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Safety and effectiveness of insulin analogues in Moroccan patients with type 2 diabetes: a sub-analysis of the A_1chieve study

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ABSTRACT

Aim: To determine the safety and effectiveness of insulin analogues in the Moroccan cohort of the prospective, multinational, non-interventional, 24-week A_1chieve study.
Methods: Moroccan patients with type 2 diabetes (T2D) starting biphasic insulin aspart 30, insulin detemir, and insulin aspart alone or in combination were included. The primary outcome was the evaluation of serious adverse drug reactions including major hypoglycaemic events. Secondary outcomes were changes in hypoglycaemic events, glycaemic parameters (HbA_{1c}, fasting plasma glucose [FPG], postprandial plasma glucose [PPPG]), systolic blood pressure (SBP), body weight and lipid profile. Quality of life (QoL) was evaluated using the EQ-5D questionnaire.
Results: In this analysis, 1641 patients (923 insulin-naive, 718 insulin-experienced) having a mean age 57.1 years, mean BMI 26.8 kg/m^2 and mean diabetes duration 10.3 years, were included. Baseline HbA_{1c} in the entire cohort was poor (9.7%, 83 mmol/mol). Insulin analogues statistically significantly improved glucose control (HbA_{1c}, FPG and PPPG, $p < 0.001$) at Week 24. The rate of hypoglycaemia decreased from 9.31 to 4.71 events/patient-year (change in proportion of patients affected, $p = 0.0002$). A statistically significant improvement in lipid parameters (except HDL cholesterol) was observed while body weight changed minimally. Additionally, QoL was positively impacted (mean change in visual analogue scores from EQ-5D was 15.8 points, $p < 0.001$).
Conclusions: Insulin analogue therapy resulted in improved glycaemic control and a significant overall decrease in hypoglycaemia in Moroccan T2D patients.

1. Introduction

In accordance with the increasing prevalence of diabetes worldwide, the Moroccan population has also seen a progressive trend in the predominance of type 2 diabetes (T2D) [1]. The prevalence of diabetes in the Middle East and North African regions is projected to increase by 83% in 2030 [2]. In 2000, the last national survey conducted in a

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representative Moroccan sample aged ⩾20 years revealed a nationwide prevalence of 6.6% [3]; however, in 2006 Nahid et al. reported 10% prevalence in Morocco [1]. Demographic and social transition involving major lifestyle modifications has been associated with the emergence of diabetes during the last decade in Morocco [4,5]. In the entire Eastern Mediterranean region, T2D is now one of the leading causes of morbidity and mortality [6].

Sustaining glycaemic control is vital to long-term diabetes management. Evidence-based guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend a target glycated haemoglobin (HbA_{1c}) level <7.0% (<53 mmol/mol) in order to minimize the risk of health-related microvascular complications [7]. However, large clinical trials have consistently reported poor glucose control at baseline [8–10]. A stumbling block to maintaining glycaemic control in newly developed/less well-resourced economies, including Morocco, is the lack of accurate clinically-supported epidemiological data.

Previously, large observational studies have demonstrated the clinical effectiveness and safety of insulin analogues [8,11–13]. Along with providing adequate glycaemic control, insulin analogues are known to have a better profile with regard to insulin-associated hypoglycaemia and weight gain that are major deterrents to patient compliance [14].

A_1chieve [10] was an observational study that evaluated clinical safety and effectiveness of insulin analogues in routine clinical practice in T2D patients. The study design included a diverse population that highlights the influence of ethnic differences on therapeutic regimens. A_1chieve study results are available online under www.A1chieve.com. Since data specific to T2D management in Morocco are scarce, this sub-analysis was conducted with an aim to elucidate effectiveness, safety and quality of life (QoL) benefits of insulin analogues in Moroccan patients in their local clinical setting.

2. Methods

2.1. Study design

A_1chieve [10] was a 24-week, international, prospective, multicentre, non-interventional, observational study conducted in T2D patients initiating basal insulin detemir (Levemir®, Novo Nordisk), bolus insulin aspart (NovoRapid®, Novo Nordisk) and biphasic insulin aspart 30 (NovoMix®, Novo Nordisk), alone or in combination, across 28 countries. Here, we report the clinical safety and effectiveness of these insulin analogues administered in routine clinical practice to a Moroccan subgroup. Patients were recruited between 15 October 2009 and 15 July 2010 at 76 study centres in Morocco. The insulin therapy including choice of insulin, starting dose and frequency of administration as well as subsequent dose or frequency changes were mutually agreed upon by the patients and their consulting physicians. A change in the use of oral glucose-lowering drugs (OGLDs) was left to the discretion of the physician. All insulin analogues used in this study were commercially available and were used in accordance with the local regulatory authority. Since there was no defined study procedure, all safety and efficacy measurements were made by the treating physician as a part of normal clinical care during routine visits. Data for analysis from the physicians' clinical notes and patients' recall and self-monitoring diary/meter was collected at baseline, during interim visit (around 12 weeks from baseline) and final visit (around 24 weeks from baseline), and transferred to a standard case report form (CRF).

2.2. Patients

In this subgroup analysis, any patient with T2D who started insulin analogue therapy at the discretion of the physician was included. Patients who had received insulin analogues (alone or in combination) for more than 4 weeks prior to the study were not eligible. Pregnant women and women who were breast-feeding or had the intention of becoming pregnant were also excluded. Concurrent use of OGLDs was permitted in all patients during the course of the study. This study was approved by the ethics committee of Morocco. All patients signed informed consent to participate in this study. Patients could withdraw at any time, following which data for analysis was collected until the time-point at which consent was withdrawn. All investigators were trained on the study protocol, CRF completion, informed consent and safety reporting procedures.

2.3. Outcome measures and assessments

The primary objective of this study was to evaluate the clinical safety of insulin analogues as determined by the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events from baseline to Week 24. Secondary safety assessments included changes in occurrence and frequency of hypoglycaemic events and the number of adverse drug reactions. Effectiveness of treatment was evaluated using changes in HbA_{1c} levels, fasting plasma glucose (FPG), post-breakfast postprandial plasma glucose (PPPG), body weight, systolic blood pressure (SBP) and lipid profile. Laboratory parameters were measured in local laboratories and were subject to local standardization and quality control procedures. A validated questionnaire, EQ-5D, evaluating mobility, self-care, usual activities, pain/discomfort and anxiety/depression was used to determine the changes in health-related QoL from baseline to Week 24. The current QoL was measured using a standard vertical 20 cm visual analogue scale (VAS, 0–100 [worst imaginable health to best imaginable health]).

2.4. Statistical methods

Statistical analyses were performed for the entire cohort (all Moroccan patients who started insulin analogues), classified as insulin-naive or insulin-experienced, and for the insulin analogue regimens used. Since patients

Table 1 – Demographic and baseline characteristics for the entire cohort and by pre-study therapy

Parameter	Entire cohort	Insulin-naive	Insulin-experienced
n (%)	1641 (100)	923 (56.2)	718 (43.8)
Gender (male/female), %	45.0/55.0	46.0/54.0	43.6/56.4
Age, years	57.1 (12.8)	57.6 (11.8)	56.4 (14.0)
Body weight (kg)	73.2 (12.7)	72.8 (12.9)	73.7 (12.4)
BMI (kg/m^2)	26.8 (4.4)	26.6 (4.4)	27.1 (4.5)
Diabetes duration (years)	10.3 (7.1)	8.6 (6.1)	12.4 (7.7)
Duration on insulin (years)	2.3 (4.1)	0.1 (0.7)	4.7 (4.9)
HbA_{1c} (mmol/mol)	83 (19)	85 (20)	78 (17)
HbA_{1c} (%)	9.7 (1.7)	9.9 (1.8)	9.3 (1.6)
Duration on OGLDs (years)	7.9 (6.1)	7.6 (5.8)	8.2 (6.5)
Prior OGLDs, n (%)			
Metformin	778 (69.0)	563 (67.1)	215 (74.7)
Sulfonylureas	806 (71.5)	694 (82.7)	112 (38.9)
Thiazolidinediones	45 (4.0)	42 (5.0)	3 (1.0)
1	464 (41.2)	258 (30.8)	206 (71.5)
2	579 (51.4)	505 (60.2)	74 (25.7)
>2	84 (7.5)	76 (9.1)	8 (2.8)

Data are presented as mean (SD) unless specified otherwise.

were not randomized, baseline characteristics such as concomitant medical conditions and choice of insulin and time of initiation were not completely elucidated. Hence, comparisons between insulin-naive and insulin-experienced patients were descriptive rather than statistical. Due to the small patient numbers, results from patients initiating IAsp were inconclusive.

Continuous and discrete variables were summarized using descriptive statistics and frequency tables (n [%]), respectively. Unless otherwise stated, all statistical analyses were conducted using two-sided tests at a pre-specified 5% significance level. The paired t-test was used to analyse the changes in HbA_{1c}, FPG, PPPG, SBP, blood lipids and QoL from baseline to Week 24. McNemar's test was used to analyse changes in hypoglycaemia from baseline in patients reporting at least one hypoglycaemic event. All analyses were performed by Novo Nordisk A/S using SAS® Version 9.1.3.

3. Results

3.1. Patients

A total of 1641 Moroccan patients (mean±SD age 57.1±12.8 years, mean body mass index 26.8±4.4 kg/m^2) were included in this analysis. The entire cohort constituted 923 insulin-naive patients (839 previously using OGLDs alone, 84 not receiving therapy) and 718 insulin-experienced patients. Demographic and baseline characteristics of patients by entire cohort and pre-study insulin type are reported in Table 1.

At baseline, HbA_{1c} <7% (<53 mmol/mol) was reported in 28 (4.8%) insulin-experienced patients and in 8 (1.1%) insulin-naive patients. Insulin-naive patients had higher baseline HbA_{1c} levels compared to insulin-experienced patients [9.9% (85 mmol/mol) vs. 9.3% (78 mmol/mol)]. In 94.9% of patients, the physician's reason for initiating insulin analogue therapy was to improve glycaemic control. Other major reasons for therapy change were patient dissatisfaction with current therapy (46.8% of patients) and reduction in plasma glucose variability (38.4% of patients).

3.2. Insulin dose

In insulin-experienced patients, the mean pre-study insulin dose was 0.56±0.26 U/kg and the mean starting insulin analogue dose was 0.59±0.27 U/kg titrated up to 0.68±0.26 U/kg at Week 24. The mean insulin analogue dose in insulin-naive patients was titrated up to 0.50±0.24 U/kg at Week 24 from an average starting dose of 0.40±0.23 U/kg. The average insulin dose in the entire cohort was 0.57±0.27 U/kg after 24 weeks. Insulin doses by regimen are reported in Tables 3 and 4 (below).

3.3. SADRs and SAEs

A total of 11 SADRs were reported in 10 patients (0.01 events/patient-year) initiating insulin analogue treatment. All SADRs reported were related to hypoglycaemic events. Overall, 22 SAEs were reported in 17 patients (0.02 events/patient-year). Metabolic and nutrition disorders were the most frequently reported events followed by cardiac disorders and nervous system disorders. Fatal outcomes in 6 patients were reported due to 10 SAEs.

Table 2 – Baseline and 24-week data for effectiveness and safety outcomes in the entire cohort and by pre-study insulin type

Parameter		Entire cohort	Insulin-naive	Insulin-experienced
HbA_{1c}, %/mmol/mol	n	984	554	430
	Baseline	9.7 (1.7)/83 (19)	9.9 (1.8)/85 (20)	9.3 (1.6)/78 (17)
	Week 24	7.6 (1.0)/60 (11)	7.6 (1.0)/60 (11)	7.5 (0.9)/58 (10)
	Change	–23 (17)/–2.1 (1.6)	–25 (19)/–2.3 (1.7)	–20 (16)/–1.8 (1.5)
	p	<0.001	<0.001	<0.001
FPG, mg/dL	n	1089	638	451
	Baseline	225.6 (80.1)	240.2 (79.6)	205.1 (76.3)
	Week 24	132.5 (38.5)	133.2 (39.0)	131.4 (37.8)
	Change	–93.2 (81.4)	–107.0 (81.5)	–73.6 (77.2)
	p	<0.001	<0.001	<0.001
PPPG, mg/dL	n	673	379	294
	Baseline	285.5 (88.7)	296.8 (86.4)	270.9 (89.6)
	Week 24	172.3 (50.3)	173.1 (49.6)	171.4 (51.2)
	Change	–113.1 (93.8)	–123.7 (94.2)	–99.6 (91.8)
	p	<0.001	<0.001	<0.001
Weight, kg	n	1200	678	522
	Baseline	73.3 (12.5)	73.0 (12.6)	73.8 (12.3)
	Week 24	74.4 (11.6)	74.4 (11.6)	74.3 (11.8)
	Change	1.0 (4.0)	1.4 (4.2)	0.5 (3.8)
	p	<0.001	<0.001	0.001
SBP, mmHg	n	1069	594	475
	Baseline	135.3 (18.0)	135.3 (17.5)	135.3 (18.6)
	Week 24	132.0 (13.8)	131.7 (13.4)	132.3 (14.3)
	Change	–3.3 (17.5)	–3.6 (17.4)	–3.0 (17.7)
	p	<0.001	<0.001	<0.001
Total cholesterol, mmol/L	n	356	205	151
	Baseline	5.1 (1.2)	5.1 (1.1)	5.1 (1.3)
	Week 24	4.7 (0.8)	4.7 (0.8)	4.7 (0.9)
	Change	–0.4 (1.1)	–0.4 (1.0)	–0.3 (1.3)
	p	<0.001	<0.001	0.002
Triglycerides, mmol/L	n	359	210	149
	Baseline	1.8 (0.9)	1.9 (1.0)	1.7 (0.8)
	Week 24	1.6 (0.6)	1.6 (0.6)	1.6 (0.5)
	Change	–0.2 (0.8)	–0.3 (0.9)	–0.1 (0.7)
	p	<0.001	<0.001	0.029
HDL cholesterol, mmol/L	n	279	165	114
	Baseline	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
	Week 24	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
	Change	0.0 (0.3)	0.0 (0.3)	0.0 (0.3)
	p	0.145	0.261	0.358
LDL cholesterol, mmol/L	n	295	168	127
	Baseline	3.2 (1.1)	3.2 (1.0)	3.2 (1.1)
	Week 24	2.8 (0.7)	2.8 (0.7)	2.9 (0.8)
	Change	–0.3 (1.0)	–0.4 (1.0)	–0.3 (1.0)
	p	<0.001	<0.001	<0.001

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Table 2 – (*continued*)

Parameter		Entire cohort	Insulin-naive	Insulin-experienced
Hypoglycaemia (events per patient-year/percent with event)				
Overall	Baseline	9.31/20.4	4.48/11.3	15.52/32.2
	Week 24	4.71/16.7	3.66/14.7	6.10/19.4
	p[a]	0.0002	0.07	<0.0001
Minor	Baseline	7.18/19.6	3.30/11.2	12.17/30.5
	Week 24	4.69/16.6	3.65/14.7	6.07/19.2
	p[a]	0.0025	0.0527	<0.0001
Nocturnal	Baseline	3.62/14.4	1.90/8.9	5.83/21.4
	Week 24	1.28/6.6	1.22/5.8	1.37/7.6
	p[a]	<0.0001	0.0002	<0.0001
Major	Baseline	2.13/9.5	1.18/6.1	3.35/13.9
	Week 24	0.02/0.1	0.02/0.1	0.02/0.2
	p[a]	<0.0001	<0.0001	<0.0001

Data are mean (SD), n or incidence.
[a] p-value is from McNemar's test in patients experiencing hypoglycaemia.

3.4. Hypoglycaemia

The rate of hypoglycaemic events decreased from 9.31 to 4.71 events/patient-year at Week 24 in the entire cohort. The proportion of patients with at least one event decreased statistically significantly from 20.4% to 16.7% ($p = 0.0002$). An increased proportion of patients reported hypoglycaemia in the insulin-naive group from baseline (11.3%) to Week 24 (14.7%); however, the incidence rate of hypoglycaemic events decreased from 4.48 to 3.66 events/patient-year. Major hypoglycaemic events were more frequent among the insulin-experienced patients (3.35 events/patient-year) compared to insulin-naive patients (1.18 events/patient-year) at baseline. Insulin analogue therapy statistically significantly decreased the proportion of patients reporting major hypoglycaemia at Week 24 ($p < 0.0001$) in both groups (Table 2). In the insulin-naive cohort, the incidence rate of minor hypoglycaemia was 3.30 events/patient-year at baseline and 3.65 events/patient-year at Week 24 (change in proportion of patients affected, $p = 0.0527$) while nocturnal hypoglycaemia decreased from 1.90 to 1.22 events/patient-year (patients affected, $p = 0.0002$, Table 2). Incidence rates of minor and nocturnal hypoglycaemia decreased from 12.17 to 6.07 events/patient-year and 5.83 to 1.37 events/patient-year, respectively, in insulin-experienced patients (change in proportion of patients affected, $p < 0.0001$, Table 2).

Changes in hypoglycaemia by insulin regimen are reported in Tables 3 and 4. The proportion of insulin-naive patients experiencing overall hypoglycaemia was statistically significantly higher in the biphasic insulin aspart 30 group at Week 24 compared to baseline ($p = 0.0061$). However, the proportion of patients affected with major hypoglycaemia decreased statistically significantly with biphasic insulin aspart 30 and insulin detemir treatment. The proportion of insulin-experienced patients having overall, major, minor and nocturnal hypoglycaemia decreased statistically significantly at Week 24 in all insulin regimens ($p < 0.0001$) with the exception of insulin aspart treatment.

3.5. Glucose control parameters

At Week 24, significant improvements were noted in the levels of HbA_{1c} (–2.1±1.6%, –23±17 mmol/mol), FPG (–93.2±81.4 mg/dL) and PPPG (–113.1±93.8 mg/dL) ($p < 0.001$, Table 2). Prior insulin users reported numerically lower changes in glucose control parameters compared to insulin-naive patients. The proportion of patients achieving the HbA_{1c} target of <7.0% (<53 mmol/mol) increased from 2.8% at baseline to 22.8% at Week 24. Metformin (81.3%) and sulfonylureas (44.5%) were the most commonly used OGLDs in all patients at Week 24.

Overall, blood glucose improvements were clinically and statistically significant with all insulin regimens in both insulin-naive and insulin-experienced patients (Tables 2–4). However, these improvements were larger in insulin-naive patients compared to insulin-experienced patients.

3.6. Body weight, blood lipids and blood pressure control

In the entire cohort, the mean increase in body weight was 1.0 kg (1.4 kg in insulin-naive patients and 0.5 kg in insulin-experienced patients; $p < 0.001$). Changes in body weight were consistent and comparable between different insulin analogues (Tables 3 and 4).

Total cholesterol levels decreased statistically significantly in the entire cohort from 5.1±1.2 mmol/L at baseline to 4.7±0.8 mmol/L at Week 24 ($p < 0.001$). A statistically significant decrease in triglycerides and low-density lipoprotein cholesterol was observed in the entire cohort ($p < 0.001$). No change was observed in high-density lipoprotein cholesterol levels (Tables 2–4). Lipid profile changes were more profound in insulin-naive patients and insulin-experienced patients receiving biphasic insulin aspart 30 compared to the other groups (Tables 3 and 4).

Table 3 – Baseline and 24-week data for effectiveness and safety outcomes by insulin analogue regimen in insulin-naive patients

Parameter		Biphasic insulin aspart 30	Insulin detemir	Insulin aspart alone	Insulin aspart + basal insulin
Insulin dose, U/kg	Pre-study	0	0	0	0
	Baseline	0.52 (0.16)	0.24 (0.16)	0.30 (0.27)	0.65 (0.25)
	Week 24	0.62 (0.21)	0.33 (0.13)	0.33 (0.17)	0.76 (0.33)
HbA_{1c},%/mmol/mol	Baseline	10.2 (2.0)/88 (22)	9.6 (1.4)/81 (15)	9.2 (0.8)/77 (9)	11.1 (2.6)/98 (28)
	Week 24	7.6 (0.9)/60 (10)	7.6 (1.1)/60 (12)	7.9 (0.8)/63 (9)	7.6 (0.8)/60 (9)
	Change	−2.5 (1.8)/−27 (20)	−2.0 (1.4)/−22 (15)	−1.2 (0.1)/−13 (1)	−3.6 (2.3)/39 (25)
	p	<0.001	<0.001	– [a]	– [a]
FPG, mg/dL	Baseline	249.2 (79.4)	224.5 (66.3)	227.3 (107.6)	278.5 (118.6)
	Week 24	134.2 (39.7)	130.9 (38.0)	175.0 (83.0)	131.9 (28.5)
	Change	−115.0 (82.9)	−93.6 (69.4)	−52.3 (80.3)	−146.6 (118.7)
	p	<0.001	<0.001	– [a]	– [a]
PPPG, mg/dL	Baseline	313.2 (80.7)	279.1 (86.7)	248.0 (.)	319.2 (123.2)
	Week 24	176.4 (51.8)	173.4 (49.5)	123.0 (.)	157.2 (30.2)
	Change	−136.8 (94.7)	−105.7 (89.4)	−125.0 (.)	−161.9 (120.9)
	p	<0.001	<0.001	– [b]	– [a]
Body weight, kg	Baseline	72.2 (12.7)	74.1 (12.4)	74.3 (8.1)	68.4 (14.1)
	Week 24	74.0 (11.3)	74.9 (11.9)	79.3 (5.1)	69.8 (11.1)
	Change	1.9 (4.6)	0.8 (3.3)	5.0 (5.2)	1.4 (6.5)
	p	<0.001	<0.001	– [a]	– [a]
SBP, mmHg	Baseline	136.0 (18.1)	133.9 (15.6)	146.0 (11.4)	143.7 (27.2)
	Week 24	131.6 (13.2)	131.8 (13.5)	140.0 (7.1)	129.5 (16.4)
	Change	−4.4 (16.6)	−2.1 (17.3)	−6.0 (11.4)	−14.2 (26.0)
	p	<0.001	0.041	– [a]	– [a]
Total cholesterol, mmol/L	Baseline	5.3 (1.2)	5.0 (1.1)	–	5.7 (0.9)
	Week 24	4.7 (0.7)	4.7 (0.7)	–	5.5 (0.4)
	Change	−0.6 (0.9)	−0.3 (1.0)	–	−0.2 (1.2)
	p	<0.001	0.003		– [a]
Triglycerides, mmol/L	Baseline	2.0 (1.1)	1.8 (0.9)	–	1.8 (0.5)
	Week 24	1.6 (0.5)	1.6 (0.6)	–	1.9 (0.3)
	Change	−0.3 (1.0)	−0.2 (0.8)	–	0.1 (0.6)
	p	0.005	0.015		– [a]
HDL cholesterol, mmol/L	Baseline	1.1 (0.3)	1.2 (0.3)	–	1.2 (0.1)
	Week 24	1.2 (0.4)	1.2 (0.3)	–	1.3 (0.1)
	Change	0.1 (0.4)	−0.0 (0.3)	–	0.1 (0.1)
	p	0.098	0.602		– [a]
LDL cholesterol, mmol/L	Baseline	3.3 (1.3)	3.0 (0.9)	–	2.8 (0.5)
	Week 24	2.8 (0.6)	2.7 (0.7)	–	4.2 (1.2)
	Change	−0.5 (1.0)	−0.3 (0.9)	–	1.4 (0.8)
	p	<0.001	0.003		– [a]

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Table 3 – *(continued)*

Parameter		Biphasic insulin aspart 30	Insulin detemir	Insulin aspart alone	Insulin aspart + basal insulin
Hypoglycaemia (events per patient-year/percent with at least one event)					
Overall	Baseline	6.49/17.9	2.07/4.9	0.00/0.0	16.50/15.4
	Week 24	5.17/24.6	1.99/5.2	0.00/0.0	3.39/4.3
	p[c]	0.0061	0.8618	–	–
Minor	Baseline	4.66/17.9	1.59/4.7	0.00/0.0	13.00/15.4
	Week 24	5.14/24.6	1.99/5.2	0.00/0.0	3.39/4.3
	p[c]	0.0061	1	–	–
Nocturnal	Baseline	2.93/14.0	0.83/3.9	0.00/0.0	5.00/15.4
	Week 24	1.33/9.4	1.13/2.6	0.00/0.0	0.00/0.0
	p[c]	0.0005	0.2207	–	–
Major	Baseline	1.82/9.9	0.48/2.2	0.00/0.0	3.50/11.5
	Week 24	0.04/0.3	0.00/0.0	0.00/0.0	0.00/0.0
	p[c]	<0.0001	0.0047	–	–

Data are presented as mean (SD) unless specified otherwise. A small number of people using other insulin regimens (n = 45) could not be included in the above classifications.
[a] p-values are not presented when the number of patients analysed was less than 100.
[b] Only 1 insulin-naive patient on insulin aspart alone reported PPPG levels.
[c] p-value is from McNemar's test in patients experiencing hypoglycaemia.

SBP decreased statistically significantly in the entire cohort from 135.3 to 132 mmHg (mean change –3.3 mmHg, $p < 0.001$). Similar changes were noted in insulin-naive patients and insulin-experienced patients (Table 2). SBP improvements were statistically significant in all groups with the exception of insulin-experienced patients receiving insulin detemir (Tables 3 and 4).

3.7. *Quality of life*

The reported EQ-5D VAS scores improved statistically significantly from 60.0 points at baseline to 75.8 points at Week 24 (mean change 15.8 points, $p < 0.001$) for the entire cohort. The change in QoL at Week 24 was numerically higher in the insulin-naive patients (17.0 points) compared to insulin-experienced patients (14.1 points).

4. Discussion

This sub-analysis demonstrated the clinical safety and effectiveness of insulin analogues (biphasic insulin aspart 30, insulin detemir and insulin aspart alone or in combination) in Moroccan patients with T2D.

As demonstrated in large multinational studies such as IMPROVE and A_1chieve [8,10], this cohort also presented with poorly controlled HbA_{1c} levels (mean 9.7%, 83 mmol/mol) at baseline. Additionally, target HbA_{1c} <7% (<53 mmol/mol) was reported only in 2.8% of patients. Insulin analogue therapy resulted in an improvement in HbA_{1c} in both insulin-naive and insulin-experienced patients. Overall, the number of patients achieving HbA_{1c} <7% also increased from 36 to 258 patients after 24 weeks. FPG and PPPG improvements were consistent with the HbA_{1c} results. Furthermore, the lipid profile and SBP improved statistically significantly thus providing evidence for a potential decrease in cardiovascular risk.

Conventionally, intensive glucose control has been associated with an increased risk of adverse drug reactions, especially hypoglycaemia, and a high risk of cardiovascular diseases [15,16]. Intensification of T2D management has also shown a dramatic increase in the frequency of major and minor hypoglycaemia in the ACCORD trial in which patients received complex combinations of OGLDs and insulin [17]. However, insulin analogues in the Moroccan cohort as well as the entire A_1chieve cohort [10] could introduce adequate glucose control along with a low incidence of SADRs, including hypoglycaemia. Overall hypoglycaemia rates decreased from 9.31 to 4.71 events/patient-year. As expected, similar to overall A_1chieve data, insulin-experienced patients reported a greater decrease in hypoglycaemic events compared with insulin-naive patients initiating insulin analogue therapy. Some of the highest hypoglycaemia reduction rates were observed in North Africa owing to the higher baseline rates compared with other regions included in the A_1chieve study [10].

A negative correlation between T2D progression and health-related QoL has been long-established. Psychosocial aspects are important determinants that influence self-care behaviours that ultimately impact glycaemic control [18]. In the Moroccan cohort, a statistically significant improvement in all 5 dimensions of the EQ-5D was reported at the end of 24 weeks thus demonstrating a positive impact on QoL.

Although this observational study, as do all studies with this design, lacks a standardized approach, it offers a broad perspective to apply therapeutic regimens in common clinical practice. The results of this study suggest that initiating insulin analogue treatment, irrespective of prior

Table 4 – Baseline and 24-week data for effectiveness and safety outcomes by insulin analogue regimen in insulin-experienced patients

Parameter		Biphasic insulin aspart 30	Insulin detemir	Insulin aspart alone	Insulin aspart + basal insulin
Insulin dose, U/kg	Pre-study	0.56 (0.24)	0.38 (0.21)	0.56 (0.28)	0.63 (0.29)
	Baseline	0.60 (0.20)	0.31 (0.13)	0.29 (0.22)	0.73 (0.26)
	Week 24	0.67 (0.20)	0.37 (0.16)	0.66 (0.26)	0.80 (0.27)
HbA_{1c}, %/mmol/mol	Baseline	9.4 (1.6)/79 (17)	8.8 (1.3)/73 (14)	9.1 (1.3)/76 (14)	9.8 (1.9)/84 (21)
	Week 24	7.5 (0.9)/58 (10)	7.6 (1.0)/60 (11)	7.5 (0.9)/58 (10)	7.5 (0.9)/58 (10)
	Change	−1.9 (1.5)/−21 (16)	−1.2 (1.3)/−13 (14)	−1.6 (1.5)/−17 (16)	−2.3 (1.8)/−25 (20)
	p	<0.001	<0.001	– [a]	– [a]
FPG, mg/dL	Baseline	206.4 (72.1)	180.9 (58.3)	196.9 (87.4)	208.3 (91.2)
	Week 24	130.8 (35.3)	127.6 (37.8)	142.5 (41.1)	131.3 (38.3)
	Change	−75.6 (73.5)	−53.3 (59.8)	−54.5 (89.8)	−77.0 (92.9)
	p	<0.001	<0.001	– [a]	– [a]
PPPG, mmol/L	Baseline	279.3 (86.7)	226.5 (57.8)	257.5 (96.7)	266.6 (94.5)
	Week 24	172.6 (49.5)	176.6 (56.5)	173.8 (45.7)	162.4 (41.3)
	Change	−106.7 (89.3)	−49.8 (83.6)	−83.6 (96.9)	−104.2 (92.6)
	p	<0.001	0.004	– [a]	– [a]
Body weight, kg	Baseline	74.5 (11.6)	77.1 (13.0)	68.7 (11.9)	71.2 (13.2)
	Week 24	75.2 (11.2)	76.5 (12.0)	69.2 (10.9)	71.4 (12.7)
	Change	0.7 (3.7)	−0.6 (3.9)	0.5 (2.5)	0.3 (3.5)
	p	0.002	0.229	0.301	– [a]
SBP, mmHg	Baseline	134.6 (15.7)	136.5 (17.8)	133.8 (17.4)	137.1 (24.9)
	Week 24	132.2 (13.4)	135.0 (14.7)	126.7 (13.1)	131.3 (15.3)
	Change	−2.4 (16.8)	−1.5 (18.9)	−7.1 (17.5)	−5.8 (20.1)
	p	0.037	0.49	– [a]	– [a]
Total cholesterol, mmol/L	Baseline	5.2 (1.1)	4.7 (1.0)	5.2 (1.0)	5.1 (1.6)
	Week 24	4.7 (0.8)	5.0 (1.4)	4.3 (1.4)	5.0 (0.9)
	Change	−0.5 (1.2)	0.3 (1.5)	−0.9 (1.8)	−0.1 (1.3)
	p	<0.001	0.401	– [a]	– [a]
Triglycerides, mmol/L	Baseline	1.7 (0.8)	2.1 (1.1)	1.7 (0.3)	1.5 (0.8)
	Week 24	1.6 (0.5)	1.8 (0.6)	1.6 (0.2)	1.5 (0.5)
	Change	−0.1 (0.7)	−0.2 (1.0)	−0.1 (0.3)	−0.0 (0.6)
	p	0.218	0.284	– [a]	– [a]
HDL cholesterol, mmol/L	Baseline	1.2 (0.3)	1.0 (0.3)	1.2 (0.3)	1.3 (0.4)
	Week 24	1.2 (0.3)	1.2 (0.4)	1.3 (0.2)	1.3 (0.3)
	Change	−0.0 (0.3)	0.3 (0.5)	0.1 (0.2)	−0.0 (0.3)
	p	0.845	0.055	– [a]	– [a]
LDL cholesterol, mmol/L	Baseline	3.3 (0.9)	2.7 (0.7)	3.2 (1.0)	3.4 (1.7)
	Week 24	2.9 (0.6)	2.8 (0.7)	3.0 (1.2)	2.9 (1.1)
	Change	−0.4 (0.8)	0.2 (0.8)	−0.2 (1.0)	−0.5 (1.5)
	p	<0.001	0.44	– [a]	– [a]

continued on next page

Table 4 – *(continued)*

Parameter		Biphasic insulin aspart 30	Insulin detemir	Insulin aspart alone	Insulin aspart + basal insulin
Hypoglycaemia (events per patient-year/percent with at least one event)					
Overall	Baseline	14.75/33.4	13.60/31.5	12.37/22.0	24.71/36.6
	Week 24	6.55/22.0	2.67/9.0	8.07/31.0	7.45/19.1
	p[b]	0.0001	0.0011	–[a]	0.0006
Minor	Baseline	11.41/31.6	10.83/31.5	8.88/22.0	20.34/34.4
	Week 24	6.55/22.0	2.67/9.0	8.07/31.0	7.33/18.2
	p[b]	0.001	0.0011	–[a]	0.0016
Nocturnal	Baseline	5.78/23.3	4.09/16.7	4.44/12.2	9.33/26.7
	Week 24	1.57/8.9	0.33/2.6	2.69/13.8	1.65/8.2
	p[b]	<0.0001	0.0008	–[a]	0.0001
Major	Baseline	3.34/14.0	2.77/14.8	3.49/12.2	4.37/14.5
	Week 24	0	0.00/0.0	0.00/0.0	0.12/0.9
	p[b]	<0.0001	0.0009	–[a]	0.0002

Data are presented as mean (SD) unless specified otherwise. A small number of people using other insulin regimens (n = 103) could not be included in the above classifications.

[a] p-values are not presented when the number of patients analysed was less than 100.

[b] p-value is from McNemar's test in patients experiencing hypoglycaemia.

insulin use, enhances effective long-term T2D management along with a good safety profile.

Conflict of interest statement

Abdelmjid Chraibi, Farida Ajdi, Jamal Belkhadir, Naoual El Ansari, Fatima Marouan and Ahmed Farouqi received funding from Novo Nordisk and other insulin manufacturers for their research, advisory and educational activities. 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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