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Article: Treatment

Initiation of insulin glargine in patients with Type 2 diabetes in suboptimal glycaemic control positively impacts health-related quality of life. A prospective cohort study in primary care

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Abstract

Aims To study prospectively the impact of initiating insulin glargine in suboptimally controlled insulin-naïve patients with Type 2 diabetes on health-related quality of life in relation to glycaemic control.

Methods Insulin-naïve Dutch patients with Type 2 diabetes in suboptimal glycaemic control ($HbA_{1c} > 53$ mmol/mol; 7%) on maximum dose of oral glucose-lowering medications were included from 363 primary care practices ($n = 911$). Patients started insulin glargine and were followed up for 6 months. At baseline (start insulin therapy), 3 and 6 months, HbA_{1c} was measured and patients completed self-report health-related quality of life measures, including emotional well-being (World Health Organization-5 well-being index), fear of hypoglycaemia (Hypoglycaemia Fear Survey) and diabetes symptom distress (Diabetes Symptom Checklist—revised). Data were analysed using generalized estimating equations analysis.

Results HbA_{1c} (mmol/mol; %) decreased from 69 ± 16 ; 8.5 ± 1.7 to 60 ± 11 ; 7.6 ± 1.0 and 57 ± 11 ; 7.3 ± 1.0 at 3 and 6 months, respectively ($P < 0.001$). Pre-insulin BMI (kg/m^2) was 30 ± 5.7 , which remained stable at 3 months (30 ± 5.8) and increased to 31 ± 5.9 at 6 months ($P = 0.004$); no significant changes in self-reported symptomatic and severe hypoglycaemia were observed, while nocturnal hypoglycaemia slightly decreased. The Hypoglycaemia Fear Survey score decreased from 14.6 ± 16.2 to 12.1 ± 15.2 and 10.8 ± 14.4 at 3 and 6 months, respectively ($P < 0.001$). The Diabetes Symptom Checklist—revised score decreased from 15 ± 14 to 10 ± 12 and 10 ± 13 ($P < 0.001$), with most pronounced reductions in hyperglycaemic symptoms and fatigue. The World Health Organization-5 score increased from 57 ± 25.3 to 65 ± 21.6 at 3-month follow-up and 67 ± 21.8 at 6-month follow-up ($P < 0.001$).

Conclusions Results of this observational study demonstrate combined glycaemic and health-related quality of life benefits of initiating insulin glargine in patients with Type 2 diabetes in routine primary care.

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Keywords emotional well-being, insulin glargine, insulin initiation, quality of life

Abbreviations DSC-r, Diabetes Symptom Checklist—revised; HFS-w, Hypoglycaemia Fear Survey—Worry subscale; ITAS, Insulin Treatment Appraisal Scale

Introduction

There is general consensus as to the need of timely insulin initiation in Type 2 diabetes [1], but both patients and physicians have concerns about possible adverse effects on quality of life [2].

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Although there is no compelling evidence that initiation of (intensive) insulin therapy does hamper quality of life [3], changing to insulin therapy is often delayed [4].

In past years, long-acting insulin analogues have been introduced as an alternative to NPH (humane isophane) insulin [5]. Insulin glargine has been shown to have a more prolonged, consistent duration of action, without the pronounced post-injection peak characteristic of NPH insulin [6,7]. Although no glycaemic benefit in terms of HbA_{1c} has been demonstrated compared with NPH insulin, the risk of hypoglycaemia is lower with glargine compared with NPH [8]. However, research into the effects of initiation of glargine on health-related quality of life is sparse [7–9].

A recent review identified only four studies that examined the effect of glargine on health-related quality of life [9]. The included studies reported improvements in treatment satisfaction, perceived health status and quality of life following initiation of glargine. However, external validity of these studies was limited because of small, selective samples and the impact of insulin glargine on fear of hypoglycaemia has received little attention [8].

Outcomes of the recently published large multinational Lantus vs. Levemir Treat-To-Target (L2T3) trial, concerning patients with Type 2 diabetes in secondary care, suboptimally controlled on oral glucose-lowering medication, who were randomized to either insulin glargine or insulin detemir and followed for 6 months. Positive trends were found on fear of hypoglycaemia, diabetes symptom distress and emotional well-being, with no significant differences between glargine and detemir [10]. However, whether these trends in health-related quality of life following initiation of a long-acting insulin analogue hold true in routine primary care needs to be tested.

This prospective observational study in routine primary care aimed to extend our understanding of the impact of initiating once-daily insulin glargine on health-related quality of life in patients with Type 2 diabetes, suboptimally controlled on oral glucose-lowering medication.

Patients and methods

Study sample

In the present analysis, data from the Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment (SPIRIT) were used, an observational study conducted in primary care between 2005 and 2009. In total, 363 general practitioners consented to participate and invited eligible patients with Type 2 diabetes to participate in the study. Data were gathered on patients who were advised to add insulin glargine to their treatment by their general practitioner, in accordance with the Practice Guideline Diabetes Mellitus Type 2 of the Dutch College of General Practitioners, which states that insulin treatment should be initiated after therapy with maximum dose of two oral agents fails to achieve good glycaemic control (HbA_{1c} > 53 mmol/mol; 7%) [11]. Insulin glargine was thus initiated as part of routine care, at the discretion of the treating

general practitioner, based on existing titration protocols. The study did not interfere with clinical routine and included only filling out a questionnaire booklet in the practice office at three consecutive consultations that took approximately 15 min of the patients' time. Inclusion criteria were: clinical need to initiate insulin glargine, in concordance with the Practice Guideline Diabetes Mellitus Type 2 of the Dutch College of General Practitioners, obtained informed consent and the ability to complete questionnaires. In view of its observational and non-invasive nature, this study was deemed not subject to the Dutch Medical Research Involving Human Subjects Act.

In total, 1063 Caucasian patients agreed to participate, of whom 43 appeared to be already using insulin and 109 appeared not suboptimally controlled (HbA_{1c} ≤ 53 mmol/mol; 7%). These subgroups were excluded from the analysis, resulting in a sample of *n* = 911 (Fig. 1). Almost all patients started once-daily insulin glargine combined with oral glucose-lowering medication (*n* = 766) based on reported co-medication after insulin initiation by 97% of 789 physicians.

Measures

Demographic and clinical data were obtained by self-report, including age, gender, weight, time since diagnosis, previous medication use, hypoglycaemic episodes during the past

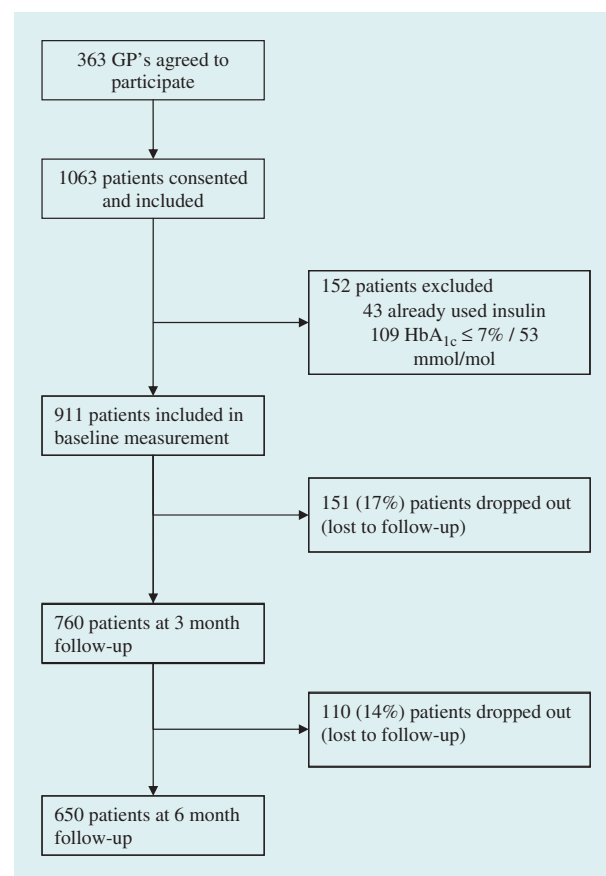


FIGURE 1 Study flow chart.

3 months, diabetes-related complications and co-morbidities. At baseline and during follow-up visits at 3 and 6 months, HbA_{1c} and fasting blood glucose were retrieved from the medical chart by hand. HbA_{1c} values older than 3 months ($n = 96$ at baseline, $n = 9$ at 3-month follow-up and $n = 7$ at 6-month follow-up) were set to missing. Physicians were asked to report relevant changes in the treatment regimen to the researchers, as well as any adverse events. During the study, two adverse events occurred, possibly related to glargine treatment; one patient had strong fluctuations in blood glucose and one patient had lipohypertrophy.

The Dutch version of the Worry subscale of the Hypoglycaemia Fear Survey; HFS-w, a well-validated 13-item instrument, was used to measure fear of hypoglycaemia [12]. To facilitate interpretation of data, HFS-w scores were transformed to a 0–100 scale.

Diabetes symptom distress was measured using the widely used revised version of the Diabetes Symptom Checklist (DSC-r), that has been shown to have good psychometric properties [13]. The DSC-r consists of 34 items grouped into eight symptom subscales: Hyperglycaemia, Hypoglycaemia, Cognitive distress, Fatigue, Cardiovascular distress, Neuropathic pain, Neuropathic sensibility and Ophthalmologic function. Each item asks about the presence of the symptom (yes/no) and, if present, the level of bothersomeness on a 5-point Likert-type scale. Scores are then transformed to a 0–100 score to obtain the DSC-r total score. The same transformation is applied to the DSC-r subscales.

General emotional well-being was assessed with the World Health Organization (WHO)-5 wellbeing index [13], a validated instrument. The WHO-5 includes five items pertaining to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested) and general interests (being interested in things). Item scores are summated to provide a total score, transformed to a 0–100 scale, with lower scores indicating poorer well-being. The WHO-5 has been found to have good screening properties for depressed mood, using a cut-off score of 28 or lower [14].

Additionally, five items from the Insulin Treatment Appraisal Scale (ITAS [15]) were included to capture negative attitudes towards insulin therapy at baseline [‘taking insulin means my diabetes has become much worse’, ‘taking insulin makes life less flexible’, ‘I am afraid of injecting myself with a needle’, ‘insulin causes weight gain’ and ‘taking insulin increases the risk of low blood glucose levels (hypoglycaemia)’]. Each item was scored on a 0–4 Likert scale (from ‘strongly disagree’ to ‘strongly agree’), resulting in a 0–20 total score. Item scores of 3 and 4 (agree/strongly agree) were taken as confirming a negative attitude and possibly reluctance to initiate insulin therapy.

In the present study, Cronbach’s alpha’s for the HFS-w, DSC-r and WHO-5 were 0.91, 0.94 and 0.90, respectively, confirming high internal consistency. Cronbach’s alpha of the five items derived from the ITAS was satisfactory (0.72).

Statistical analyses

The primary outcome was change in health-related quality of life, defined by HFS-w, DSC-r and WHO-5 from baseline (prior

to insulin therapy) to 3 and 6 months following insulin initiation. This was assessed modelling time as an independent dummy variable using generalized estimating equations analysis. Secondary outcomes (3- and 6-month change in HbA_{1c}, fasting blood glucose, the number of symptomatic, nocturnal and severe hypoglycaemic episodes during the past 3 months and weight) were analysed in a similar manner. Variables with a right-skewed distribution were transformed using the natural logarithm. This was the case for HbA_{1c}, the number of symptomatic, nocturnal and severe hypoglycaemic episodes during the past month, the HFS-w, the DSC-r total score and the sub-dimensions of the DSC-r. Analyses were based on the intention-to-treat principle; patients who withdrew from glargine use ($n = 99$; 11%) were thus included in the analyses. Reasons for withdrawal were not known for 49 patients. For the remaining patients, most frequent reported reasons as noted by the physicians were: insufficient effectiveness ($n = 16$), low compliance ($n = 14$) and co-morbidity ($n = 7$). Logistic regression analyses, with dropout (yes/no) as the dependent variable and demographic data, glycaemic data and total scores of the health-related quality of life measures revealed that dropout was not selective.

Confounding and effect modification were tested for age, educational level, time since diabetes diagnosis, BMI (kg/m²), the number of diabetes-related complications, the number of co-morbidities, intensification of diabetes therapy by other means than insulin glargine and baseline values for both the primary and the secondary outcomes. Observational studies run a high risk of missing data, attributable to the naturalistic setting and lack of monitoring. For the HFS, missing data was noted for 28% of the participants at the start to 50% at 6-month follow-up. For the DSC-r, these percentages were 28 and 50%. For the WHO-5, they were 18 and 43%. Multiple imputation was used for missing data, as multiple imputation minimally alters variance of data and thus gives best estimates of missing data [16]. Imputation was performed using the ICE package for Stata version 10.0 (StataCorp, College Station, TX, USA), resulting in ten data sets. Analyses on these data sets were combined using Rubin’s rules for multiple imputation [17]. *P*-values of < 0.05 were considered to be statistically significant. Analyses were carried out using Stata version 10.0.

Results

Baseline patient characteristics of the study population and changes in clinical outcomes over time are shown in Table 1.

Prior to initiating insulin glargine, patients received oral glucose-lowering medication as mono [$n = 149$, 18% of physicians who correctly reported co-medication before glargine initiation ($n = 839$)], dual ($n = 534$, 63%) or triple ($n = 156$, 19%) therapy. At initiation of insulin glargine treatment, 389 patients [49% of physicians who correctly reported co-medication after glargine initiation ($n = 789$)] received combination therapy with one oral glucose-lowering medication. This percentage decreased to 42% at 3-month

follow-up and increased to 48% at 6-month follow-up. Forty-seven per cent of the patients ($n = 374$) received dual oral therapy in combination with glargine. This percentage decreased to 44% at 3 months and 32% at 6 months. Three patients (<1%) received triple oral therapy on top of insulin. No patients received combination therapy with three oral agents at 3 and 6 months. Twenty-three patients (3%) received mealtime insulin as combination therapy. This percentage increased to 13 and 20% at 3 and 6 months, respectively.

Before insulin initiation, median HbA_{1c} was 67 mmol/mol; 8.3% (25th percentile: 61 mmol/mol, 7.7%; 75th percentile: 67 mmol/mol, 9.2%; range: 54–181 mmol/mol, 7.1–18.7%), confirming a need for therapy intensification and decreased to a median (25th, 75th percentile) of 60 (53, 67) mmol/mol; 7.6 (7.0, 8.3)% and 56 (50, 63) mmol/mol; 7.3 (6.7, 7.9)% at 3 and 6 months, respectively ($P < 0.001$). Fasting blood glucose showed a similar pattern, falling from 10.8 (± 3.3) mmol/l at baseline to 7.7 (± 2.2) at 3-month follow-up and 7.4 (± 2.2) at 6-month follow-up ($P < 0.001$). Mean weight increased by 1.2 \pm 8.1 kg and mean BMI increased by 0.4 \pm 2.8 kg/m² during the study period. Thirty-seven per cent of the patients ($n = 334$) reported to have experienced ≥ 1 mild hypoglycaemic episode in a 3-month period before initiating insulin. This percentage did not significantly change at 3-month follow-up, but increased to 44% ($n = 397$) at 6-month follow-up ($P = 0.042$). Fourteen per cent ($n = 128$) had experienced one or more nocturnal hypoglycaemic episode at baseline. This did not significantly change at 3-month follow up, but increased to 18% ($n = 166$) at 6-month follow-up ($P = 0.016$). Three per cent of the patients ($n = 29$) had experienced one or more severe hypoglycaemic episode before insulin initiation. This did not change at 3-month follow-up, but significantly increased to 6% ($n = 52$; $P = 0.029$) at 6-month follow-up.

Mean score on the five items derived from the ITAS (insulin perceptions) was 8.5 \pm 4.4. Highest mean score was found for the item 'taking insulin means my diabetes has become much worse' (2.2 \pm 1.3). Approximately a quarter of the patients (26%) had a mean score of ≥ 12 at baseline, suggesting a negative attitude towards insulin, while agreeing to start insulin therapy.

HFS-w scores (fear of hypoglycaemia) were low at baseline (median 8, 25th percentile 2, 75th percentile 22), but nevertheless decreased slightly to a median of 4 (25th percentile 0, 75th percentile 15) at 6-month follow-up ($P = 0.001$, corrected for demographics and combination therapy) (Table 2).

A small proportion of the patients reported not to have experienced any of the 34 DSC-r symptoms at baseline (5%). This increased slightly at 3 and 6 months (9 and 13%, respectively; $p = 0.019$). Six per cent of the population reported no symptom distress at baseline. At 3 and 6 months, this percentage was 10 and 11%, respectively ($P < 0.001$). As for the different sub-domains of the DSC-r, most pronounced reductions were observed for the domains Fatigue [from median 25, 25th and 75th percentiles 6 and 50 to a median score of 13, 25th and 75th percentiles 0 and 31 at 6 months ($P < 0.001$)] and Hyperglycaemia [from a median of 13 (25th

and 75th percentiles 0 and 26) to 6 (0, 16, $P < 0.001$) at 6 months] (Table 2).

Mean WHO-5 (well-being) scores improved from 57 \pm 26 to 65 \pm 21 at 6-month follow-up ($P < 0.001$) (Table 2). Correction for HbA_{1c} in the analyses with the WHO-5 showed no significant changes (data not shown).

Discussion

In this 6-month observational study conducted in multiple primary care practices in the Netherlands, we found pronounced positive psychological effects following initiation of once-daily insulin glargine in insulin naïve patients with Type 2 diabetes. An overall fall in HbA_{1c} to a median of 56 mmol/mol; 7.3% was observed during the 6-month period, which is still above the currently recommended goal of 53 mmol/mol; 7%. Yet, it could be regarded a safe target, in view of recent findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials [18]. Furthermore, a significant improvement was observed on all three health-related quality of life measures. Interestingly, and in contrast to common belief [19], fear of hypoglycaemia did not significantly increase after insulin initiation. This could be explained by the stable profile of insulin glargine with a low risk of nocturnal hypoglycaemic episodes.

For symptomatic hypoglycaemic events, a non-significant downward trend was observed. In contrast, a statistically significant increase in the number of severe hypoglycaemic events was observed. However, this increase was very small and it can be argued whether it is clinically relevant. Interestingly, on both the Hypoglycaemia DSC-r subdomain and the HFS-w, a significant decrease was observed.

Although patients were in suboptimal control at baseline, the number of reported symptoms, as well as symptom distress (DSC-r), were overall rather low compared with previous studies [20–22]. Nevertheless, both symptom frequency and symptom distress further decreased following insulin initiation. Most pronounced benefits were observed in the subdomains Hyperglycaemia, Cognitive complaints, Fatigue, Cardiovascular complaints and Ophthalmologic symptoms.

For the DSC-r and the HFS, a cut-off point for clinical significance is not available. Thus, to further explore clinical significance of the observed changes in the health-related quality of life measures, effect sizes (Cohen's *d*) were calculated based on comparison of baseline with 6-month values. An effect size of 0.8 is considered large, 0.5 moderate and 0.2 small. We found a Cohen's *d* of -0.14 for the HFS-w, 0.39 for the WHO-5 and -0.34 for the DSC-r total score. As to the DSC-r subdomains, an effect size of -0.43 was found for Hyperglycaemia, -0.26 for Hypoglycaemia, -0.28 for Cognitive functioning, -0.41 for Fatigue, -0.17 for Cardiovascular functioning and a Cohen's *d* of -0.23 was found for Ophthalmologic function. These positive changes following insulin initiation are to be considered small to moderate. General emotional wellbeing (WHO-5) significantly improved following the start of insulin therapy. A mean improvement of 8 points was

Table 1 Description of baseline population characteristics and changes in clinical outcomes during the study period

	Baseline	3 months	6 months	<i>P</i> baseline –3 months	<i>P</i> 3 months –6 months	<i>P</i> baseline –6 months
Age	62 ± 11					
Male/female	479/432					
Durations of diabetes (years)	5 (3–9)					
<i>n</i> , % lower educated*	503, 55%					
BMI (kg/m ²)	30 ± 6	30 ± 6	31 ± 6	0.192	0.004	0.003
Weight (kg)	88 ± 19	88 ± 18	89 ± 18	0.245	0.003	0.003
HbA _{1c} (mmol/mol)	67 (61–77)	60 (53–67)	56 (50–63)	< 0.001	< 0.001	< 0.001
HbA _{1c} (%)	8.3 (7.7–9.2)	7.6 (7.0–8.3)	7.3 (6.7–7.9)	< 0.001	< 0.001	< 0.001
Fasting blood glucose (mmol/l)	10.8 ± 3.3	7.7 ± 2.2	7.4 ± 2.2	< 0.001	< 0.001	< 0.001
Hypoglycaemic episodes during the past 3 months†						
Symptomatic	2.6 ± 6.5	2.3 ± 5.3	1.9 ± 3.7	0.633	0.647	0.972
<i>n</i> , % 0 episodes	572 (63%)	524 (58%)	514 (56%)	0.054	0.698	0.042
<i>n</i> , % 1 episode‡	63 (7%)	88 (10%)	92 (10%)			
<i>n</i> , % 2 episodes‡	52 (6%)	72 (8%)	87 (10%)			
<i>n</i> , % 3 episodes‡	49 (5%)	52 (6%)	53 (6%)			
<i>n</i> , % ≥4 episodes‡	175 (19%)	175 (19%)	165 (18%)			
Nocturnal	0.6 ± 2.6	0.6 ± 2.7	0.6 ± 2.2	0.947	0.445	0.497
<i>n</i> , % 0 episodes	783 (86%)	781 (86%)	746 (82%)	0.525	0.074	0.016
<i>n</i> , % 1 episode‡	35 (4%)	46 (5%)	80 (9%)			
<i>n</i> , % 2 episodes‡	27 (3%)	40 (4%)	30 (3%)			
<i>n</i> , % 3 episodes‡	17 (2%)	7 (1%)	18 (2%)			
<i>n</i> , % ≥4 episodes‡	49 (5%)	37 (4%)	37 (4%)			
Severe	0.05 ± 0.3	0.05 ± 0.3	0.08 ± 0.4	0.742	0.199	0.031
<i>n</i> , % 0 episodes	882 (97%)	872 (96%)	860 (94%)	0.356	0.109	0.029
<i>n</i> , % 1 episode‡	14 (2%)	29 (3%)	27 (3%)			
<i>n</i> , % ≥2 episodes‡	15 (2%)	10 (1%)	24 (3%)			

Raw mean ± SD are presented for variables with a normal distribution, raw median (25th–75th percentile) are presented for variables with a right-skewed distribution and number and per cent of respondents are presented for dichotomous variables.

P-values are adjusted for age, educational level, diabetes duration, BMI, the number of diabetes-related complaints, the number of co-morbidities, intensification or relief of diabetes therapy by means other than insulin glargine and baseline values.

*Primary education or lower general secondary education.

†Based on self-report.

‡Calculation of *P*-values not possible because of lack of statistical power.

found, close to the level of clinical significance defined as a change of 10 points by the authors of the WHO-5 [13].

Several limitations of the study need to be mentioned. The non-randomized design can be considered a limiting factor, threatening internal validity because of selection bias and the lack of a control group. We have no information on those who refused to participate, but our study was conducted in a large and heterogeneous sample of primary care patients across different regions of the country. The socio-demographic and clinical profiles of the patients do not seem dissimilar to what is reported in the L2T3 trial [10], where a similar recruitment strategy was employed.

We cannot exclude the possibility of a study effect. However, patients were not participating in a clinical trial, but rather received usual care, with no additional benefits or incentives. Moreover, the actual glycaemic improvement achieved during the study period clearly exceeds the commonly observed decrease in HbA_{1c} as a result of a Hawthorne effect [23] and is similar to

previously reported results from comparable studies with a longer follow-up [24,25].

As with glycaemic control, the observed improvements in health-related quality of life at 3 months was sustained at 6 months following insulin initiation. It would seem highly unlikely that these changes are simply attributable to an expectancy effect. In fact, it would seem more logical to assume that the opposite has occurred, i.e. patients have experienced real benefits and symptom relief following insulin initiation, despite initial worries and negative attitudes towards insulin and having to inject on a daily basis [4]. Indeed, just over a quarter (26%) of the patients scored high on the five insulin attitude items, indicating a negative appraisal of insulin therapy at baseline. This percentage is in line with earlier reported findings [4]. Furthermore, we did not have data on whether patients were living alone or not, which may be a possible effect modifier on the health-related quality of life outcomes, especially hypoglycaemia fear.

Table 2 Description of changes in health-related quality of life during the study period

	Baseline	3 months	6 months	P baseline–3 months	P 3 months–6 months	P baseline–6 months
HFS-w total score	8 (2, 22)	6 (0–15)	4 (0–15)	0.002	0.429	0.001
DSC-r total distress score	12 (5, 22)	8 (3–17)	8 (3–16)	< 0.001	0.266	< 0.001
DSC-r sub-domains						
Hyperglycaemia	13 (0–26)	6 (0–19)	6 (0–16)	< 0.001	0.591	< 0.001
Hypoglycaemia	8 (0–24)	4 (0–17)	4 (0–17)	0.001	0.659	0.004
Cognitive	13 (0–26)	6 (0–19)	6 (0–19)	< 0.001	0.587	< 0.001
Fatigue*	25 (6–50)	17 (0–34)	13 (0–31)	< 0.001	0.034	< 0.001
Men	19 (4–44)	13 (0–31)	13 (0–29)	< 0.001	0.143	0.001
Women	30 (9–56)	19 (6–38)	19 (0–33)	< 0.001	0.049	< 0.001
Cardiovascular	6 (0–19)	6 (0–16)	6 (0–14)	0.007	0.985	0.022
Neuropathic pain	6 (0–17)	1 (0–13)	3 (0–14)	0.033	0.271	0.475
Neuropathic sensory	4 (0–17)	4 (0–14)	4 (0–16)	0.325	0.773	0.590
Ophthalmologic	5 (0–15)	1 (0–13)	3 (0–10)	< 0.001	0.854	< 0.001
WHO-5 total score	57 ± 26	63 ± 21	65 ± 21	< 0.001	0.003	< 0.001

Raw mean ± SD are presented for variables with a normal distribution, raw median (25th–75th percentile) are presented for variables with a right-skewed distribution.

P-values are adjusted for age, educational level, diabetes duration, BMI, the number of diabetes-related complaints, the number of co-morbidities, intensification or relief of diabetes therapy by means other than insulin glargine and baseline values.

*Interaction for gender was found ($P = 0.003$), results are presented separately for men and women.

DSC-r, Diabetes Symptom Checklist—revised; HFS-w, Hypoglycaemia Fear Survey—Worry subscale; WHO-5, World Health Organization-5.

As mentioned, the relatively large number of missing data is a potential weakness of observational studies and the present study is no exception. However, we used multiple imputation, which can be viewed as the most robust way of dealing with missing data [16].

In summary, the present study is the first large population-based study to report on the improvement in glycaemic control and health-related quality of life following initiation of insulin glargine in patients with Type 2 diabetes suboptimally controlled on oral therapy. Our findings strongly suggest that improvement of glycaemic control contributed to the observed improvements in well-being, in particular vitality and general mood, corroborating earlier findings [26,27]. It would seem safe to conclude that initiating insulin glargine in patients with Type 2 diabetes who are suboptimally controlled has a positive effect on patients' quality of life. Conveying this information to patients and healthcare providers would seem important in combating the generally observed delay of insulin therapy.

Competing interests

RdeG is an employee of sanofi-aventis. FH has acquired funds for his activities as a principal investigator and steering committee member for a multinational trial sponsored by sanofi-aventis. MD is a consultant and speaker for Eli Lilly and Company, Novo Nordisk and Merck, Sharp and Dohme, and a consultant for sanofi-aventis. Through MD, the VU University Medical Center in Amsterdam has received research grants from Amylin Pharmaceuticals Inc., Eli Lilly and Company, Novo Nordisk, Merck, Sharp and Dohme, Novartis and Takeda. FJS has received a research grant via the VU Medical Centre from sanofi-aventis for two observational studies related to

psychological outcomes of insulin glargine therapy; he has consulted for sanofi-aventis on the topic of quality-of-life measurement and received speakers fee from sanofi-aventis for lectures delivered in the context of continuous medical education. There are no other potential conflicts of interest relevant to this article.

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