Contents lists available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Insulin detemir in the management of type 2 diabetes in non-Western countries: Safety and effectiveness data from the A$_1$chieve observational study☆,☆☆

Alexey Zilov[a,*], *Nabil El Naggar*[b], *Siddharth Shah*[c], *Chunduo Shen*[d], *Jihad Haddad*[e]

[a] *Department of Endocrinology, First Moscow State Medical University, Moscow, Russia*
[b] *Internal Medicine, Hai Aljamea Hospital, Jeddah, The Kingdom of Saudi Arabia*
[c] *Bhatia Hospital, Mumbai, India*
[d] *Novo Nordisk International Operations, Zurich Switzerland*
[e] *Division of Endocrinology, Prince Hamazah Hospital, Amman, Jordan*

ARTICLE INFO

Keywords:
A$_1$chieve
Insulin detemir
Non-interventional study
Type 2 diabetes

ABSTRACT

Aims: This subgroup analysis of the A$_1$chieve study examined data from 15,545 people who started treatment with insulin detemir ± oral glucose-lowering drugs in routine clinical care.

Methods: A$_1$chieve was a 24-week, international, prospective, non-interventional study of people with type 2 diabetes from non-Western nations starting treatment with basal insulin detemir, bolus insulin aspart or biphasic insulin aspart 30, alone or in combination, to evaluate their safety and effectiveness in routine clinical practice.

Results: HbA$_{1c}$ for the global cohort improved after 24 weeks from 9.5 ± 1.6% by –2.0 ± 1.6% [80 ± 17 by –22 ± 17 mmol/mol] (–2.1 ± 1.6% [–23 ± 17 mmol/mol] for insulin-naïve participants; –1.6 ± 1.7% [–17 ± 19 mmol/mol] for prior insulin users). Fasting plasma glucose and postprandial plasma glucose were also significantly reduced ($p < 0.001$), irrespective of prior therapy or geographical region. The incidence of major hypoglycaemia decreased significantly over 24 weeks in both the insulin-naïve and insulin-experienced groups ($p < 0.0001$). Mean body weight decreased overall by –0.4 ± 4.0 kg and blood pressure, lipid profiles, and self-reported quality of life improved over 24 weeks for all people starting treatment with insulin detemir.

Conclusion: People with type 2 diabetes in poor glycaemic control starting treatment with insulin detemir reported significant improvements in glycaemic control with improved treatment tolerability, irrespective of prior treatment and geographical region, after 24 weeks.

1. Introduction

The primary aim of diabetes management is to achieve satisfactory levels of glycaemic control, thereby reducing the risk of serious long-term diabetes related complications [1–3]. Published data, however, suggest that the majority of people with type 2 diabetes (T2D) worldwide are not achieving the recommended targets set for good glycaemic

☆ This study was funded by Novo Nordisk.
☆☆ Clinical trial registration: Clinicaltrials.gov, NCT00869908.
* *Corresponding author*: Alexey Zilov, MD PhD, Department of Endocrinology, First Moscow State Medical University, 1 Pogodinskaya Street, Office 622, Moscow, Russia. Tel.: +7 9037180050.
E-mail address: avzilov@hotmail.com (A. Zilov).
0168-8227/$ – see front matter © 2013 The Authors. Published by Elsevier Ireland Ltd. All rights reserved.
doi: 10.1016/j.diabres.2013.06.003

control [4–8]. The progressive loss of beta-cell function that characterises T2D ideally requires concurrent changes in treatment to allow people to reach and then maintain adequate glycaemic control and most will require insulin therapy to achieve this [9,10]. Currently, insulin analogues are gaining wide acceptance and are frequently prescribed due to their distinguished pharmacodynamic and pharmacokinetic profile and based on evidence of their effectiveness and safety in clinical trials [11], yet effectual use in the management of glycaemia remains a challenge, particularly in developing countries where there is a sustained rise in prevalence of diabetes.

The introduction of basal insulin is a simple, effective and well-validated choice to start people with T2D on insulin therapy [12,13]. Randomised controlled trials (RCTs) have shown that the basal analogue insulin detemir can effectively improve glycaemic control with a lower risk of hypoglycaemia than with intermediate-acting human insulin NPH [14–17], and is associated with less weight gain than NPH and the basal insulin analogue glargine [14,15,17,18]. Complementary evidence from real-life clinical practice in large heterogeneous populations provides further support for the clinical benefits that insulin detemir may offer for insulin-naïve patients with T2D starting basal therapy and for those changing treatment from existing insulin treatment (efficacy, lower risk of hypoglycaemia and less weight gain) [7,12,14,19,20].

A_1chieve was an observational study designed to examine the safety and clinical effectiveness of insulin analogues in T2D. The global scope of A_1chieve, which included 28 countries with different healthcare resources and ethnic diversity, allows insights into regional and country effects on clinical outcomes. The aim of this sub-group analysis is to examine data from people who started treatment with insulin detemir ± oral glucose-lowering drugs (OGLDs) in routine clinical care. Outcomes from patients on different pre-study therapies are compared, along with regional differences.

2. Methods

2.1. Study design

A_1chieve was a 24-week, international, prospective, multicentre, non-interventional study of people with T2D who had started using basal insulin detemir, bolus insulin aspart or biphasic insulin aspart 30 alone or in combination, to evaluate their safety and effectiveness in routine clinical practice [7,21]. The study was carried out in 28 countries across Asia, Africa, Latin America and Europe, grouped into seven geographical regions: China, South Asia, East Asia, North Africa, Middle East/Gulf, Latin America and Russia. A total of 66,726 people participated in the study from 3166 clinical sites, recruited between January 2009 and June 2010.

2.2. Participants and treatment

Clinical outcomes are reported here for people with T2D who were prescribed insulin detemir by their physician in the course of normal clinical practice. They were eligible for enrolment provided prior pharmaceutical therapy did not include exposure to the study insulins for >4 weeks prior to acceptance. Patients with a hypersensitivity to the study drug or the excipients, and women who were pregnant, breastfeeding, or had the intention of becoming pregnant within the next 24 weeks were excluded from the study. When prescribed, insulin detemir was commercially available and was funded according to local practice in routine care. The selection of patients and any changes to dose and concomitant therapy were made at the discretion of the participant and consulting physician. Ethical approval was obtained in each country.

2.3. Assessments and outcome measures

The primary safety assessment was evaluation of the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, considered related to insulin detemir between baseline and final visit. Secondary safety assessments included the change in number of hypoglycaemic events in the last 4 weeks before the interim and final visits (approximately 12 and 24 weeks from baseline), compared with the last 4 weeks before the baseline visit, and the number of adverse drug reactions (ADRs) from baseline to final visit.

Effectiveness assessments were change in HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight between baseline and interim and final visits, and change in systolic blood pressure (SBP) and lipid profile at final visit. Assessments were recorded by physicians during routine clinical visits and data were collected from medical records, patient diaries, and recall, and laboratory measurements were made in local laboratories. The physician's rationale for prescribing insulin detemir was also recorded.

Health-related quality of life (HRQoL) was measured using the EQ-5D questionnaire [22] at baseline and after 24 weeks of therapy. This questionnaire was designed to assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and provides a visual analogue scale (VAS) for individuals to rate their current HRQoL between 0 and 100, with a higher score indicating better self-perceived health. Full study design details, assessments, and outcome measures have been published previously [7].

2.4. Statistical methods

Analysis of safety and efficacy outcomes was performed on any participant entered into the study who had data relevant to that analysis. Analyses were performed for the entire cohort prescribed insulin detemir, categorised by prior insulin-treated or insulin-naïve and by geographical regions (defined in study design). Comparison between pre-study therapy and regions are reported as descriptive statistics only. Changes from baseline for HbA_{1c}, FPG, PPG, lipids, and QoL were analysed using a paired *t*-test, with the majority of data expressed as mean (standard deviation [SD]), unless otherwise stated. Due to the low number of participants in this sub-group analysis from China, descriptive data only are presented in the tables to represent the entire regional pro-

file. For hypoglycaemia change from baseline, the percentage of people reporting at least one event was analysed using McNemar's test.

3. Results

3.1. *Study participants*

Among the 66,726 people who were enrolled in the A_1chieve study, 15,545 started insulin therapy with or switched to detemir ± OGLDs. A total of 86.9% completed the study treatment period, 13.1% withdrew, 7.5% lost contact with their physician, 5.4% citied other reasons, and 0.2% reported adverse drug reactions. Prior to enrolment, 4.8% were receiving no medication for diabetes and 72.9% were being treated with OGLDs alone. Of the remaining 22.3% who were changing their insulin therapy, 64.4% transferred from human insulin (sub-divided as 50.6% from NPH, 35.6% from human premix, 8.1% from human soluble insulin, 4.2% from basal–bolus NPH/human insulin, and the remaining 1.5% from other insulins), 26.9% transferred from the basal insulin analogue glargine, and 8.7% transferred from other insulin therapies. Globally, mean (±SD) duration of diabetes was higher in the prior insulin user cohort (11.0 ± 7.0 vs. 7.6 ± 5.5 years). For insulin-naïve participants, the percentage of people using more than two OGLDs decreased by 58% (27.7% pre-study, 11.7% at 24 weeks). Metformin use was maintained (84%), but there were reductions in the percentages of people using sulphonylureas (84.3% pre-study, 64.0% at 24 weeks) and thiazolidinediones (23.6% pre-study, 11.3% at 24 weeks). For the participants changing insulin therapy, metformin use also remained consistent (~80%), while sulphonylurea and thiazolidinedione use decreased (61.5% to 53.4%, and 14.0% to 9.2%, respectively. At the end of the study, the percentage of previously insulin-experienced participants using more than two OGLDs decreased from 11.5% (pre-study) to 9.9% after 24 weeks using insulin detemir.

Baseline demographics and regional distribution are shown in Table 1. The majority of patients starting basal insulin or switching to insulin detemir came from the Middle East/Gulf and East Asian regions (28.8 and 27.2%, respectively) (Table 1). Patient characteristics followed similar trends to the global cohort; regional differences of note were that the majority of patients from Russia were female (70.0%), while 65.5% from the Middle East/Gulf were male. Overall duration of diabetes was highest in Latin American countries and lowest in South Asia (11.6 ± 8.3 vs. 5.8 ± 4.3 years). Mean (±SD) body weight was highest at baseline in the Middle East and Gulf region and Russia (87.3 ± 15.0 and 85.0 ± 15.4 kg) and lowest in East Asia (64.6 ± 12.1 kg). In the prior insulin users groups, the mean duration of insulin treatment was 3.2 ± 3.9 years for the global cohort and was similar for most of the regions. Exceptions of note were Russia, where the mean duration of insulin treatment prior to the start of the trial was 2.5 ± 2.7 years and Latin America, where participants had been using insulin for 5.0 ± 5.5 years.

The majority of people were insulin-naïve in all regions at baseline (range: 63.0% in Latin America to 84.7% in South Asia). Of the prior insulin users, the majority transferred from a human or analogue basal insulin regimen (64.7%). For the overall cohort, this was approximately a 50:50 split between basal analogue and human basal insulin but, regionally, basal analogue was more frequently prescribed in all regions except Russia and Latin America, where basal human insulin accounted for >85% of pre-study basal insulin choice. Overall, 23.8% of prior insulin users switched from a premix regimen (96.4% human insulin premix), which was most popular in South Asia (49.3%).

Baseline glucose control was poor regardless of pre-study

Table 1 – Patient numbers and characteristics by pre-study therapy and regional distribution in the insulin detemir subgroup and entire A_1chieve study population.

Demographic	Insulin detemir subgroup population			A_1chieve study population		
	Global cohort	Insulin-naïve	Insulin-experienced	Global cohort	Insulin-naïve	Insulin-experienced
n (%)	15,545 (100)	12,078 (77.7)	3467 (22.3)	66,726 (100)	44,872 (67.2)	21,854 (32.8)
Gender, M/F (%)	54.1/45.9	55.0/45.0	51.3/48.7	55.6/44.4	57.3/42.7	51.9/48.1
Age (years)	54.6 (11.5)	54.0 (11.3)	56.8 (11.9)	54.0 (12.0)	53.2 (11.6)	55.6 (12.5)
Body weight (kg)	76.6 (16.3)	76.5 (16.3)	76.7 (16.3)	72.9 (15.0)	71.7 (14.4)	75.3 (15.9)
BMI (kg/m^2)	28.2 (5.3)	28.2 (5.3)	28.4 (5.5)	27.1 (5.0)	26.7 (4.7)	27.9 (5.50
Duration of diabetes (years)	8.4 (6.0)	7.6 (5.5)	11.0 (7.0)	8.0 (19)	80 (19)	79 (20)
>2 OGLDs, *n* (%)	1608 (11.7)	1320 (12.1)	288 (10.2)	10,981 (20.1)	8971 (23.1)	2010 (12.7)
HbA_{1c} (% [mmol/mol])	9.5 (1.6) [80]	9.5 (1.6) [80]	9.3 (1.7) [78]	9.5 (1.7) [80]	9.5 (1.7) [80]	9.4 (1.8) [79]
Geographic region (% of cohort)						
China	137 (100)	88 (64.2)	49 (35.8)	11,020 (100)	8206 (74.4)	2814 (25.6)
South Asia	3079 (100)	2608 (84.7)	471 (15.3)	22,447 (100)	18,067 (80.5)	4380 (19.5)
East Asia	4230 (100)	3195 (75.5)	1035 (24.5)	10,032 (100)	6594 (65.7)	3438 (34.3)
North Africa	1746 (100)	1250 (71.6)	496 (28.4)	4039 (100)	1969 (48.7)	2070 (51.3)
Middle East and Gulf	4474 (100)	3560 (79.6)	914 (20.4)	14,976 (100)	7501 (50.1)	7475 (49.9)
Latin America	643 (100)	405 (63.0)	238 (37.0)	1138 (100)	636 (55.9)	502 (44.1)
Russia	1236 (100)	972 (78.6)	264 (21.4)	3074 (100)	1899 (61.8)	1175 (38.2)

Data are mean (SD), unless otherwise stated.
BMI, body mass index; OGLD, oral glucose-lowering drug.

treatment or geographical region. Baseline HbA_{1c} was lowest in people switching from treatment with basal insulin glargine (9.0 ± 1.7% [75 mmol/mol]) and highest in the insulin-naïve cohort (9.5 ± 1.6% [80 mmol/mol]). Regionally, baseline HbA_{1c} was lowest in North Africa 9.3 ± 1.7% [78 mmol/mol]) and highest in Latin America (9.6 ± 2.2% [81 mmol/mol]).

The most frequent reason given by physicians for introducing insulin detemir was to improve glycaemic control (95.5%). Other reasons included: to reduce plasma glucose variability (27.7%), reduce the risk of hypoglycaemia (23.9%), address patient dissatisfaction with current therapy (22.3%), control unstable diabetes (21.2%), and improve weight control (21.0%).

The prevalence of diabetic complications at baseline for the overall cohort were as follows: cardiovascular (26.8%), renal (28.4%), eye (26.5%), foot ulcer (4.4%), and neuropathic (40.1%). Figures were similar for most regions with the exception of Russia, where the prevalence of diabetes-related cardiovascular, eye, and neuropathy complications was notably higher (70.3, 64.7, and 81.1% respectively). Russia was also the only region to report similar prevalence of complications in both the insulin-naïve and prior insulin users. Diabetic renal complications were most prevalent in the Middle East/Gulf region (39.2%).

3.2. *Primary safety outcomes*

Out of a total of 15,545 patients, seven SADRs were reported by seven people; instances of hypoglycaemia were noted in four people and hyperglycaemia in three; of these adverse events, five instances were assessed as probably being related to treatment and two as possibly related.

3.3. *Effectiveness outcomes*

3.3.1. *By pre-study therapy*

Significant improvements in glycaemic control were associated with insulin detemir from baseline to final visit in insulin-naïve patients and prior insulin users. Mean reductions in HbA_{1c}, FPG, and PPG were greater in the insulin-naïve subgroup than for prior insulin users (Table 2). Overall, the proportion of patients reaching HbA_{1c} <7.0% [53 mmol/mol] increased from 3.0% at baseline to 31.5% after 24 weeks; similar results were reported for the pre-study therapy subgroups (Table 2).

In the insulin-naïve cohort, mean daily insulin dose was 0.24 ± 0.13 U/kg/day at baseline and 0.35 ± 0.18 U/kg/day at the end of the study. In prior insulin users, the pre-study mean insulin dose was 0.42 ± 0.24 IU/kg/day, and 0.45 ± 0.24 U/kg/day of insulin detemir at 24 weeks (Table 2). For the 3467 prior insulin users starting insulin therapy with detemir at baseline, the majority switched from NPH (32.6%, n = 1131), insulin glargine (26.9%, n = 934), or premix insulin (23.8%, n = 825).

Pre-study mean basal insulin doses were 0.38 ± 0.21 IU/kg/day (NPH) and 0.33 ± 0.17 U/kg/day (glargine); at 24 weeks insulin doses for these subgroups were 0.47 ± 0.23 U/kg/day and 0.42 ± 0.22 U/kg/day, respectively. Prior users of premix insulin reported a mean dose change from 0.51 + 0.24 IU/kg/day to 0.46 ± 0.24 U/kg/day of insulin detemir at 24 weeks. Prior to switching to insulin detemir, 53.6% of patients were on a once-daily insulin regimen. At the end of the study, 79.1% of people initiating insulin with detemir, and 70.0% of those transferring insulin therapy to detemir were using a once-daily regimen.

HbA_{1c} decreased significantly from 9.1 ± 1.8% [76 mmol/mol] at baseline by –1.4 ± 1.7% [15 mmol/mol] ($p < 0.001$) by the end of the study for NPH users, from 9.0 ± 1.7% [75 mmol/mol] by –1.3 ± 1.7 [14 mmol/mol] for patients switched from insulin glargine, and from 9.5% ± 1.7% [80 mmol/mol] by –2.1 ± 1.7 [23 mmol/mol] in people changing from premix therapy ($p < 0.001$ for all). Significant improvements ($p < 0.001$) were also observed for FPG and PPG: –2.4 ± 3.6 mmol/L and –3.2 ± 4.0 mmol/L for NPH, –2.0 ± 3.3 mmol/L and –3.1 ± 4.3 mmol/L for prior insulin glargine users, and –3.4 ± 3.2 mmol/L and –4.9 ± 4.4 mmol/L for prior premix users, respectively.

3.3.2. *Regional differences*

At the end of the study, the percentage of people using a once-daily regimen with insulin detemir ranged from 38.4% in Russia to 88.1% in East Asia; figures were similar irrespective of prior study therapy. Mean insulin dose by region are reported in Supplementary Table 1.1.

HbA_{1c} decreased significantly from baseline ($p < 0.001$) for all regions, ranging from –2.2% [24 mmol/mol] in the Middle East/Gulf region (n = 4474) to –1.4% [15 mmol/mol] in North Africa (n = 1746). The proportion of patients reaching HbA_{1c} <7.0% [53 mmol/mol] ranged from 36.8% in the Middle East and Gulf to 23.8% in North Africa. FPG and PPG values decreased significantly from baseline ($p < 0.0001$) for all regions (Supplementary Table 1.1), with the greatest reductions being observed in the Middle East and Gulf region (–4.2 mmol/L FPG; –6.0 mmol/L PPG) and Latin America (–4.1 mmol/L FPG; –6.5 mmol/L PPG).

3.4. *Safety outcomes*

3.4.1. *Hypoglycaemia by pre-study therapy*

The reported incidence of major hypoglycaemia decreased significantly over 24 weeks in both the insulin-naïve and prior insulin user subgroups ($p < 0.0001$). For people changing insulin to treatment with insulin detemir, significant reductions were also reported in the incidence of overall, minor, and nocturnal events ($p < 0.0001$ for all) (Fig. 1). The change in the incidence of overall hypoglycaemia from baseline to 24 weeks was from 12.44 to 2.26 events per patient-year for people previously treated with NPH, from 5.08 to 2.38 events per patient-year for prior insulin glargine users, and from 8.08 to 1.14 events per patient year for people switching from premix insulin.

3.4.2. *Hypoglycaemia by region*

A reduction in the incidence of hypoglycaemic events was reported for all regions, but baseline values and the degree of the reduction varied greatly (Supplementary Table 1.2). Baseline rates for major hypoglycaemic events were highest in North Africa and Latin America (0.59 and 0.53 events per patient-year in 2.7 and 1.9% of the regional populations, re-

Table 2 – Outcome measures by pre-study therapy in the insulin detemir subgroup and entire A_1chieve study population.

Outcome measure		Insulin detemir subgroup population			A_1chieve study population		
		Global cohort	Insulin-naïve	Insulin-experienced	Global cohort	Insulin-naïve	Insulin-experienced
Insulin dose (U/kg/day)	*n*	15,545	12,078	3467	66726	44872	21854
	Pre-study	0.42 (0.24)	–	0.42 (0.24)	0.55 (0.29)	–	0.55 (0.29)
	Baseline	0.27 (0.15)	0.24 (0.13)	0.35 (0.19)	0.44 (0.24)	0.38 (0.20)	0.55 (0.27)
	Week 24	0.37 (0.20)	0.35 (0.18)	0.45 (0.24)	0.50 (0.26)	0.44 (0.22)	0.62 (0.30)
HbA_{1c} (% [mmol/mol])	*n*	10,581	8459	2122	44,661	30, 369	14,292
	Baseline	9.5 (1.6) [80]	9.5 (1.6) [80]	9.3 (1.7) [78]	9.5 (1.7) [80]	9.5 (1.7) [80]	9.4 (1.8) [79]
	Week 24	7.5 (1.2) [58]	7.4 (1.1) [57]	7.6 (1.3) [60]	7.4 (1.1) [57]	7.4 (1.0) [57]	7.6 (1.2) [60]
	Change	–2.0 (1.6) [22]	–2.1 (1.6) [23]	–1.6 (1.7) [17]	–2.1 (1.7) [23]	–2.2 (1.7) [23]	–1.8 (1.7) [19]
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
People reaching HbA_{1c} <7.0% [53 mmol/mol] (%)	*n*	13,190 (100.0)	10,376 (100.0)	2814 (100.0)	57,250 (100.0)	38,639 (100.0)	18,611 (100.0)
	Baseline	3.0	2.1	6.2	3.9	3.0	5.6
	Week 24	31.5	31.7	30.3	31.8	32.0	31.3
FPG, pre-breakfast (mmol/L)	*n*	10742	8560	2182	48,191	33,087	15,104
	Baseline	10.9 (3.3)	11.2 (3.2)	9.9 (3.3)	10.9 (3.5)	11.2 (3.4)	10.5 (3.7)
	Week 24	7.1 (2.0)	7.0 (1.9)	7.3 (2.3)	7.1 (1.9)	7.1 (1.8)	7.2 (2.2)
	Change	–3.9 (3.3)	–4.2 (3.2)	–2.6 (3.5)	–3.8 (3.5)	–4.1 (3.3)	–3.2 (3.8)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
PPG (mmol/L), post-breakfast	*n*	7148	5757	1391	33,742	23,334	10,408
	Baseline	14.8 (4.2)	15.0 (4.2)	13.8 (4.3)	15.1 (4.4)	15.5 (4.3)	14.2 (4.5)
	Week 24	9.6 (2.9)	9.5 (2.8)	9.9 (3.2)	9.7 (2.9)	9.8 (2.9)	9.7 (3.0)
	Change	–5.1 (4.3)	–5.5 (4.2)	–3.8 (4.3)	–5.4 (4.5)	–5.8 (4.4)	–4.5 (4.6)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Body weight (kg)	*n*	11,934	9336	2598	50,059	33,716	16,343
	Baseline	76.6 (16.3)	76.5 (16.3)	76.7 (16.3)	73.3 (14.8)	72.1 (14.3)	75.7 (15.7)
	Week 24	76.2 (15.5)	76.2 (15.4)	76.0 (15.7)	73.3 (14.1)	72.2 (13.5)	75.7 (15.1)
	Change	–0.4 (4.0)	–0.3 (4.0)	–0.7 (3.6)	0.1 (3.7)	0.1 (3.7)	–0.0 (3.6)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.081
SBP (mmHg)	*n*	11,620	9077	2543	45,285	29,595	15,690
	Baseline	133.2 (16.7)	133.3 (16.7)	133.0 (16.9)	134.2 (17.8)	134.0 (17.7)	134.7 (18.0)
	Week 24	128.0 (14.9)	127.9 (15.2)	128.4 (13.7)	127.9 (13.5)	127.3 (13.3)	129.0 (13.7)
	Change	–5.2 (17.3)	–5.4 (17.7)	–4.5 (15.6)	–6.3 (17.1)	–6.6 (17.4)	–5.7 (16.6)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Total cholesterol (mmol/L)	*n*	5791	4529	1262	20, 293	11,994	8299
	Baseline	5.3 (1.3)	5.3 (1.2)	5.2 (1.4)	5.3 (1.3)	5.4 (1.3)	5.2 (1.3)
	Week 24	4.8 (1.0)	4.8 (0.9)	4.8 (1.0)	4.8 (1.0)	4.8 (1.0)	4.8 (1.0)
	Change	–0.5 (1.1)	–0.6 (1.1)	–0.4 (1.1)	–0.5 (1.2)	–0.6 (1.2)	–0.4 (1.2)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HDL cholesterol (mmol/L)	*n*	4388	3418	970	17,306	10,189	7117
	Baseline	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.2 (0.4)	1.1 (0.4)
	Week 24	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)	1.2 (0.4)	2.7 (0.4)	1.2 (0.4)
	Change	0.0 (0.4)	0.0 (0.3)	0.0 (0.4)	0.1 (0.4)	0.1 (0.4)	0.0 (0.4)
	p-value	<0.001	<0.001	0.012	<0.001	<0.001	<0.001
LDL cholesterol (mmol/L)	*n*	4428	3459	969	17,494	10,304	7190
	Baseline	3.1 (1.0)	3.1 (1.0)	3.0 (1.0)	3.1 (1.0)	3.2 (1.0)	3.1 (1.1)
	Week 24	2.7 (0.8)	2.7 (0.8)	2.7 (0.9)	2.8 (0.9)	2.7 (0.9)	2.8 (0.9)
	Change	–0.4 (1.0)	–0.4 (1.0)	–0.3 (0.9)	–0.4 (1.0)	–0.4 (1.0)	–0.3 (0.9)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Triglycerides (mmol/L)	*n*	5413	4251	1162	19,856	11,672	8184
	Baseline	2.1 (1.0)	2.1 (1.0)	1.9 (1.0)	2.1 (1.1)	2.1 (1.1)	2.0 (1.1)
	Week 24	1.7 (0.7)	1.7 (0.7)	1.7 (0.8)	1.8 (0.7)	1.7 (0.7)	1.8 (0.7)
	Change	–0.3 (0.9)	–0.4 (0.9)	–0.2 (0.9)	–0.3 (0.9)	–0.4 (1.0)	–0.3 (0.9)
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are mean (SD) unless otherwise stated.
FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPG, postprandial plasma glucose; SBP, systolic blood pressure.

spectively). South Asia reported the lowest baseline values, with 0.08 events per patient-year in 0.5% of the regional population (Supplementary Table 1.2). Overall, minor, and nocturnal hypoglycaemic events were observed to be highest at baseline in North Africa, Latin America, and Russia, while all three regions observed a decrease in the events per patient-year. Russia, unlike the other two regions, did not observe a significant decrease in the percentage of patients

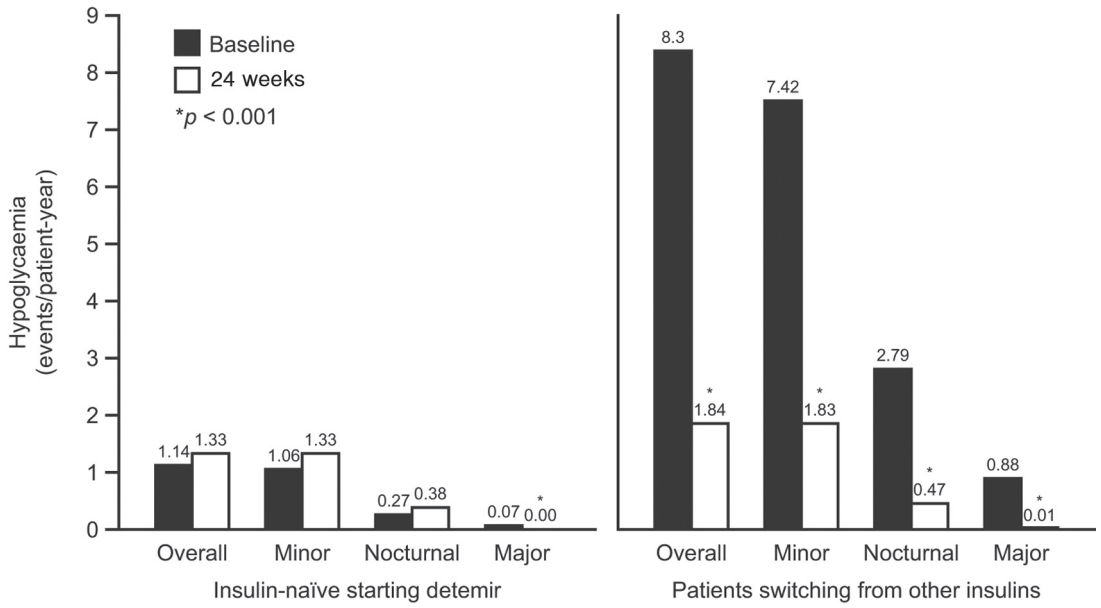

Fig. 1 – Changes in the incidence of hypoglycaemia in insulin-naïve and prior insulin users after 24 weeks of treatment with insulin detemir ± oral glucose-lowering drugs.

experiencing these events. South Asia reported the lowest incidence of overall and minor events at baseline, which were significantly reduced in the region at the end of the study (Supplementary Table 1.2).

3.5. *Secondary clinical outcome measures*

3.5.1. *By pre-study therapy*

The mean change in body weight over 24 weeks for all patients treated with insulin detemir was –0.4 ± 4.0 kg ($p < 0.001$). Both insulin-naïve and prior insulin user subgroups reported a reduction in body weight (Table 2). Mean change in body weight at 24 weeks was –0.6 ± 3.2 kg for the prior NPH users, –0.4 ± 3.9 kg for prior glargine users, and –1.0 ± 3.6 kg for people previously treated with premix insulin ($p < 0.001$ for all). Mean SBP decreased significantly for the entire cohort (–5.2 ± 17.3 mmHg; $p < 0.001$) to 128.0 ± 14.9 mmHg by the end of the study and in both pre-study therapy subgroups (Table 2). Mean blood lipid profiles improved overall by –0.5 ± 1.1 mmol/L; there was no clinically meaningful change in high-density lipoprotein (HDL) cholesterol, but low-density lipoprotein cholesterol (LDL) values fell by –0.4 ± 1.0 mmol/L and triglycerides by –0.3 ± 0.9 mmol/L ($p < 0.001$) (Table 2). There were no notable differences between the insulin-naïve and insulin experienced subgroups.

3.5.2. *Regional differences*

Five of the seven regions observed a reduction in mean body weight (China, South Asia, Middle East and Gulf, Russia and Latin America; see Supplementary Table 1.1). Mean SBP decreased in all regions. The largest decrease was observed in Russia (–8.5 ± 13.7 mmHg; $p < 0.001$), where mean baseline values were the highest of any participating region (141.2 ± 16.3 mmHg), with the smallest reduction being reported in North Africa (–1.6 ± 24.2 mmHg; $p = 0.012$). Total cholesterol values at baseline ranged between 4.6 ± 1.1 mmol/L (North Africa) and 6.0 ± 1.2 mmol/L (Russia). Reductions were reported for all regions between –0.2 ± 1.2 mmol/L (North Africa) and –0.6 ± 1.3 mmol/L (East Asia) and –0.6 ± 1.0 mmol/L (Middle East and Gulf). HDL cholesterol values remained generally unchanged as reported for the overall cohort, and all regions reported a decrease in LDL cholesterol and triglyceride levels (Supplementary Table 1.1). The degree of reduction in blood lipid profile values observed regionally did not appear to be related to the baseline value.

4. Health-related quality of life

HRQoL scores improved significantly irrespective of pre-study therapy ($p < 0.001$). For all users of insulin detemir, the self-assessed VAS rating (0–100) increased by +14.3 points: +15.2 points in the insulin-naïve subgroup and +10.9 points for prior insulin users. Scores at baseline were similar for the overall cohort and in the insulin-naïve and prior insulin user subgroups (62.6, 62.1, and 64.3, respectively).

HRQoL scores at baseline varied between regions. South Asia and Russia reported the lowest scores of 55.4 and 56.0 points; North Africa, Latin America, and East Asia had baseline scores between 63.3 and 68.5 points; and the Middle East and Gulf region had the highest pre-study score of 71.2 points. HRQoL improved significantly by week 24 in all regions ($p < 0.001$). The degree of improvement in HRQoL varied from +22.4 points on the VAS scale in South Asia to +8.3 points in East Asia.

5. Discussion

Clinically and statistically significant improvements in HbA_{1c}, FPG, and PPG were observed in people with T2D either starting insulin therapy with or changing to insulin detemir as part of the A_1chieve study. These improvements in glycaemic profile were reported consistently across all participating regions and irrespective of prior treatment regimen. The improvements in glycaemic control were accompanied by reduced rates of major hypoglycaemia, low rates of SADRs, improved patient perception of HRQoL, and the absence of clinically significant increase in body weight. Using Tables 1 and 2, these findings can be directly compared against those from the entire A_1chieve study population.

The majority of people starting insulin detemir were insulin-naïve at baseline and reported greater improvements in HbA_{1c} (–2.1% [23 mmol/mol]) than participants changing insulin therapy (–1.6% [17 mmol/mol]), despite similar baseline values. This is consistent with data previously reported for insulin detemir from observational studies and RCTs of basal-only insulin replacement in insulin-naïve people with T2D. Comparable results were also seen with regards to the change in number of hypoglycaemic events and modest weight loss [12,14,15,18,20,23,24]. Improvements in FPG and PPG were also greater in the insulin-naïve subgroup; however, mean baseline values were higher than those reported for insulin-experienced people.

In insulin-experienced people, mean HbA_{1c} was reduced by 1.6% [17 mmol/mol], a similar change to data previously reported for patients switching to detemir [19,20]. This may be a result of the very poor level of glycaemic control at baseline, not only in this treatment cohort but for the entire A_1chieve study population, for whom a reduction of 1.8% [19 mmol/mol] was reported [7]. Significant improvements in all measures of glycaemic control were seen regardless of prior insulin regimen, human or analogue, which supports previous findings from a clinical practice [19]. The proportion of patients reaching HbA_{1c} <7.0% [53 mmol/mol] with insulin detemir ± OGLDs was ~30%, irrespective of prestudy therapy; similar to that reported for the entire A_1chieve study cohort (31.8%) [7] and for basal insulin analogue therapy in RCTs [25,26]. Likewise, overall mean reductions in FPG and PPG reported at the end of the study (–3.9 ± 3.3 and –5.1 ± 4.3 mmol/L, respectively) are comparable to those seen for the entire A_1chieve cohort (–3.8 ± 3.5 mmol/L; $p < 0.001$ and –5.4 ± 4.5 mmol/L; $p < 0.001$, respectively) [7], suggesting that statistically significant improvements in blood glucose control are universal with insulin analogue therapy, irrespective of prior insulin regimen.

Regionally, both the poor level of glycaemic control at baseline and the magnitude of improvement were remarkably consistent. The proportion of patients attaining HbA_{1c} <7.0% [<53 mmol/mol] varied considerably (Supplementary Table 1.1). China reported the lowest baseline HbA_{1c} of 8.4 ± 1.7% [68 mmol/mol] but too few patients started a regimen with insulin detemir in the region ($n = 137$) to be considered in the regional comparison. This low number was due to the fact that insulin detemir was not available in China during patient recruitment, and only gained marketing approval towards the end of the study. This exclusion from the regional comparison is unfortunate as, in the entire A_1chieve study population, patients in China reported the largest reduction in HbA_{1c} (2.5% [28 mmol/mol]) [7] and it would have been interesting to see if this trend was consistent in patients initiated on insulin detemir

Insulin-experienced people reported significant reductions in the rate of overall, major, minor, and nocturnal hypoglycaemic events, while insulin-naïve patients, not unexpectedly, reported a reduction in the rate of major events only. The incidences of overall, minor, and nocturnal hypoglycaemic events were highest in Latin America and Russia at baseline, yet, despite similar improvements in glycaemic control and a comparative daily insulin dose after 24 weeks of treatment with insulin detemir, reductions in the event rates and the percentage of people experiencing hypoglycaemic events was markedly different between the two regions. There are a number of non-drug hypoglycaemia-precipitating factors that may influence this reported outcome, such as manual work, alcohol consumption, nutritional differences, patient age, and degree of insulin resistance. However, despite regional differences, a reduction in the incidence of hypoglycaemic events was observed, which, for such a heterogeneous population, may result from study-related improvement in self-management, although the observation is consistent with previous publications [7,14–17,19,20,23].

A modest reduction in body weight was observed in both pre-study therapy subgroups, in contrast to the weight gain that is usually associated with insulin initiation. This evidence supports previously published data associating insulin detemir with minimal weight change (14,15,17,18,27). Changes in weight reported by region were minimal, with greater significant reductions being observed where reductions in HbA_{1c} were greater, rather than a higher baseline weight. As the majority of the people from all regions were insulin-naïve at baseline, weight change ranging between –1.1 and +0.5 kg is modest considering the geographical and lifestyle differences. Interestingly, in the entire A_1chieve study population, although no clinically significant weight change was reported, a larger range was seen (–0.8 and +0.9 kg) [7]. Changes in SBP and blood lipid profiles were also favourable for both the insulin-naïve and insulin-experienced subgroups, which reflects the results seen for the entire A_1chieve study cohort [7].

The A_1chieve study, by nature of its design, has a number of limitations that must be considered when interpreting the data [7]. Results can be difficult to conclude due to the heterogeneity of the population and healthcare systems encompassed by the geographical reach of the study. The lack of a control group reduces certainty that results are attributable to the insulin treatment alone. The consulting physicians may have initiated confounding interventions at the same time as the decision to start treatment with the study insulin, and the level of education in diabetes management provided, especially for the 73% of patients included in this analysis who were previously insulin-naïve, may have influenced the outcomes for the duration of the study follow-up period. Additionally, the duration of the study was relatively short, thus the observed beneficial findings may, in part, be due to an 'entry into study' effect that may not be sustain-

able in the long term. A small percentage of people were switched from basal–bolus treatment to basal insulin, which may not have been the ideal course of treatment optimisation. Certain endpoints were dependant on patient recall diaries and records, which may subject the data to recall bias. Despite limitations that are inherent in any observational study design, observational studies can help to assess treatment effects in diverse patient groups in different clinical environments and broaden the clinical evidence base provided by RCTs.

6. Conclusion

People with T2D in poor glycaemic control who started treatment with insulin detemir in routine clinical care reported significant improvements in glycaemic control irrespective of prior treatment and geographical region after 24 weeks. These improvements were achieved without any safety or tolerability complications, and were associated with an improvement in patient self-assessment of HRQoL. These safety and effectiveness data for insulin detemir in the A_1chieve study are consistent with those from previous study publications. The addition of evidence from predominantly less well-resourced countries expands the global picture of the role insulin detemir fulfils in real-life clinical practice.

Conflicts of interest

All authors were members of the A_1chieve study advisory board and received support from Novo Nordisk to attend advisory board meetings. Prof. Shah has no other conflicts of interest to declare. Dr Zilov is an opinion leader and lecturer for Novo Nordisk, Sanofi-Aventis, Novartis, MSD, Merck & Co, Berlin-Chemi, and Abbott. Dr El Naggar has received speaker fees from Pfizer, MSD, Novartis, Novo Nordisk, AstraZeneca, Sanofi-Aventis, and Merck Serono, and has participated in advisory boards for Eli Lilly, Bristol-Myers Squibb, and Sanofi-Aventis. Chunduo Shen is employed by Novo Nordisk. Dr Haddad has acted as a consultant for Sanofi-Aventis, Eli Lilly, Takeda, MSD, Bristol-Myers Squibb, and GlaxoSmithKline, for which he received honoraria.

Acknowledgments

The authors take full responsibility for this paper but are grateful to Watermeadow Medical (supported by Novo Nordisk) for writing assistance.

Appendix A. Supplementary data

The Supplementary Tables associated with this article will be made available in the online version, at doi: 10.1016/j.diabres.2013.06.003.

REFERENCES

[1] UK Prospective Diabetes Study (UKPDS). Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[2] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.
[3] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al.; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.
[4] Del Prato S, Felton AM, Munro N, Nesto R, Zimmet P, Zinman B; Global Partnership for Effective Diabetes Management. Improving glucose management: ten steps to get more patients with type 2 diabetes to glycaemic goal. Recommendations from the Global Partnership for Effective Diabetes Management. Int J Clin Pract Suppl 2007; (157):47–57.
[5] Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. Br J Gen Pract 2007;57(539):455–60.
[6] Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al.; IMPROVE Study Group Expert Panel. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract 2009;63:522–31.
[7] Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A_1chieve study. Diabetes Res Clin Pract 2011;94:352–63.
[8] Khunti K, Damci T, Meneghini L, Pan CY, Yale JF; SOLVE Study Group. Study of Once Daily Levemir (SOLVE™): insights into the timing of insulin initiation in people with poorly controlled type 2 diabetes in routine clinical practice. Diabetes Obes Metab 2012;14:654–61.
[9] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005–12.
[10] Tibaldi J, Rakel RE. Why, when and how to initiate insulin therapy in patients with type 2 diabetes. Int J Clin Pract 2007; 61:633–44.
[11] Freeman JS. Insulin analog therapy: improving the match with physiologic insulin secretion. J Am Osteopath Assoc 2009;109:26–36.
[12] Selam JL, Koenen C, Weng W, Meneghini L. Improving glycemic control with insulin detemir using the 303 Algorithm in insulin naïve patients with type 2 diabetes: a subgroup analysis of the US PREDICTIVE 303 study. Curr Med Res Opin 2008;24:11–20.
[13] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577–96.

[14] Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetes Care 2006;29:1269–74. Erratum in: Diabetes Care 2007;30:1035.
[15] Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. Clin Ther 2006;28:1569–81. Erratum in: Clin Ther 2006;28:1967.
[16] Blonde L, Merilainen M, Karwe V, Raskin P; TITRATE Study Group. Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. Diabetes Obes Metab 2009;11:623–31.
[17] Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial. Diabet Med 2008;25:916–23.
[18] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. Diabetologia 2008; 51:408–16.
[19] Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lüddeke HJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. Diabetes Obes Metab 2007;9:418–27.
[20] Dornhorst A, Lüddeke HJ, Sreenan S, Kozlovski P, Hansen JB, Looij BJ, et al.; PREDICTIVE Study Group. Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. Int J Clin Pract 2008;62:659–65.
[21] Shah SN, Litwak L, Haddad J, Chakkarwar PN, Hajjaji I. The A_1chieve study: a 60000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice. Diabetes Res Clin Pract 2010;88(Suppl 1):S11–6
[22] EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
[23] Meneghini L, Koenen C, Weng W, Selam JL. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes – results of the randomized, controlled PREDICTIVE 303 study. Diabetes Obes Metab 2007;9:902–13.
[24] Meneghini LF, Dornhorst A, Sreenan S; PREDICTIVE Study Group. Once-daily insulin detemir in a cohort of insulin-naïve patients with type 2 diabetes: a sub-analysis from the PREDICTIVE study. Curr Med Res Opi 2009; 25:1029–35.
[25] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[26] Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, et al.; INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28:260–5.
[27] Hollander P, Cooper J, Bregnhøj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. Clin Ther 2008; 30:1976–87.