (0)***

Due to the observational nature of the study not all measures were reported/collected
OGLDs oral glucose-lowering drugs
*** $p < 0.001$ vs. baseline
** $p < 0.01$ vs. baseline
* $p < 0.05$ vs. baseline
[a] *n* for each cohort same as for hypoglycemia (overall) data

injection frequency and number of OGLDs received. No other adverse reactions or serious adverse reactions were reported that were considered possibly related to the study treatment.

Glucose Control

There were statistically significant improvements in measures of blood glucose control (PPG, FPG and HbA_{1c}) after 24 weeks of treatment with insulin aspart regardless of concomitant OGLD use ($p < 0.001$ versus baseline for all measures across all sub-groups in both the insulin-naive and insulin-experienced cohorts; Table 5). There were no obvious differences in these parameters between sub-groups (Table 5).

Body Weight

Body weight remained stable throughout the study for insulin-experienced patients, irrespective of the number of OGLDs received (Table 5). In the insulin-naive cohort, there was a significant mean weight gain (0.6 kg) from baseline at 24 weeks in patients receiving no OGLDs at baseline and a significant weight loss (−0.2 kg) in the sub-group receiving ≥two OGLDs at baseline (Table 5).

Table 5 Effectiveness outcomes before and after 24 weeks of treatment with insulin aspart alone or with OGLDs

Measurement	Insulin-experienced				Insulin-naive			
	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline	All	No OGLDs at baseline	One OGLD at baseline	≥Two OGLDs at baseline
Mean (SD) HbA_{1c} (%)								
Baseline	9.1 (2.1)	9.0 (2.2)	9.3 (2.1)	9.1 (1.6)	9.5 (1.9)	9.4 (2.2)	9.7 (1.9)	9.3 (1.5)
24 weeks	7.4 (1.1)	7.4 (1.2)	7.5 (1.1)	7.5 (1.0)	7.2 (1.1)	7.2 (1.1)	7.2 (1.1)	7.3 (1.1)
Change after 24 weeks	−1.7 (1.9)***	−1.6 (2.1)***	−1.9 (1.9)***	−1.7 (1.6)***	−2.2 (2.0)***	−2.1 (2.2)***	−2.4 (2.0)***	−2.1 (1.8)***
n	279	123	101	55	794	226	309	259
Mean (SD) HbA_{1c} (mmol/mol)								
Baseline	76 (23)	75 (24)	78 (23)	76 (17)	80 (21)	79 (24)	83 (21)	78 (16)
24 weeks	57 (12)	57 (13)	58 (12)	58 (11)	55 (12)	55 (12)	55 (12)	56 (12)
Change after 24 weeks	−19 (21)***	−17 (23)***	−21 (21)***	−19 (17)***	−24 (22)***	−23 (24)***	−26 (22)***	−23 (20)***
n	279	123	101	55	794	226	309	259
Mean (SD) FPG (mmol/l)								
Baseline	9.9 (3.7)	9.6 (3.9)	10.1 (3.4)	10.0 (3.7)	10.8 (3.5)	10.2 (3.6)	11.7 (3.5)	10.3 (2.9)
24 weeks	7.1 (2.0)	7.1 (2.1)	7.0 (1.9)	7.3 (2.3)	7.4 (2.0)	7.1 (1.7)	7.9 (2.3)	7.0 (1.6)
Change after 24 weeks	−2.8 (3.6)***	−2.5 (3.9)***	−3.1 (3.2)***	−2.7 (3.3)***	−3.4 (3.0)***	−3.1 (3.3)***	−3.8 (3.0)***	−3.2 (2.7)***
n	329	155	119	55	990	303	412	275
Mean (SD) PPG (mmol/l)								
Baseline	13.4 (4.5)	13.1 (4.8)	13.6 (4.1)	14.2 (4.3)	15.8 (4.7)	14.9 (5.2)	16.5 (4.4)	16.0 (4.1)
24 weeks	9.9 (2.9)	9.7 (2.7)	10.0 (3.0)	10.4 (3.3)	10.1 (3.2)	9.2 (2.9)	10.7 (3.4)	10.3 (2.8)
Change after 24 weeks	−3.5 (4.2)***	−3.4 (4.2)***	−3.6 (3.8)***	−3.8 (5.1)***	−5.8 (4.5)	−5.7 (5.0)***	−5.8 (4.3)***	−5.7 (4.1)***
n	262	119	105	38	735	255	316	164
Mean (SD) body weight (kg)								
Baseline	68.6 (13.8)	67.4 (13.7)	68.9 (14.7)	71.3 (11.9)	66.9 (12.4)	65.1 (12.8)	66.9 (11.6)	69.1 (12.7)
24 weeks	68.6 (13.1)	67.6 (12.9)	68.9 (14.2)	70.8 (10.7)	67.1 (11.8)	65.7 (12.0)	67.0 (11.1)	68.9 (12.4)
Change after 24 weeks	0.0 (2.6)	0.2 (2.6)	0.0 (2.5)	−0.5 (2.4)	0.2 (2.8)	0.6 (3.7)**	0.1 (2.4)	−0.2 (1.8)*
n	377	176	137	64	999	313	413	273
Mean (SD) HRQoL (UK VAS)								
Baseline	0.672 (0.278)	0.706 (0.287)	0.694 (0.253)	0.567 (0.277)	0.621 (0.304)	0.768 (0.258)	0.577 (0.314)	0.513 (0.271)
24 weeks	0.840 (0.163)	0.846 (0.180)	0.822 (0.147)	0.859 (0.152)	0.816 (0.162)	0.863 (0.159)	0.798 (0.163)	0.791 (0.154)
Change after 24 weeks	0.168 (0.260)***	0.141 (0.268)***	0.128 (0.246)***	0.292 (0.230)***	0.195 (0.295)***	0.095 (0.264)***	0.220 (0.304)***	0.277 (0.281)***
n	331	145	116	70	926	293	399	234

Due to the observational nature of the study not all measures were reported/collected

FPG fasting plasma glucose, pre-breakfast measurement, *HbA_{1c}* glycated hemoglobin, *HRQoL* health-related quality of life, *OGLDs* oral glucose-lowering drugs, *PPG* post-prandial plasma glucose, 90–120 min after the beginning of breakfast, *VAS* visual analog scale

*** $p < 0.001$ vs. baseline

** $p < 0.01$ vs. baseline

* $p < 0.05$ vs. baseline

Health-Related Quality of Life

Following 24 weeks of insulin aspart therapy, statistically significant improvements from baseline in UK VAS scores were observed in all sub-groups of insulin-experienced and insulin-naive patients ($p < 0.001$ versus baseline for all measures across all sub-groups in both the insulin-naive and insulin-experienced cohorts; Table 5).

DISCUSSION

In this sub-analysis of the A_1chieve study, patients who switched to/initiated therapy with insulin aspart ± OGLDs, as part of routine clinical practice, experienced statistically significant improvements in HbA_{1c}, FPG, and PPG following 24 weeks of treatment. This was achieved irrespective of previous insulin experience and the number of concomitant OGLDs received. Whereas the reduction in PPG is expected with the use of insulin aspart, the reduction in FPG level is not necessarily anticipated with the use of prandial insulin only. However, although few studies have examined the effectiveness of bolus-only insulin aspart, particularly as add-on to OGLDs, available data are in line with current findings [22, 28, 29]. In the INSTIGATE (INSulin TItration—GAining an understanding of the burden of Type 2 diabetes in Europe) observational study, for example, reductions in FPG were observed following 24 months of prandial insulin therapy ± OGLDs, and reductions in HbA_{1c} (−2.2%) were similar to those reported here [29].

Overall, 52% of the patients who switched to/initiated therapy with insulin aspart alone or in combination with OGLDs continued on this insulin regimen for the duration of the study. In the INSTIGATE study, 31% of the total cohort who were receiving prandial insulin at baseline continued to be managed on this regimen after 2 years of treatment [29]. These data suggest that a prandial insulin regimen is able to effectively control glucose levels over an extended time in many patients.

While weight increases have been reported with the longer-term use of prandial insulin [22], weight remained stable from baseline to 24 weeks in this study, irrespective of prior insulin experience and concomitant OGLD use. There was a significant, but numerically small, weight gain (0.6 kg) in a single sub-group; the insulin-naive cohort receiving no OGLDs at baseline.

Importantly, significant improvements in glycemic control with insulin aspart were also achieved without increasing the risk of hypoglycemia events irrespective of insulin injection frequency and OGLD use. There were significant reductions in the proportion of patients receiving bid or tid insulin aspart injections who reported hypoglycemia events regardless of prior insulin experience. This is pertinent given the greater risk of hypoglycemia events that might be expected with increasing injection frequency. While there were numerical reductions in the proportions of insulin-experienced patients experiencing hypoglycemia events in the groups receiving qd or qid insulin injections, these might have failed to reach statistical significance due to low patient numbers. The proportion of patients reporting hypoglycemia events in the insulin-naive group not receiving OGLDs at baseline did not significantly change between baseline and 24 weeks. Improvements in hypoglycemia were also achieved despite a high proportion of patients in the insulin-experienced and insulin-naive cohorts receiving sulfonylureas at 24 weeks (35.4% and 41.4% of patients, respectively). There were no reports of major

hypoglycemia events in the 4 weeks preceding the assessment at 24 weeks, and nocturnal hypoglycemia was reduced to low rates (<0.6 events/person-year) in all sub-groups of patients, as would be expected from the clinical profile of insulin aspart [10]. While guidelines recommend discontinuation of sulfonylureas on commencement of prandial insulin therapy to minimize the risk of hypoglycemia episodes, this does not always occur in practice [30].

The limitations of the A_1chieve study design have been discussed previously [20] and include the following: the lack of randomization, the absence of a control arm, and the absence of control for concomitant medication, dietary or lifestyle changes. In addition, the reporting of hypoglycemia events was based on patient recall of events over the preceding 4 weeks; although unlikely to affect the recording of major hypoglycemia episodes, this may have resulted in underestimation of mild events. Another limitation was that dose titration to optimize glycemic control was not a stipulation of this observational study and, therefore, glycemic control could have been better than recorded. A further improvement in glycemic control with up titration of insulin dose would appear realistic given the low rate of hypoglycemia events. Statistical power may also be limited in this sub-analysis as it includes a small proportion of the total A_1chieve cohort of patients. Despite these limitations, the results from this analysis are highly informative, given that they are derived from a large number of patients, and also from a wide geographical range, including many less developed world economies, whose standards of clinical practice with respect to type 2 diabetes mellitus are less well documented.

The A_1chieve study demonstrated that some healthcare professionals prefer to start patients on insulin therapy with prandial rather than basal insulin [20], and add basal insulin when required. Our sub-analysis shows that this strategy can be effective and well tolerated for the management of type 2 diabetes mellitus in patients poorly controlled on other treatment regimens. These findings warrant further investigation in clinical trials, given recent calls for an individualized approach to initiation of insulin regimens in people with type 2 diabetes mellitus and sub-optimal glycemic control [31].

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Compliance with ethics guidelines. All participants gave informed consent and were free to withdraw from the study at any time. The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2008 and Guidelines for Good Pharmacoepidemiology Practice.

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