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Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: Results from the A$_1$chieve observational study☆,☆☆

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ABSTRACT

Aims: To determine the effects on quality of life after starting insulin with, or switching to, insulin analogue therapies in the 24-week, prospective, non-interventional, observational A$_1$chieve study conducted across four continents in people with type 2 diabetes.
Methods: Health-related quality of life (HRQoL) was assessed at baseline and at 24 weeks by the validated EQ-5D questionnaire (visual analogue score [VAS] and five dimensions) in 66,726 people who had started using basal insulin detemir, mealtime insulin aspart (with or without a basal insulin) or biphasic insulin aspart 30.
Results: For the overall cohort, reported HRQoL increased significantly by 13.8 points from 63.4 points at baseline to 77.2 points at 24 weeks ($p < 0.001$) (scale 1–100, 100 = best health imaginable). Beginning or changing insulin was associated with a significant increase in HRQoL score (+15.0 points and +11.1 points, respectively), resulting in a similar score at 24 weeks in the two populations (77.8 and 75.9 points). Reported HRQoL also increased statistically significantly in people administering any insulin analogue regimen and across all regions, although there were some marked regional differences in reported HRQoL at baseline.
Conclusion: Compared with baseline scores, beginning insulin with, or switching to, insulin analogue therapies are associated with increased HRQoL.

1. Introduction

It is widely recognised that having type 2 diabetes (T2DM) has a negative impact on quality of life (QoL) [1]. Having to deal with lifestyle change, complex treatment regimens, potentially having to manage self-injection, and sometimes fear of hypoglycaemia and weight gain can contribute to poor QoL and adverse perceptions of diabetes therapies [2–4]. Consequently, people with T2DM and their physicians often delay starting or optimizing insulin therapy, despite the current

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burdens of poor glycaemic control [4–7]. Alongside effective glycaemic control, maintaining or improving QoL is an integral part of the successful management of diabetes. Indeed, it is known that measured QoL improves with better glycaemic control [8].

Literature reporting the effect of insulin analogues on QoL is scarce, with one recent systematic review investigating basal insulin analogues being unable to identify any suitable trials measuring QoL in people with T2DM [9].

As the largest observational study ever conducted in insulin therapy, and with a broad geographical base, the A_1chieve study evaluated the safety and effectiveness of starting insulin with, or switching to, insulin analogue-based regimens in a large and diverse population from a wide variety of clinical environments [10]. It is then well placed to investigate health-related quality of life (HRQoL). The aim of the current analysis was to determine the effects on HRQoL of insulin analogue therapies in people with T2DM.

2. Methods

2.1. Study design

This was a 24-week, international, prospective, non-interventional, observational study of people with T2DM who had begun using biphasic insulin aspart 30 (premix), insulin aspart, or insulin detemir with or without oral glucose-lowering drugs (OGLDs). The study was carried out in 28 countries across four continents (Asia, Africa, Latin America and Europe): Algeria, Argentina, Bahrain, Bangladesh, China, Egypt, India, Indonesia, Iran, Jordan, Kuwait, Libya, Malaysia, Mexico, Morocco, Oman, Pakistan, Philippines, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Taiwan, Tunisia, Turkey, United Arab Emirates and Yemen. Participants were recruited between January 2009 and June 2010, with an average observation period of 6 months. The insulin therapies were prescribed by a physician in the course of normal clinical practice, were commercially available, and were funded according to local practice in normal routine care. Further study design details and biomedical findings are given elsewhere (Home et al., submitted to Diabetes Res. Clin. Pract., this issue).

2.2. Health-related quality of life

Health-related quality of life (HRQoL) was measured using the EQ-5D questionnaire [11] at baseline and after 24 weeks of therapy with insulin analogues. This questionnaire is a descriptive system of HRQoL states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each of these states can take one of three responses recording different levels of severity: no problems (=1), some or moderate problems (=2) and extreme problems (=3). These scores are not cardinal. The questionnaire also includes a rating for an individual's current HRQoL state, measured by a standard vertical 20 cm visual analogue scale (VAS). This EQ-5D VAS score ranges from 0 (worst imaginable health) to 100 (best imaginable health). The five health-state dimensions can be converted to a single utility value using a EQ-5D value set, in this case the UK VAS set, and are anchored by '1.00' representing full health and '0.00' representing the state 'dead'.

2.3. Statistical analysis

Analyses were performed for people who completed the EQ-5D questionnaire at both baseline and 24 weeks. Change from baseline in HRQoL with the EQ-5D VAS as a continuous variable was analysed with the Wilcoxon signed-rank test. The change in percentage of people experiencing no problem in any of the measures was analysed with a chi-square test.

Analyses were further performed for the following groups: insulin-naïve people (people not taking insulin therapy at the time of entering into the study) and previously insulin-experienced people (current insulin users); by insulin analogue regimen (biphasic insulin aspart 30, insulin detemir alone, insulin aspart alone, insulin aspart used with any basal insulin [analogue or otherwise]); by seven geographical regions (for details of these see primary report, Home et al., submitted to Diabetes Res. Clin. Pract., this issue).

3. Results

3.1. Metabolic control and hypoglycaemia

Data for insulin doses, blood glucose control, and body weight change are given in a separate manuscript (Home et al., submitted to Diabetes Res. Clin. Pract., this issue). Broadly, blood glucose control measures improved markedly in both insulin-naïve and prior insulin users, for groups starting insulin detemir, insulin aspart, or biphasic insulin aspart 30, and in all geographical regions (HbA_{1c} change −1.5% to −2.5%). Similarly, reported hypoglycaemia rates were lower for the most part in all these subpopulations. Very little body weight change was observed during the study, some groups gaining <1.0 kg and some losing up to 1.0 kg.

3.2. Quality of life in the entire cohort

As measured by the visual analogue scale from the EQ-5D (on a scale of 0–100), reported QoL increased significantly by almost 14 points from 63.4 points at baseline to 77.2 points at 24 weeks ($p < 0.001$; Table 1). Across the other summary dimensions of quality of life there was an increase from baseline to Week 24 (Table 1). Large changes were seen for numbers reporting no problems in the descriptive QoL measures, including those relating to mental and physical functioning. By the end of the study over 75% of all people reported no problems with each of the dimensions of anxiety/depression, self-care, performing usual activities, pain or discomfort, and walking.

3.3. Quality of life for prior insulin-naïve or insulin-experienced populations

Baseline EQ-5D VAS score was similar for insulin-naïve and prior insulin-treated populations at baseline (62.8 and 64.8 out of 100; Table 2). Beginning insulin or changing insulin was associated with a significant increase in QoL score (+15.0

Table 1 – Quality of life results for the entire cohort.

	n	Baseline	24 weeks	Change	*p*-value
QoL UK (scale 0–1)	43,170	0.67 (0.28)	0.83 (0.18)	0.16 (0.28)	<0.001
EQ-5D VAS (scale 0–100)	41,749	63.4 (16.9)	77.2 (11.7)	13.8 (17.3)	<0.001
Not anxious or depressed (%)	43,491	50.5	75.6	25.1	<0.001
No problems with self-care (%)	43,503	65.4	82.4	17.0	<0.001
No problems with performing my usual activities (%)	43,538	56.5	78.7	22.2	<0.001
No pain or discomfort (%)	43,552	46.3	71.2	24.9	<0.001
No problems walking (%)	43,598	59.0	84.2	25.2	<0.001

Data are utility value 0–1 (mean (SD)), visual analogue scale 0–100 (mean (SD)), and people scoring no problems in the five dimensions (%).

points and +11.1 points, respectively), resulting in a similar score at 24 weeks in the two populations (77.8 and 75.9 points). At baseline there were similar QoL scores across all dimensions for the two populations, apart from self-care, for which 62.6% of insulin-naïve people and 72.0% of insulin-experienced people reported no problems. During the study, QoL significantly increased in both groups, resulting in >80% of participants, irrespective of prior insulin status, reporting no problems with self-care. By 24 weeks, the biggest difference between the two groups was in the pain/discomfort dimension, with 73.3% of prior insulin-naïve people now reporting no problems, against 66.3% of prior insulin-experienced people.

Table 2 – Quality of life results in those people who were insulin naïve or who were insulin experienced prior to study.

		Insulin naïve, *n* = 44,872	Insulin experienced, *n* = 21,854
QoL UK (scale 0–1)	*n*	30,291	12,879
	Baseline	0.65 (0.29)	0.70 (0.25)
	Week 24	0.83 (0.18)	0.82 (0.19)
	Change	0.18 (0.29)	0.12 (0.26)
	p	<0.001	<0.001
EQ-5D VAS (0–100)	*n*	29,248	12,501
	Baseline	62.8 (17.0)	64.8 (16.6)
	Week 24	77.8 (11.1)	75.9 (13.0)
	Change	15.0 (17.4)	11.1 (16.9)
	p	<0.001	<0.001
Not anxious or depressed (%)	*n*	30,513	12,978
	Baseline	49.6	52.7
	Week 24	76.8	72.5
	Change	27.2	19.8
	p	<0.001	<0.001
No problems with self-care (%)	*n*	30,518	12,985
	Baseline	62.6	72.0
	Week 24	81.7	84.3
	Change	19.1	12.3
	p	<0.001	<0.001
No problems with performing my usual activities (%)	*n*	30,548	12,990
	Baseline	54.8	60.5
	Week 24	78.9	78.3
	Change	24.1	17.8
	p	<0.001	<0.001
No pain or discomfort (%)	*n*	30,553	12,999
	Baseline	46.1	46.6
	Week 24	73.3	66.3
	Change	27.2	19.7
	p	<0.001	<0.001
No problems walking (%)	*n*	30,587	13,011
	Baseline	57.9	61.4
	Week 24	85.6	81.1
	Change	27.7	19.7
	p	<0.001	<0.001

Data are utility value 0–1 (mean (SD)), visual analogue scale 0–100 (mean (SD)), and people scoring no problems in the five dimensions (%).

Table 3 – Quality of life results by new insulin regimen.

		Biphasic insulin aspart 30, n = 40,917	Insulin detemir, n = 15,545	Insulin aspart alone, n = 3898	Insulin aspart + any basal, n = 4107
QoL UK (0–1)	n	28,044	8998	2752	2269
	Baseline	0.66 (0.29)	0.68 (0.26)	0.64 (0.29)	0.71 (0.25)
	Week 24	0.83 (0.18)	0.83 (0.18)	0.84 (0.17)	0.82 (0.20)
	Change	0.17 (0.29)	0.14 (0.26)	0.20 (0.30)	0.11 (0.25)
	p	<0.001	<0.001	<0.001	<0.001
EQ-5D VAS (0–100)	n	26,964	8829	2676	2217
	Baseline	63.5 (16.8)	62.6 (16.9)	63.4 (17.3)	63.8 (17.7)
	Week 24	77.4 (11.3)	76.8 (12.6)	77.8 (11.1)	76.8 (12.8)
	Change	13.8 (16.9)	14.3 (18.4)	14.4 (17.3)	12.9 (18.0)
	p	<0.001	<0.001	<0.001	<0.001
Not anxious or depressed (%)	n	28,246	9072	2779	2283
	Baseline	50.7	50.1	48.6	50.5
	Week 24	76.2	74.5	78.1	69.9
	Change	25.5	24.4	29.5	19.4
	p	<0.001	<0.001	<0.001	<0.001
No problems with self-care (%)	n	28,229	9079	2794	2280
	Baseline	63.1	71.2	60.3	74.3
	Week 24	81.1	85.5	80.7	87.8
	Change	18.0	14.3	20.4	13.5
	p	<0.001	<0.001	<0.001	<0.001
No problems with performing my usual activities (%)	n	28,282	9059	2794	2283
	Baseline	55.8	58.4	54.9	58.2
	Week 24	78.4	79.4	79.3	79.1
	Change	22.6	21.0	24.4	20.9
	p	<0.001	<0.001	<0.001	<0.001
No pain or discomfort (%)	n	28,277	9088	2789	2281
	Baseline	46.6	45.4	46.0	46.3
	Week 24	72.3	68.0	76.9	65.2
	Change	25.7	22.6	30.9	18.9
	p	<0.001	<0.001	<0.001	<0.001
No problems walking (%)	n	28,307	9087	2799	2285
	Baseline	58.4	60.6	56.2	62.1
	Week 24	85.2	82.2	86.6	79.5
	Change	26.8	21.6	30.4	17.4
	p	<0.001	<0.001	<0.001	<0.001

Data are utility value 0–1 (mean (SD)), visual analogue scale 0–100 (mean (SD)), and people scoring no problems in the five dimensions (%).

3.4. *Quality of life results by treatment regimen*

Quality of life scores were similar at baseline irrespective of the insulin analogue treatment begun (visual analogue scores of approximately 63 points; Table 3), with the exception of the people moving to the insulin aspart + basal regimen who on two measures appeared to experience better quality of life. Reported QoL then increased clinically and statistically significantly in users of all the insulin analogue regimens, such that by 24 weeks scores were very similar in all groups. Final EQ-5D VAS scores then clustered around 77 (out of 100) for all four regimens (Table 3).

3.5. *Quality of life results by region*

There were some marked regional differences in reported QoL at baseline across the regions involved in the study, and these were consistent on all the four summary measures (Table 4). Russia and south Asia had the lowest QoL scores, with 55.1 and 55.7 (out of 100) on the EQ-5D VAS. East Asia, north Africa, the Middle East/Gulf and Latin America had similar baseline scores in the range of 62.6–68.4 (out of 100). China had the highest QoL score at baseline on all summary measures, with 75.9 (out of 100) on the VAS. Reported QoL increased clinically and statistically significantly across all regions by Week 24 (Table 4). The greatest increases were in those regions with the lowest QoL scores at baseline, such that by the end of study differences between regions were quite small. Thus by the end of the study EQ-5D QoL visual analogue scores ranged between 74.0, Russia, and 81.7, China (out of 100).

4. Discussion

This analysis of HRQoL, measured by the validated EQ-5D questionnaire, in the international, 24-week A_1chieve study

Table 4 – Quality of life results by geographical region.

		China, n = 11,020	South Asia, n = 22,447	East Asia, n = 10,032	North Africa, n = 4039	Middle East + Gulf, n = 14,976	Latin America, n = 1138	Russia, n = 3074
QoL UK (0–1)	n	7845	17,438	8006	2949	3155	881	2896
	Baseline	0.87 (0.19)	0.50 (0.27)	0.80 (0.21)	0.73 (0.22)	0.73 (0.22)	0.68 (0.25)	0.63 (0.20)
	Week 24	0.89 (0.17)	0.80 (0.17)	0.88 (0.17)	0.82 (0.19)	0.81 (0.19)	0.81 (0.21)	0.79 (0.19)
	Change	0.02 (0.22)	0.30 (0.29)	0.08 (0.22)	0.09 (0.23)	0.07 (0.23)	0.13 (0.24)	0.16 (0.21)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
EQ-5D VAS (0–100)	n	7710	16,371	7925	2959	3082	880	2822
	Baseline	75.9 (13.7)	55.7 (13.8)	68.4 (15.3)	62.6 (17.9)	67.0 (15.7)	67.4 (18.8)	55.1 (17.2)
	Week 24	81.7 (10.9)	76.2 (9.3)	77.0 (12.7)	74.4 (14.5)	76.4 (12.9)	79.9 (14.4)	74.0 (14.5)
	Change	5.9 (15.0)	20.6 (15.8)	8.6 (16.5)	11.8 (18.3)	9.4 (16.1)	12.5 (17.8)	18.9 (17.7)
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Not anxious or depressed (%)	n	7883	17,536	8040	2976	3220	890	2946
	Baseline	73.1	35.3	67.6	46.7	52.4	47.5	36.8
	Week 24	76.3	76.7	81.4	64.3	67.8	70.1	72.4
	Change	3.2	41.4	13.8	17.6	15.4	22.6	35.6
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
No problems with self-care (%)	n	7897	17,588	8030	2980	3180	890	2938
	Baseline	91.7	36.7	86.0	85.1	78.9	84.4	70.4
	Week 24	91.5	71.0	92.0	91.1	85.3	90.3	86.5
	Change	−0.2	34.3	6.0	6.0	6.4	5.9	16.1
	p	0.6881	<0.001	<0.001	<0.001	<0.001	0.0002	<0.001
No problems with performing my usual activities (%)	n	7890	17,605	8037	2963	3222	888	2933
	Baseline	87.5	33.5	74.3	72.3	65.3	65.0	34.3
	Week 24	87.4	73.7	85.3	82.4	75.8	79.2	66.7
	Change	−0.1	40.2	11.0	10.1	10.5	14.2	32.4
	p	0.9235	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
No pain or discomfort (%)	n	7874	17,599	8044	2978	3219	893	2945
	Baseline	75.3	32.5	57.7	44.4	42.7	37.4	27.7
	Week 24	81.9	72.6	73.7	60.1	57.6	62.4	55.9
	Change	6.6	40.1	16.0	15.7	14.9	25.0	28.2
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
No problems walking (%)	n	7896	17,604	8043	2980	3227	894	2954
	Baseline	87.7	36.7	78.3	76.0	68.0	57.9	35.2
	Week 24	90.7	85.5	87.2	85.1	80.0	72.7	58.8
	Change	3.0	48.8	8.9	9.1	12.0	14.8	23.6
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are utility value 0–1 (mean (SD)), visual analogue scale 0–100 (mean (SD)), and people scoring no problems in the five dimensions (%). For details of which countries are in which region see Home et al. (submitted to Diabetes Res. Clin. Pract., this issue).

found that people with T2DM starting insulin with, or switching to, insulin detemir, insulin aspart, or biphasic insulin aspart 30 experienced significantly increased overall HRQoL, with significant improvements across all five component health dimensions. Irrespective of people's previous insulin experience, the HRQoL significantly improved with the insulin analogues used in this study. Overall HRQoL also improved across all regions, although not in all individual health dimensions. That these changes were associated with large changes in HbA_{1c} (overall reduction of $-2.1 \pm 1.7\%$ from baseline), and despite this no marked weight gain (-0.1 ± 3.7 kg) or increase in hypoglycaemia (as reported in Home et al., submitted to Diabetes Res. Clin. Pract., this issue), suggests that the overall experience of these people in starting the insulin analogue was very positive, perhaps suggesting that overall engagement with healthcare also improved, as did self-management activities such as dietary control. This in turn would explain why the improvements in HRQoL were for the most part independent of insulin type chosen, and indeed of baseline insulin use or geographical region.

It is important to determine QoL when evaluating treatments, as physicians may otherwise make only subjective assessments about their patients' QoL when taking clinical decisions. Measuring QoL is also of value as often there is only a modest difference in efficacy and/or safety outcomes between treatments when investigated in a clinical trial setting, and therefore choices taking QoL into account could beneficially aid management.

There are few randomised controlled trials looking at the effect on QoL of insulin analogues in insulin-naïve or insulin-experienced people with T2DM, in particular for the population studied by A_1chieve, outside of western Europe or North America. More often, treatment satisfaction questionnaires are used, measuring something which may not reflect specific impact on QoL. In one 16-week, randomised controlled trial in 308 insulin-naïve people with T2DM, the Diabetes Health Profile and the World Health Organization's Diabetes Treatment Satisfaction Questionnaire (DTSQ) were used to measure the effect of twice- or three-times daily biphasic insulin aspart 30 plus metformin compared with OGLDs alone [12]. Treatment satisfaction scores significantly improved for all groups from baseline, and all subjects experienced improvements in psychological distress and barriers to activity scores.

However, there are some prospective and retrospective observational data investigating insulin analogues and their effect on QoL in people with T2DM, and the results from the A_1chieve study support the few findings from these studies [13–15]. For example, in the Indian cohort of the 26-week IMPROVE observational study, QoL was measured using the DiabMedSat questionnaire in 349 people with T2DM being treated with biphasic insulin aspart 30 [13]. Overall QoL score and the sub-parameters of relief of burden, relief of symptoms, and effectiveness significantly increased from baseline. Similar observations were made in the Iranian cohort of the IMPROVE™ study, with a significantly higher DiabMedSat score, including significant increases in all three subscale scores, at study end in 478 people who were insulin naïve or insulin experienced [14].

There appear to be no other data on the effect of QoL by starting insulin with, or switching to, insulin analogues, given prior insulin status, and across a wide range of populations, as in A_1chieve. It is thus reassuring to see that starting such insulin in insulin-naïve people is not detrimental to QoL, at least in a population with poor blood glucose control at baseline. Likewise, QoL in people being treated with a potentially more complex insulin aspart and basal insulin regimen was not lower than other insulin regimens by study end, even where there were differences at baseline.

It is difficult to compare overall HRQoL values and those observed in the regions of the A_1chieve study with those of general or other T2DM populations, as HRQoL data should be country-specific and no HRQoL papers have been published in these regions. Measured QoL did appear to vary by region at baseline, but some care is required in interpreting these and other aspects of the findings. A_1chieve is an observational study, which can generate useful data from routine clinical practice, but is naturally subject to study effects, which cannot be distinguished from either the effect of the insulins themselves, or the circumstances in which the insulin was started. Furthermore, the interaction between QoL and diabetes is complicated and it is difficult to ascertain which features of management or treatment are responsible for any changes in QoL. In A_1chieve, QoL significantly improved for people irrespective of prior insulin status, and it is known that improvements in glycaemic control are associated with improvements in QoL [8]. It is also recognised that hypoglycaemia has an impact on QoL [16], and it is possible that the reduction in events seen in previous insulin users in this study also contributed to an improvement in score.

There could also be some limitations regarding the comparative validity of the EQ-5D questionnaire over such diverse geographical regions as were investigated in A_1chieve, or the implausibility of the results in the pain/mobility subdimensions. However, the EQ-5D questionnaire is known to be a validated, reliable and responsive instrument in T2DM [17], and is thus a reasonable choice for the purposes of the current study. It will be used alongside other measures in a major upcoming European prospective observational study [18].

In summary, observations from the A_1chieve study provide new insights and support previous findings regarding the beneficial effect on HRQoL of starting insulin analogues in people with neglected blood glucose control, whether insulin naïve or insulin experienced, in routine clinical practice across diverse geographical regions.

Contribution

All authors advised on the design and conduct of the study. All authors reviewed the results of the study, and took part in writing and reviewing the manuscript.

Conflicts of interest

Professor Shah is a member of an advisory board panel for Novo Nordisk. Dr. Zilov is an opinion leader and lecturer for Novo Nordisk. Professor Malek is an advisory board member and lectures for Novo Nordisk. Dr. Soewondo is on an advisory panel for Novo Nordisk. Dr. Bech is an employee of Novo

Nordisk. Dr. Litwak lectures for Novo Nordisk. This study was sponsored by Novo Nordisk A/S Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies including insulin, or continuing clinical management of the participants.

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