# IMPROVING TREATMENT SATISFACTION AND OTHER PATIENT-REPORTED OUTCOMES IN PEOPLE WITH TYPE 2 DIABETES: THE ROLE OF ONCE-DAILY INSULIN GLARGINE

Clare Bradley[1], Charles JB Gilbride[2]

[1]Royal Holloway, University of London, Surrey, UK; [2]University of Warwick, Coventry, UK

**Please forward all correspondence to:**

Clare Bradley, PhD, Professor of Health Psychology

Royal Holloway, University of London

Egham

Surrey

TW20 0EX

Tel: +44 1784 443708 (direct) 3714 (admin)

Fax: +44 1784 471168

Email: c.bradley@rhul.ac.uk

**Running title:** Insulin glargine, treatment satisfaction and patient reported outcomes

**Word count (summary):** 271
**Word count (text):** 10,191
**Number of tables/figures:** 0/0

## ABBREVIATIONS

ADDQoL = Audit of Diabetes-Dependent QoL

AWI = average weighted impact

DAFNE = Dose Adjustment For Normal Eating

DSC-R = Diabetes Symptom CheckList-Revised

DTSQ = Diabetes Treatment Satisfaction Questionnaire

DQOL = Diabetes Quality Of Life

EQ-5D = EuroQoL measure of health status including thermometer overall health rating and 5 domain ratings.

GHb = glycosylated haemoglobin

GLP-1 = glucagon-like peptide-1

HFS = Hypoglycaemic Fear Survey

INSIGHT = implementing new strategies with insulin glargine for hyperglycaemia treatment

ITSQ = Insulin Treatment Satisfaction Questionnaire

MacDQoL = Macular disease Dependent QoL

OHAs = oral hypoglycaemic agents

PROs = patient-reported outcomes

QoL = quality of life

RetDQoL = diabetic Retinopathy Dependent QoL

SF-36 = 36-item short form of a health status measure

TFS = Treatment Flexibility Scale

TZDs = thiazolidinediones

UKPDS = UK Prospective Diabetes Study

W-BQ = Well-Being Questionnaire

## ABSTRACT

Insulin therapy becomes essential for many people with Type 2 diabetes. After starting insulin, people with diabetes that is poorly controlled with oral agents typically report improved well-being and treatment satisfaction. However, healthcare professionals and people with Type 2 diabetes are often reluctant to begin insulin treatment, citing such concerns as time/resources needed to educate patients, increased risks of hypoglycaemia and fear of injections, which lead them to focus on intensifying conventional oral therapy. Insulin glargine, which offers people with diabetes a once-a-day injection regimen with low risk of hypoglycaemia, is more likely to overcome such initial barriers than other more complex insulin regimens. Once-daily insulin glargine, in combination with modern glucose-dependent oral agents that do not need to be chased with food to prevent hypoglycaemia, does not require the fixed meal times and set amounts of carbohydrates necessary with twice-daily injection mixes and older sulphonylureas. We know it is such dietary restrictions that cause the most damage to quality of life (QoL). To avoid damaging QoL unnecessarily and to ensure optimal satisfaction with treatment it is important to evaluate the effects of treatment on QoL, treatment satisfaction and other patient-reported outcomes using questionnaires validated for this purpose, such as the widely used Diabetes Treatment Satisfaction Questionnaire and the Audit of Diabetes-Dependent Quality of Life measure. A systematic electronic literature search identified reports of studies evaluating patient-reported outcomes associated with insulin glargine in comparison with other treatments. The studies demonstrate that insulin glargine is usually associated with greater improvements in treatment satisfaction and other patient-reported outcomes compared with intensifying oral therapy or alternative insulin regimens.

**INTRODUCTION**

Meeting therapeutic targets, including those concerned with glycaemic control, is important in management of Type 2 diabetes in order to reduce the risk of complications [1,2]. Initial pharmacological therapy with metformin and sulphonylureas often becomes inadequate, resulting in a need for more intensive therapy, often with insulin. Pharmacological options, such as the older sulphonylureas and twice-daily premixed insulin, have unwanted effects on quality of life (QoL) in terms of dietary restrictions, particularly the need to eat fixed amounts of carbohydrate at set mealtimes. Such restrictions on dietary freedom have been shown to be the aspect of diabetes management that has the greatest negative impact on QoL [3-5]. The joint American Diabetes Association/European Association for the Study of Diabetes consensus statement recommends a number of options for intensifying treatment [6], including a third oral agent, such as a thiazolidinedione (TZD) or insulin (basal, prandial or premixed insulin). However, healthcare professionals and people with diabetes are often reluctant to commence insulin therapy [7] and a recent retrospective cohort study showed that insulin initiation was delayed for nearly 5 years in 50% of patients after oral hypoglycaemic agents (OHAs) had failed even in the presence of diabetes-related complications [8]. The time and resources needed to educate patients in insulin use has been identified as one of the reasons for reluctance by health professionals [9]. The risk of hypoglycaemia is another concern and a barrier to achieving euglycaemia [10]. Polonsky and colleagues [7] studied responses to 9 statements that might explain reluctance to begin insulin therapy in 708 people with Type 2 diabetes who were not taking insulin and were attending conferences for people with diabetes. Twenty-eight percent of these people reported they were unwilling to begin insulin if prescribed, each endorsing several of the nine items offered expressing reasons for avoiding insulin. Most common reasons endorsed were concerns about the demands of insulin therapy, the restrictions (e.g., harder to travel, eat out), feelings of personal failure in managing diabetes, the permanence of insulin injections, anticipated pain of injections and problematic hypoglycaemia [7]. Difficulties that patients experience by adhering to treatment recommendations may be reduced by minimising dosing frequency [11]. Patients' perceived QoL is usually the single most important clinical and research outcome from the patients' points of view [12], though patients, like their clinicians, are also concerned to optimise diabetes control with a view to reducing the risks of long-term complications [13], which would also be associated with impaired QoL [3,4]. Thus, an insulin that offers people with diabetes a simple regimen that does not limit dietary freedom (including the freedom not to eat), has a low risk of hypoglycaemia and improves glycaemic control, is likely to overcome barriers to initiating insulin and may offer patients better treatment satisfaction, greater energy, improved QoL and the potential for better long-term adherence. The advantages of insulin glargine (as discussed in detail elsewhere in this

supplement) with once-daily dosing and low risk of hypoglycaemia, together with the dietary freedom that it most importantly allows, would be expected to overcome some of the barriers to insulin therapy. However, it is important to measure patient-reported outcomes (PROs), such as treatment satisfaction and psychological well-being, to study the expected impact of insulin glargine. Therefore, the aim of this paper is to review the results of clinical studies that have assessed the impact of adding insulin glargine to the therapeutic regimen in terms of PROs, particularly patient satisfaction with treatment and QoL.

**Measures of treatment satisfaction and quality of life**

There are a number of validated measures used to assess treatment satisfaction and QoL and other PROs [e.g. [14]. Those used in studies reviewed here are described below. including the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [15,16], Insulin Treatment Satisfaction Questionnaire (ITSQ) [17], the Audit of Diabetes-Dependent QoL (ADDQoL) individualised measure of the impact of diabetes on quality of life [3-5], Diabetes Symptom Checklist-Revised (DSC-R) [18] and Well-Being Questionnaire (W-BQ) [19], among others [14].

***Diabetes Treatment Satisfaction Questionnaire***

The DTSQ (status version; DTSQs) is an eight-item questionnaire, of which six questions assess treatment satisfaction and the other two assess perceived frequency of hyperglycaemia and hypoglycaemia [15,16]. Each item is scored from 6 (e.g., very satisfied) to 0 (e.g. very dissatisfied) such that the Treatment Satisfaction scale can range from 36 (e.g., very satisfied) to 0 (e.g., very dissatisfied) and the perceived frequency of hyperglycaemia and hypoglycaemia scores range from 6 (most of the time) to 0 (none of the time).The DTSQ was identified by the World Health Organization and International Diabetes Federation as useful in assessing outcomes of diabetes care [20] along with the W-BQ described below. The DTSQs has been extensively used and is sensitive to changes in response to a variety of interventions, including the start of insulin, or switch between insulin regimens [e.g. [21-23]. Although the DTSQs has proved highly sensitive to change, in many studies where patients are very satisfied with treatment used at baseline, the DTSQs cannot show improvements when they switch to a new treatment even though they might be even more satisfied with the new treatment. To overcome this limitation of the DTSQ (status version), a change version (DTSQc) has also been developed, which asks participants to rate how their current treatment compared with their previous treatment [24,25]. Responses are given on 7-point scales ranging from 3 (e.g., much more satisfied now) to –3 (e.g., much less satisfied now) and the Treatment Satisfaction change scale score can range from 18 (optimal improvement in satisfaction) to –18 (greatest reduction in satisfaction). The DTSQc,

used in conjunction with the DTSQs, overcomes the problem of ceiling effects that are often encountered when the status measure is used alone. The DTSQc has been demonstrated to show greater sensitivity to changes in treatment than the DTSQs and is particularly valuable when ceiling effects occur [26]. A major advantage of the DTSQ (s and c versions) is that it has been developed to be suitable for people with Type 1 or Type 2 diabetes using a wide range of treatments, including various methods of insulin delivery, oral medications and diet alone and is, therefore, appropriate for use before and after patients switch between very different treatment regimens.

### Insulin Treatment Satisfaction Questionnaire

The ITSQ is a 22-item questionnaire with five subscales to measure regimen inconvenience (5 items), lifestyle flexibility (three items), glycaemic control (three items), hypoglycaemic control (five items) and satisfaction with the insulin delivery device (six items): a total score can also be obtained [17]. All items are scored on a 7-point response scale ranging from 1 to 7 labelled at the extremes, e.g., 'not at all' to 'extremely'. The ITSQ is scored by transforming all items to a scale of 0–100 with a higher score suggestive of better treatment satisfaction. Subscale scores are obtained by taking the mean of the relevant items and the total score is the mean of all 22 items transformed to the 1–100 scale. The ITSQ is only suitable for people with diabetes who use insulin as part of their treatment regimen, not for people with diabetes treated with tablets and/or diet. As it can only be completed by people using insulin it is not suitable for use at baseline in trials investigating intensification of treatment in people who are treated with oral hypoglycaemic agents. Although the ITSQ can be used at follow up in such trials where insulin is used to intensify treatment, it will not be possible to know how satisfied patients were with their previous treatment regimen or if patients in different treatment groups differed in their satisfaction with treatment at baseline. The ITSQ gives more specific information than the DTSQ about patients' views of insulin treatment but this greater specificity also limits the value of the ITSQ. The DTSQ has the great advantage of being useful in comparing different treatment regimens that do not necessarily involve insulin.

### Audit of Diabetes-Dependent Quality of Life measure

This individualised measure is designed to enable respondents to rate not only the impact of diabetes on different aspects of their lives but also to say how important those aspects are for their QoL on a second scale associated with each item. Items that may not be applicable to everyone (such as family life and work) have a 'not applicable' option. The original ADDQoL [3] had items to measure 13 aspects of life in addition to two overview items to measure present QoL ('In general my quality of life is:') and diabetes-dependent QoL ('If I

didn't have diabetes my quality of life would be:'). Additional items were added following work with people who had complications of diabetes, including renal failure, and the ADDQoL18 was developed [4]. It is the ADDQoL18 that was used in the papers by Gerstein and colleagues [27] and by Houlden and colleagues [28] reviewed here. The latest version of the ADDQoL (ADDQoL19) [5] was simplified in various ways in the light of development of the Macular disease Dependent QoL (MacDQoL) for people with macular disease [29] and diabetic Retinopathy Dependent QoL (RetDQoL) for people with diabetic retinopathy [30]. An average weighted impact (AWI) score is calculated by multiplying the impact and importance ratings for each applicable item and dividing by the number of applicable items to give an ADDQoL18 AWI score ranging from –9 (greatest negative impact of diabetes on QoL) to +9 (greatest positive impact). Two overview items elicit overall ratings of present QoL (rated from +3 'excellent' to –3 'extremely bad') and diabetes-dependent QoL is scored from –3 'very much better' to 3 'very much worse'.

### Treatment Flexibility Scale

The Treatment Flexibility Scale (TFS) has 10 items that were included in a collection of scales evaluated for use in multinational clinical trials [31]. Five of the items assess how much choice the respondent has in relation to the content and timing of meals/snacks. Three items are about choice in planning activities and the remaining two are about making or changing plans spontaneously. Responses are made on 5-point scales ranging from 'a great deal of choice' (scored 1) to 'no choice' (scored 5). Scores were standardised in the original work [31] to range from 0 to 100, where 100 indicated greatest flexibility. The measure has been shown to have good internal consistency as a single 10-item scale and some evidence of discriminant validity [31,32], though the two-factor structure found by Hayes and Bowman [32], separating the five food-related items from the five items concerned with other activities, suggests that the value of two subscales might be worth exploring.

### Well-Being Questionnaire

The WB-Q was originally developed by the first author as a 22-item instrument with four subscales back in the early 1980s [16,19]. A 12-item version of this parent instrument was developed to improve on the structure of the W-BQ22 as well as to provide a short form. The resulting W-BQ12 includes three four-item subscales to measure negative well-being, energy and positive well-being [33,34]. The W-BQ12 has been shown to have a clearer factor structure and to be as sensitive to change as the longer parent version in studies of people with diabetes [34-36]. This generic tool has been shown to work well in many populations of people with other chronic conditions (e.g., macular disease [37] and adult growth hormone deficiency [38]) in addition to diabetes [35].

***Diabetes Symptom Checklist-Revised***

The original DSC was designed in the Netherlands and written in Dutch to assess diabetes-related symptoms and symptom discomfort in people with Type 2 diabetes [18]. The English translation of the original DSC asked respondents to rate the 'discomfort' of any symptoms experienced on four-point scales. Grootenhuis and colleagues [18] reported that the DSC was reduced to thirty-four symptoms loading on six factors in factor analysis. The DSC-R is a revision of the original DSC using a more economical layout commonly used in other symptom measures (e.g., the dialysis symptom index [39]), using a simple yes/no option to establish if the symptom occurred 'over the last month' rather than a frequency scale, and instead of asking about 'discomfort', the English translation now asks about how 'troublesome' any symptoms experienced were; this is rated from 1 (not at all) to 5 (extremely) instead of the previous 4-point scale. Scoring guidelines accompanying the DSC (which is still available for use) and DSC-R give instructions for obtaining a total score and for scoring eight subscales: hyperglycaemia, hypoglycaemia, psychological-cognitive, psychological-fatigue, cardiovascular, neurological-pain, neurological-sensory and ophthalmologic. The guidelines recommend standardising the scores to range between 0 and 10 or 0 and 100 to allow easier comparison across scales with different numbers of items. Higher scores indicate more symptoms and/or more troublesome symptoms. Vinik and Zhang [40] refer to the latter as 'symptom distress scores', when strictly speaking these are 'symptom troublesomeness scores'; however, Vinik and Zhang's terminology reads better and may well be close enough to what was measured. There are no publications, as yet, reporting the rationales for the considerable changes to the DSC and their impact on the factor structure and scoring of the instrument (Prof F. J. Snoek, personal communication), although Vinik and Zhang did include a brief mention in their paper [40] that they found adequate goodness of fit in confirmatory factor analysis of the measure used. However, the measure they used included items from the SF-36 as well as the 34 DSC-R items and few details were provided about how the goodness of fit was tested. DSC-R has now been used in a number of studies including several reviewed here all of which have used the DSC-R rather than the DSC. Treatments now in use are very different from those in use at the time of the design of the original DSC but the content has not been updated to assess possible side effects of new treatments. For example, the DSC-R includes no respiratory symptoms and these should be included when it is used in clinical trials of inhaled insulin where the risk of respiratory symptoms is a concern. Of relevance to the present review is the lack of gastrointestinal symptoms, such as nausea, in the DSC-R as these are needed for assessment of symptoms associated with exenatide [41,42]. Places to report and rate 'any other symptoms' at the end of the DSC-R go some way to overcome the limited selection of symptoms, though respondents are more likely to endorse listed symptoms than report

symptoms not listed, and none of the papers reviewed here reported whether or not any additional symptoms were mentioned.

### EQ-5D/EuroQoL

The EQ-5D measure of health status, also misleadingly called the EuroQoL, is a measure of health status, not a measure of QoL as one of the names would suggest. It comes in two parts; the first page has a thermometer with a scale of 0 to 100 on which respondents are asked to rate 'your own health state today' and ranges from (0) 'worst imaginable health state' to (100) 'best imaginable health state'; the second page of the EQ-5D asks about five aspects of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each aspect is assessed by a single item with three response options: no problems, some problems and severe problems. These five ratings are used to produce a single EQ-5D index score representing overall health on a scale from 0 to 1, where 1 represents optimum health on this scale. Secnik Boye and colleagues [42] reported that mean index scores on the EQ-5D for patients with Type 2 diabetes in three previous studies ranged from 0.69 to 0.77, and that scores tend to be somewhat lower in people who have diabetic complications, people treated with insulin, people who are overweight and older people. It is important to recognise that the EQ-5D is a measure of health rather than a measure of QoL for several reasons discussed in detail elsewhere [43]; in particular it is possible for people to score highly on the EQ-5D indicating good health, while nevertheless having a profoundly negative score on the ADDQoL, indicating that diabetes is severely damaging their QoL. Furthermore, the EQ-5D is usually only sensitive to major changes in health and is unlikely to detect differences due to a change of insulin even if the patients much prefer the new insulin and would register improvements on the DTSQ or ADDQoL. A direct comparison between the EQ-5D and a sister instrument to the ADDQoL, the MacDQoL for people with macular disease, showed good evidence that the MacDQoL was measuring QoL appropriately with greater impact among those with more severe visual impairment, but there was no evidence that the EQ-5D was measuring QoL at all [44].

### SF-36 health status measure

The SF-36 is, like the EQ-5D, a generic measure of health status [45] but, with 36 items, it measures more aspects of health than does the EQ-5D. It has been widely used in diabetes, though many of the items are unlikely to be responsive to specific changes in treatment or improvements in glycaemic control. Comparison has been made between the SF-36 health status measure and the ADDQoL measure of the impact of diabetes on QoL [46]. Both measures indicated greater impairment in people with complications of diabetes than in those free of complications while, as expected, only the SF-36 showed greater impairment in

people with comorbidities unrelated to diabetes [46]. The single general health item is often singled out for use on its own: 'In general, would you say your health is: excellent/very good/good/fair/poor', with a higher score indicating better health [40,47,48] . A five-item mental health/emotional well-being scale from the SF-36 was also selected for use in these studies ([40] [47,48]). The vitality subscale of the SF-36 is sometimes used separately as this is likely to be responsive to improvements in $HbA_{1c}$ levels: it is used by Secnik Boye and colleagues [42] (work reviewed below). The vitality subscale includes four items: two are positively worded to measure energy (e.g., 'did you have a lot of energy?') and two are negatively worded to measure fatigue (e.g., 'did you feel tired?'). Scores range from 0 to 100 with higher scores reflecting more energy/less fatigue.

## SEARCH METHODS

This review summarizes an electronic search of the literature (MEDLINE on Pubmed) using the search terms *insulin glargine*, *treatment satisfaction*, *quality of life and patient-reported outcomes* in the year range 2000–2007 in adults. The congress proceedings (2005–2007) of the annual American Diabetes Association and European Association for the Study of Diabetes were also searched. As insulin glargine has been compared against a number of active comparators, we did not restrict the search to a single comparator, but instead we have grouped the studies according to the type of comparator. Two further studies were identified (via other papers) that included no comparator drug treatment. One examined PROs of initiating insulin glargine treatment in an observational study of people with Type 1 and Type 2 diabetes [48] and the other examined the effects of group versus individual education in initiation of insulin glargine [9].

## RESULTS

### Insulin glargine versus insulin avoidance

Healthcare professionals commonly favour an approach of maximising oral therapy and delaying insulin initiation, perhaps on the mistaken assumption that patients will prefer oral therapy, although numerous studies have shown, using the DTSQ, that OHA-treated patients are more satisfied with treatment once they start on insulin [21-23]. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) study was designed to test whether people taking no OHAs, or one, or two OHAs can safely achieve recommended $HbA_{1c}$ levels faster and more frequently with the addition of insulin glargine versus intensifying/maximising oral therapy [27]. People taking 0, 1 or 2 OHAs (excluding those with a need for or use of TZDs), where at least one was at or below the half-maximal dose, were eligible for this 24-week, open-label study, and a total of 405

people were randomized to either 1) addition of insulin glargine to their current therapy administered with a pen injector or 2) conventional glycaemic management based on avoidance of insulin and intensification of oral therapy (TZDs were available for addition to current therapy, as were metformin, sulphonylureas, repaglinide and nateglinide and insulin if required (but not insulin glargine). Participants randomized to insulin glargine were 1.68-times (95% CI: 1.0, 2.83; p=0.049) more likely to achieve the primary endpoint of two consecutive HbA$_{1c}$ levels ≤6.5% than participants randomised to intensify OHA therapy. Participants completed the DTSQs at baseline, Week 12 and at endpoint (Week 24); greater improvements in treatment satisfaction were reported by those in the insulin glargine group at 12 weeks (+2.21 vs +1.91, p=0.005) and at 24 weeks (+2.23 vs +1.87, p=0.001) compared with those in the intensified OHA therapy group [28]. Baseline DTSQ scores reported in the initial paper [27], which concentrated on biomedical outcomes, were out of range and personal communication with Dr H. C. Gerstein, the first author, confirmed that the DTSQ baseline results were incorrectly reported there. Gerstein referred us to the subsequent Houlden et al paper for the detailed analysis of PRO data [28]. It seems that Houlden and colleagues took the average of the six-item scores that make up the treatment satisfaction scale when reporting baseline scores [28] instead of summing the scores as we usually recommend, though the change scores they present in Table 2 are too large to be changes in the average and appear to be changes in summed scores of the six items. 'Total score' is also reported in the treatment satisfaction results table and this appears to be the sum of all eight items in the DTSQ, inappropriately adding in the two items measuring perceived frequency of hyper- and hypoglycaemia for which there is no justification: these 'total scores' should be ignored as they are misleading. It is the treatment satisfaction scores (made up of six of the eight DTSQ items) and the separate perceived frequency of hyperglycaemia and hypoglycaemia items that are of interest. Perceived frequency of hyperglycaemia was substantially reduced in the insulin glargine group by 12 weeks with no change in the adjusted OHA group and a significant between-group difference at that time point. The OHA group showed a modest reduction in perceived frequency of hyperglycaemia by 24 weeks and the between-group difference was no longer significant. The picture was reversed for perceived frequency of hypoglycaemia, which was reduced in the adjusted OHA group at 12 weeks with little change in the insulin glargine group and a between-group difference approaching significance (p=0.054). The insulin glargine group caught up at 24 weeks with a similar reduction in perceived frequency of hypoglycaemia (−0.46 vs −0.43) compared with the adjusted OHA group. The insulin glargine group's ADDQoL scores showed marked benefits for present QoL at 12 weeks, which were maintained at 24 weeks, with significantly more benefits for QoL reported by the insulin glargine group compared with the adjusted OHA group (0.44 vs 0.25, p=0.023 at 24 weeks) [28]. There were no group

differences in the diabetes-specific ADDQoL scores suggesting that the insulin glargine patients reported improved QoL following insulin initiation, but did not attribute this improved QoL to their diabetes treatment. It may be that the improvement is mediated by the greater energy that is often reported following the introduction of insulin treatment [49], but energy was not measured in this study. Although not reported in the two published papers, Dr Gerstein provided the results from the use of the DTSQc at the 24-week endpoint of the study using the baseline DTSQs scores as covariates (personal communication December 2007); these confirmed the improvement in satisfaction in both groups, which was significantly greater for the insulin glargine group (mean of 2.16 (standard error 0.07) for insulin glargine and 1.85 (0.07) for adjusted OHAs; p<0.0015). It is interesting to see that satisfaction with treatment improved significantly more in the insulin glargine group despite the introduction of a daily insulin injection and that patients appreciated the reduction in hyperglycaemia and improved QoL. Furthermore, although the adjusted OHA group reported significantly less frequent unacceptably low blood glucose levels compared with the insulin glargine group at 12 weeks, the insulin glargine group reported similar improvements for hypoglycaemia by 24 weeks.

Fischer and colleagues reported an observational study of the introduction of insulin glargine to people with Type 1 (n= 135) or Type 2 diabetes (n=180) treated with insulin or OHAs in a single clinic [48]. PRO measures were given to a subset of the 'first 50 consecutive patients to accept', at baseline and Weeks 2, 6, 12 and 16. The majority of these 50 patients had prior insulin experience (66%) with only 36% previously treated with OHAs. Unfortunately it was not reported how many of the PRO subset had Type 2 diabetes and the analyses presented did not distinguish between patients according to type of diabetes or prior treatment. Nevertheless it is clear that at least the 36% of this PRO sub-sample treated with OHAs had Type 2 diabetes. PRO measures included the DSC-R (producing total symptom scores and symptom distress scores) and selected scales from the SF-36 (the single item measuring general health – sometimes erroneously referred to within the paper as 'overall well-being' and the five-item mental health scale to measure emotional well-being.) Despite the relatively small number in this subset completing PRO measures there was a highly significant improvement in $HbA_{1c}$ (mean change −1.47, p<0.0001 from a baseline mean of 9.2 ± 2.0 standard deviations) and significant improvements in all the PRO measures: general health; emotional well-being, total symptom score and total symptom distress. In the total sample reductions in hypoglycaemia as well as $HbA_{1c}$ were reported at 12 months, with no significant change in body mass index. Although only 66% of the PRO subset was using insulin prior to the study, the vast majority of the total sample was using insulin (including 87.5% of the subset with Type 2 diabetes). The strategy of taking those patients accepting

first as the PRO subset resulted in a sample that differed from the main sample and it is unclear how well the PRO results would generalise to the full sample. However, the results are encouraging in suggesting that significant improvements in $HbA_{1c}$, symptoms, reports of general health and well-being could be achieved in a naturalistic observational study in a clinical practice setting. The authors overstate the PRO findings when they refer to them as QoL benefits when in fact they are more specific benefits in symptoms, general health and well-being, and it is not surprising that improvements in PROs were greater in patients who had hyperglycaemic complaints at baseline – this will be because many of the symptoms measured were hyperglycaemia-related (e.g., fatigue, vision) and it is inappropriate to suggest that 'symptoms of hyperglycaemia may predict the strength of the association between $HbA_{1c}$ and QoL'. This would be less likely to be the case if a genuine QoL measure, such as the ADDQoL, were used and may simply be an artefact of using symptom measures but referring to them as QoL measures. Nevertheless the benefits in terms of symptoms and other health status measures associated with insulin glargine use in this study were substantial and important.

Yki-Järvinen and colleagues [9] reported marked and significant improvements in $HbA_{1c}$ and DTSQs scores in 121 patients with Type 2 diabetes (HbA1c 7-12% initially) previously treated with sulphonylurea and/or metformin, randomised to individual versus group education in insulin use. DTSQc was reported to have been used at endpoint but results were not mentioned, nor were results from items 2 and 3 of the DTSQs measuring perceived frequency of hyper- and hypoglycaemia. The staff time taken for visits/phone calls to initiate insulin was 48% less with group than with individual education. $HbA_{1c}$ and treatment satisfaction improved significantly for both modes of education but there was significantly less weight gain in the individually educated patients than in those educated in groups. The authors commented that these results suggested that patients in individual education sessions may have received more dietary advice than those in groups, However, it is perhaps also possible that the dietary advice given was better tailored to their individual needs and thereby more useful without necessarily taking any more time.

These three studies showed that $HbA_{1c}$, treatment satisfaction and QoL improved significantly with initiation of insulin glargine in patients with poorly controlled Type 2 diabetes. There was some weight gain but no change or improvement in hypoglycaemia compared with OHA therapy. Individualised education may minimise weight gain.

**Insulin glargine versus thiazolidinediones**

In the US, for people taking metformin and sulphonylurea combination therapy, there is an option of adding a TZD , such as rosiglitazone or pioglitazone. In a 24-week, multicentre, open-label study, 217 people on ≥50% maximal-dose sulphonylurea and metformin were randomized to receive add-on insulin glargine or add-on rosiglitazone [50]. Although the overall mean changes in $HbA_{1c}$ between baseline and endpoint were similar in both groups (insulin glargine –1.66 vs rosiglitazone –1.51%; p=0.1446), for participants with baseline $HbA_{1c}$ >9.5%, improvements in $HbA_{1c}$ were significantly greater with insulin glargine (p<0.05). Furthermore, insulin glargine was, in the full sample, associated with greater improvements in fasting plasma glucose (–3.60 vs –2.57 mmol/L; p=0.001). In this study, participants completed the five-item mental health scale and the single general health item from the SF-36, and the DSC-R [40]. The eight symptom subscales were converted to a 0-100 scale. There was a tendency towards more symptoms at baseline in the insulin glargine group and greater symptom distress but these differences were not statistically significant. Participants in the insulin glargine group reported significantly greater improvements for both total symptom score (unadjusted scores: –5.67 vs –1.15 (taken from Figure 1A of ref [40]); adjusted difference between groups for change from baseline: 7.59, p=0.005) and total symptom distress score (unadjusted scores: –2.81 vs –1.06; adjusted difference between groups for change from baseline: 1.92, p=0.03). Four symptom subscale scores showed significantly greater improvements in the insulin glargine group and these were for hypoglycaemic symptoms (or 'mood symptoms' as Vinik and Zhang argued is a more accurate label), ophthalmologic symptoms, ophthalmologic symptom distress and fatigue distress. It is not clear if the analyses controlled for the tendency to baseline differences between groups on all the DSC-R scores. (Domain scores were reported to have been normalised to reduce undue influence of outliers, and this may be the adjustment referred to above, but it remains possible that baseline levels were also controlled for). The SF-36 general health item scores improved more strongly with insulin glargine than with rosiglitazone (p=0.047). Changes in SF-36 emotional well-being scores in the two groups were not reported and we assume there were no group differences in this variable. It was reported that study completion was associated with improved emotional well-being (p=0.0434) as well as three of the symptom subscale scores (cognitive symptoms, cognitive distress and 'mood' [hypoglycaemic] symptoms) even after controlling for change in $HbA_{1c}$. More of those enrolled in the rosiglitazone group discontinued the study prematurely than did those in the insulin glargine group (21 (18.8%) versus 8 (7.6%) p=0.0104) and it seems likely that the experience of more side effects in the rosiglitazone group contributed to the high rate of early withdrawals. It is not clear if those who withdrew early contributed PRO data immediately prior to withdrawal of if earlier baseline PRO values had to be used. The

difference between the benefits of glargine over rosiglitazone may be an underestimate if on-treatment DTSQ scores were not available for those withdrawing early from the study. We can be confident that in terms of symptoms and overall general health perceptions, those using insulin glargine reported greater improvement in outcomes than those using rosiglitazone despite the introduction of one injection a day in the insulin glargine group and similar improvements in $HbA_{1c}$. Although the authors talk about the 'health-related quality-of-life' impact in the title and throughout the paper, they were in fact measuring aspects of health rather than QoL with the instruments selected. It would be more accurate to say that the perceived health and experience of symptoms improved more in the insulin glargine group than in the rosiglitazone group.

In a 48-week, open-label study, 388 people treated with metformin or sulphonylurea were randomised to receive add-on therapy of either insulin glargine (n=189) or pioglitazone (n=199) [51]. Improvements in $HbA_{1c}$ were greater with insulin glargine than pioglitazone at endpoint (–2.6 vs –2.3%; p≤0.05), but more patients experienced confirmed hypoglycaemia with insulin glargine than with pioglitazone (49 vs 19 patients), and more experienced severe hypoglycaemia with insulin glargine (7 patients) than with pioglitazone (1 patient) [47]. In this study, participants completed the DSC-R along with the SF-36 mental health scale and general health item [51], as previously used by others [40,48]. Only 230 of the 388 randomised patients completed baseline and Week 48 PRO measures and the reasons for the high levels of missing data are not specified in the abstract. Participants in the insulin glargine group reported greater improvements for 17 out of 20 PROs at endpoint versus baseline, compared with pioglitazone. In particular, findings were statistically significant (p<0.05) for the domains measuring distress (troublesomeness) associated with hyperglycaemic symptoms, fatigue and total symptom-related distress. In multivariate repeated measures analyses, insulin glargine was associated with significantly better outcomes for hyperglycaemic and ophthalmologic symptoms, and with distress associated with fatigue, hyperglycaemic, hypoglycaemic, ophthalmologic and cardiovascular symptoms. The better scores for the insulin glargine group on the 'hypoglycaemic distress' subscale of the DSC-R might be thought surprising given the earlier report of increased rates of hypoglycaemia including severe hypoglycaemia in the insulin glargine group. This apparent contradiction supports the suggestion [52] that the 'hypoglycaemic symptoms' label given to the three DSC-R items ('*Moodiness*', '*Irritability just before a meal*', and '*Easily irritated or annoyed*') may be a misnomer and should perhaps be relabelled 'Moodiness'. However, it is also possible that those experiencing such symptoms in response to mild hypoglycaemia are better able to avoid severe hypoglycaemia to which those with a lack of awareness of hypoglycaemic symptoms will be particularly at risk. Thus the symptoms of hypoglycaemia,

though troublesome, may also be valuable in preventing the much worse consequences of severe hypoglycaemia, which are not measured in the DSC-R but were recorded by the study investigators and reported in the first abstract concerned primarily with biomedical outcomes [47].

**Insulin glargine versus alternative insulin regimens**

For those people for whom oral agents do not provide adequate glycaemic control, starting insulin therapy can help reduce HbA$_{1c}$. However, the patient and healthcare professional need to choose from a number of regimens, including basal, prandial or premixed insulin in addition to, or instead of, existing oral therapy.

*Insulin glargine versus NPH insulin*

In a one-year, multicentre, open-label clinical study, 570 people with Type 2 diabetes, aged 34–80 years, were randomized to receive either insulin glargine or Neutral Protamine Hagedorn (NPH) insulin, both in combination with oral agents (sulphonylureas alone or combined with acarbose, metformin, or metformin alone). Glycosylated haemoglobin (GHb) decreased similarly (p=0.415) with insulin glargine (–0.46%) and NPH insulin (–0.38%) and a similar proportion of patients experienced hypoglycaemia in both groups [53]. However, fewer people in the insulin glargine group experienced nocturnal hypoglycaemia (NPH 24% vs insulin glargine 12%; p=0.002) and this was also the case in the subgroup of patients who were overweight (BMI >28kg/m$^2$) (NPH 22.2% vs insulin glargine 9.5%; p=0.0006). In this study, the DTSQ and W-BQ were completed at baseline and at 8, 20, 36 and 52 weeks [49]. Treatment satisfaction improved significantly (p<0.01) in both groups, and showed a non-significant tendency to be greater with insulin glargine versus NPH insulin (+1.98 vs +1.67; p=0.063). Furthermore, both groups reported significant (p<0.01) improvements in perceived frequency of hyperglycaemia, which also showed a non-significant tendency to be better with insulin glargine. However, both treatment groups also showed a worsening in perceived frequency of hypoglycaemia measured by item 3 of the DTSQc (insulin glargine: +0.30, p=0.0124; NPH insulin: +0.20, p=0.0368; p=0.683 for between-group differences). Although general well-being did not differ within or between groups [49], analysis of W-BQ subscales showed significant increases in the energy subscale with both insulin glargine and NPH insulin.

*Insulin glargine versus prandial insulin*

In the APOLLO Study (A 44-week, Parallel, open, randomized, multinational, multicentre study comparing the efficacy and safety of an OAD regimen plus either once-daily insulin gLargine or mealtime insulin LisprO) in patients with type 2 diabetes, for whom oral

treatment was failing to achieve sufficient glycaemic control, a total of 418 people were randomized to once-daily insulin glargine or prandial insulin lispro [54]. The majority of patients in both groups received metformin throughout the study and most received glimepiride (having been switched to glimepiride during screening if they were previously taking a different sulphonylurea). HbA$_{1c}$ improved significantly with both insulin glargine (−1.71%; p < 0.0001) and insulin lispro (−1.87%; p < 0.0001), which were shown to be equivalent within the pre-established 0.4% limit for non-inferiority. Overall, insulin glargine was associated with better improvements in nocturnal and fasting blood glucose, whereas insulin lispro was associated with better improvements in postprandial blood glucose [54]. A total of 188 people in the insulin glargine group and 191 people in the insulin lispro group completed the DTSQs at end-point [54]. Treatment satisfaction scores were similar in both groups (approximately 26), and both groups showed significant improvements at end-point. There was significantly greater improvement in the insulin glargine group. Participants in the insulin glargine group also reported significantly better scores for perceived frequency of hyperglycaemia at end-point (1.60 vs. 2.5; p=0.0036) and a significantly less marked perceived frequency of hypoglycaemia (1.20 vs. 1.96; p<0.0001). The insulin lispro group injected three times a day instead of the once-daily injections of the insulin glargine group. Insulin doses were adjusted by a forced titration regimen to a target fasting blood glucose of 5.5 mmol/L or less in the insulin glargine group and a preprandial blood glucose of 5.5 mmol/L or less in the insulin lispro group. This involved more blood glucose monitoring in the insulin lispro group than in the insulin glargine group as well as more injections in the insulin lispro group. The greater number of injections and blood glucose monitoring required in the insulin lispro group may have contributed to the lesser improvements in treatment satisfaction in the insulin lispro group than in the insulin glargine group.

However, the Dose Adjustment For Normal Eating (DAFNE) study shows us that increased injections and blood glucose monitoring are not necessarily a reason for reduced satisfaction with treatment [55]. This said, DAFNE patients were trained in insulin adjustment for the purpose of allowing dietary freedom in terms of timing and content of snacks and meals, which could be missed entirely if desired. The lispro-treated patients in the APOLLO study had no such training to provide for dietary freedom and it is not surprising that they found their treatment less flexible and less convenient than did patients using insulin glargine.

*Insulin glargine versus premixed insulin*
Two studies have determined the levels of treatment satisfaction associated with starting insulin with insulin glargine versus premixed insulin. In the 28-week INITIATE study [56], 233 people using metformin alone or in addition to other oral hypoglycaemic agents and with

poor glycaemic control (HbA$_{1c}$ ≥8%) were randomised to receive either once-daily insulin glargine (administered using a vial and syringe) or twice-daily biphasic insulin aspart 70/30 (BiAsp 70/30 [30% soluble insulin aspart and 70% protamine crystallised insulin aspart]; administered using an insulin pen device), both in addition to existing oral therapy after adjusting the metformin dose and discontinuing secretogues and α-glucosidase inhibitors: pioglitazone was continued if taken pre-study. Those taking rosiglitazone were switched to pioglitazone as only pioglitazone not rosiglitazone was approved at that time for use with insulin. At the study end with 209 patients completing the study, BiAsp 70/30 was associated with greater improvements in HbA$_{1c}$ than insulin glargine (−2.79 vs −2.36%; p<0.01), but a significantly greater incidence of minor hypoglycaemia, defined as blood glucose values <3.1 mmol/L with or without symptoms that were self treated (3.4 vs 0.7 episodes/year; p<0.05) and greater weight gain (5.4 vs 3.5 kg; p<0.01) [56]. Treatment satisfaction was assessed using the ITSQ, but no significant treatment group differences were found in the total ITSQ score or for any of the domains [57], although actual results were not given. Without seeing the distribution of scores for the ITSQ scale and subscales we cannot be sure that ceiling effects didn't prevent differences appearing between treatment groups though with the insulin glargine group having to use a syringe and vial it is unlikely that they scored highly on the last six items of the ITSQ, which are designed to pick up benefits of insulin delivery devices such as pen-injectors. Under these circumstances together with the greater improvements in HbA$_{1c}$ values it is perhaps surprising that the biphasic analogues administered by pen-injector did not show benefits on the ITSQ compared with insulin glargine. The two items concerning the need to plan meals and snacks would have been likely to favour insulin glargine as would the 5 items concerned with hypoglycaemia. If insulin glargine had been administered by a convenient pen-injector in this study it is likely that ITSQ scores overall would have favoured insulin glargine. No baseline measurement of treatment satisfaction was possible with this ITSQ measure, which is specifically designed for people taking insulin and at baseline none of these patients were using insulin. Thus it was not possible to evaluate change in satisfaction with this ITSQ measure and the DTSQ would have been a better choice of instrument for this particular study.

In the 24-week LAPTOP study, 371 people with Type 2 diabetes poorly controlled on sulphonylurea plus metformin and with no experience of insulin, were randomised to either once-daily insulin glargine in the morning plus oral agents (glimepiride and metformin) or to twice-daily (before breakfast and dinner) premixed human insulin (30% regular/70% NPH insulin) without oral therapy. The insulins were injected using Optipen® 1E (sanofi-aventis GmbH, Frankfurt, Germany) for insulin glargine and NovoPen® (Novo Nordisk, Copenhagen, Denmark) for the premixed insulin [58]. Improvements in HbA$_{1c}$ (−1.64 vs −1.31%; p=0.0003)

and fasting blood glucose (9.5 reduced to 6.4 vs 9.6 reduced to 7.4 mmol/L; p<0.0001) were significantly greater with insulin glargine plus oral agents than with premixed human insulin. Although a similar proportion of patients experienced one or more episodes of hypoglycaemia in both groups, the incidence of hypoglycaemia was significantly lower with insulin glargine (4.07 vs 9.87 events per patient–year; p<0.0001). In this study, a total of 159 and 164 people in the insulin glargine and premixed insulin groups completed the DTSQs at both baseline and endpoint [59]. Overall, participants in both groups reported significant improvements in treatment satisfaction (p<0.0001), which were significantly greater with insulin glargine than with premixed insulin (+4.0 vs +2.3; p=0.0022). DTSQc scores at endpoint also showed greater improvements in treatment satisfaction in the insulin glargine group compared with the premixed insulin group (14.0 vs 11.5; p=0.0028).

The premix used in the LAPTOP trial was human rather than analogue. It has been suggested that the analogue premix used in the INITIATE trial would have had advantages for HbA$_{1c}$ levels [56] and that the removal of oral agents may have disadvantaged the premix group. Use of pen-injectors in both groups in the LAPTOP trial, albeit different devices, levels the playing field, at least with respect to method of insulin delivery, in comparing PROs associated with these two insulin regimens.

*Insulin glargine versus exenatide*
Glucagon-like peptide-1 (GLP-1) analogues provide an alternative to insulin therapy in Type 2 diabetes, as discussed elsewhere in this supplement by George Dailey. In brief, GLP-1 improves glycaemic control by various mechanisms, including secretion of glucose-dependent insulin, suppression of inappropriately high glucagon levels, delay of gastric emptying and reduction of food intake [60]. The current GLP-1 analogues, including exenatide and liraglutide, are injected once or twice daily and are associated with significant improvements in glycaemic control and some weight loss [41,60]. The clinical efficacy of exenatide versus insulin glargine has been assessed in a 26-week, multicentre, open-label comparator-controlled trial. In this study, 549 patients were randomized to add either twice-daily exenatide (15 minutes before morning and evening meals) or once-daily insulin glargine (at bedtime) to their oral treatment regimen. Baseline and endpoint PRO measures were administered (the SF-36 vitality scale, the DSC-R, the EQ-5D, the TFS, and the DTSQ) and analysed within each treatment group as well as between groups [42]. It was found that that both insulin glargine and exenatide were associated with improvements in DSC-R (p<0.0001 for exenatide and p=0.0002 for insulin glargine), DTSQ (p<0.0001 for both treatment groups) and vitality (p=0.005 for exenatide and p<0.04 for insulin glargine) when added to oral medications (sulphonylurea and metformin) among patients with Type 2

diabetes. There was no change in TFS scores for either group perhaps because the sulphonylureas used remained unchanged in both groups. Details of the sulphonylureas used were not given but if these were of the older type requiring fixed amounts of carbohydrates to be eaten at fixed times, they may limit the advantages of insulin glargine and exenatide, which may not require such dietary restrictions. We know that such dietary restrictions impact negatively on QoL [3,4]. EQ-5D scores improved significantly in the insulin glargine group but improvements did not reach significance in the exenatide group and the change in EQ5D scores did not differ significantly between groups. Exenatide has been associated with a high incidence of nausea and, in this trial, 126 patients on exenatide reported this symptom while only 22 insulin glargine-treated patients reported having the symptom at some point in the trial. Nevertheless significant improvements in DTSQ scores were found for these subgroups despite their experience of nausea. It is possible, as the authors suggested, that the weight reducing benefits of exenatide, outweighed the disadvantages of nausea (which anyway may only be experienced initially) and the need for two injections per day timed in relation to meals instead of one injection with insulin glargine at bedtime. Overall both treatment groups reported a significant reduction in DSC-R symptoms but unfortunately the DSC-R does not include gastrointestinal symptoms [18]. Symptom measures to be used in future trials of exenatide need to ensure that nausea and other relevant gastrointestinal symptoms are specifically included in the questionnaire used. Secnik Boye and colleagues acknowledged that only 455 patients considered per protocol were included in the analyses of PROs. Heine et al in their paper focusing on the biomedical outcomes [41] reported that 19.4% of exenatide patients and 9.7% of insulin glargine patients withdrew from the study, 9.5% and 0.7% respectively, due to adverse events. Had endpoint DTSQ scores been available from these patients when they withdrew, it may well be that the overall results for satisfaction with exenatide would look considerably less positive while the results for insulin glargine patients would be little affected.

## DISCUSSION

Healthcare professionals and people with Type 2 diabetes are often reluctant to start insulin therapy, and instead focus on intensifying conventional oral therapy, either by increasing doses, or by adding a third agent, such as a TZD (where allowed). In the three studies discussed here, which compared the addition of insulin glargine to existing oral therapy versus adding a TZD [40,51] or intensifying conventional oral therapy [27,28], insulin glargine was associated with greater improvements in treatment satisfaction and/or other PROs. It is likely that the improvements in PROs in part reflect an increased feeling of the greater improvements in glycaemic control achieved with insulin glargine compared with intensifying oral therapy, particularly the reduction in unwanted symptoms of hyperglycaemia

and increased energy/vitality associated with improved $HbA_{1c,}$ even though insulin glargine may sometimes be associated with a greater risk of hypoglycaemia (at least initially) and a need for injections. Overall, in the studies that compared the addition of insulin glargine versus other insulin formulations [53,54,58], participants reported greater improvements in treatment satisfaction, and other PROs, with insulin glargine rather than with the alternative therapies [49,54,59].

It seems likely that the lower incidence of hypoglycaemia with insulin glargine than with the other insulin preparations used in these studies may also drive some of the improvements in PROs. Indeed, a study by Currie et al [61], statistically modelled the degree of fear of hypoglycaemia experienced by people with diabetes based on pooled data from two previous postal surveys (1305 responses) and demonstrated that each severe hypoglycaemic event resulted in a change of 5.9 units on the Hypoglycaemia Fear Survey (HFS) worry score [62,63], while one or more symptomatic events resulted in a change of 1.8 units on the HFS worry score. Although this study was not designed to assess the impact of insulin glargine on fear of hypoglycaemia, the lower risk of hypoglycaemia with insulin glargine is likely to be associated with reduced worry about hypoglycaemia and to contribute to the improved PROs with insulin glargine compared with other insulin therapies described above. Greater treatment satisfaction with insulin glargine may also reflect the lower risk of other adverse symptoms, the perceived simplicity of once-daily insulin glargine and lack of dietary restrictions compared with other insulins, whereas NPH insulin, premixed insulin and insulin lispro are typically administered twice or three-times daily, and premixed and lispro insulins need to be matched to appropriate levels of carbohydrate intake.

In the studies reported above, participants were not taught carbohydrate counting and flexible dose adjustment. This approach was used in the DAFNE study [55]. It may be that if patients were offered education for increased flexibility of mealtime and meal content with suitable dose adjustment, the DTSQ flexibility ratings with insulin lispro in the APOLLO study [54], for example, may have been increased to match those obtained with insulin glargine. However, this would entail more extensive training and thus expense and the convenience of three-times-daily insulin lispro would be unlikely to match that of once-daily insulin glargine either for the patients or the clinicians. While a single insulin glargine injection together with oral agents can enable patients to achieve acceptable diabetes control, this approach is likely to be preferable to multiple insulin injection regimens in terms of PROs and financial cost. Additional prandial insulin injections may need to be added as glycaemic control deteriorates with disease progression, but by that point any initial psychological resistance to

insulin initiation will be likely to have been overcome with the once-daily insulin glargine injection.

Treatment satisfaction was measured in two studies comparing insulin glargine with premixed insulin (BiAsp 70/30 or premixed human insulin), with the two studies yielding conflicting results. In the INITIATE study, there was no difference in treatment satisfaction, which may reflect a combination of the clinical efficacy (better overall glycaemic control with BiAsp vs a lower risk of hypoglycaemia and less weight gain and greater convenience with once-daily insulin glargine) and the different administration methods (BiAsp was administered using a more convenient pen device while insulin glargine was administered using a less convenient vial and syringe). Previous studies have reported a greater patient preference or/and greater improvements in treatment satisfaction (measured by the DTSQ or ITSQ) with pen devices compared with the vial and syringe [64-68], which may have obscured the results of the INITIATE study. In contrast, in the LAPTOP study [59], improvements in treatment satisfaction were significantly greater with insulin glargine than with premixed insulin. In this study, the improvements in treatment satisfaction may reflect not only the greater convenience of once-daily insulin glargine vs twice-daily premixed insulin (both administered by pen-injectors), but also the greater improvements in glycaemic control achieved with insulin glargine. Although QoL measured by the ADDQoL has been shown to be more negatively impacted by diabetes in those using insulin than in those treated with tablets and/or diet [3-5], it is nevertheless the case that PROs improve when patients with Type 2 diabetes, poorly controlled with oral agents, intensify treatment with the addition of insulin. The improvements in energy experienced have been detected with the W-BQ energy scale [49] and the SF-36 vitality scale [40], DSC-R symptoms have lessened [40,42] and ADDQoL present QoL scores have been shown to improve following the introduction of insulin glargine [27] (perhaps also via improvements in energy associated with improved glycaemic control). Davis and colleagues studied QoL using the Diabetes QoL (DQOL) measure used in the DCCT [69] between groups of patients with Type 2 diabetes using or not using insulin (type of insulin unspecified) and within-groups following introduction of insulin in a subgroup of patients [70]. They found worse DQOL scores in the group already on insulin compared with those on stable oral therapy, but no deterioration following insulin initiation in a subgroup of 38 patients after they commenced insulin. They suggested plausibly that 'although positive factors including increased support and improved hyperglycaemic symptoms may initially offset unfavourable aspects of insulin self-administration, their effect wanes and a lower QoL supervenes after 1–2 years' [70]. The studies discussed above all show an improvement in PROs, including treatment satisfaction, which may also lead to greater treatment adherence. Indeed, in a preliminary analysis of the

two studies comparing the addition of insulin glargine or a TZD to existing oral therapy, the improved PROs achieved with insulin glargine were associated with a higher study completion rate compared with TZD therapy [52]. This may also be true of other studies but the data provided about completion rates and PROs in those withdrawing early are rarely sufficient. If patients using comparator medications such as exenatide and rosiglitazone are more likely to drop out of trials due to adverse events than patients on insulin glargine [e.g. [40-42] then differences in PRO scores among those completing the studies are likely to be underestimates of the advantages of insulin glargine. It is always important to obtain endpoint data from patients who withdraw from studies early whenever possible and this is particularly the case where PRO measures are concerned.

It is vitally important to pay close attention to the nature of PRO measures used in trials evaluating new treatments. All too often, authors refer to the measures used as 'quality of life' measures when they are using more specific measures of symptoms, general health, well-being or treatment satisfaction. When the questionnaires used are actually measuring health status but are discussed as if they are measuring QoL the reader may be seriously misled as pointed out elsewhere [43]. It is no more appropriate to refer to all PROs as 'QoL measures' than it is to refer to all biomedical measures as measures of 'glycaemic control' when we have measures of lipids and blood pressure in the mix as well as $HbA_{1c}$, fasting and post prandial measures of blood glucose. When intensified treatment in the UK Prospective Diabetes Study (UKPDS) was said to lead to no change in QoL, readers were reassured, but when we realise that a health status measure (EQ-5D) was used and not a measure of QoL, what actually happened was that there was no change in perceived health with intensified treatment and we still don't know what effect there was on QoL in the UKPDS [71]. We need to use instruments that really do measure QoL (e.g., ADDQoL) and not just quality of health (e.g., SF-36 and EQ-5D) and we need to describe and interpret the measures we use appropriately. More subtly, we need to ensure that measures of symptoms used include the symptoms likely to occur with the latest drugs under investigation and that the measures of treatment satisfaction used are relevant to treatments used at baseline as well as to those used at follow up. When referring to a collection of PRO measures it is rarely if ever accurate to refer to them as 'QoL' outcomes: the term PRO is usually more appropriate. Many of the studies reviewed here have used only health status (selected SF-36 subscales) and symptom (DSC-R) measures of PROs, which are only a small step up from the biomedical outcomes [40,48,50,51]. While these instruments provide some useful information about patient's experiences it is a leap of faith to assume that symptom distress, general health perceptions and mental health will necessarily be associated with treatment satisfaction or QoL in any linear fashion and there is no substitute for measuring satisfaction

with treatment for diabetes and the impact of diabetes on QoL both in clinical trials and in routine clinical practice. We can't use all the PRO measures all of the time but we can make sure that we describe accurately the results of the measures we do use and make sure we do not go beyond the data in assuming that an improvement in symptoms necessarily means an improvement in QoL. With so many treatment options now available there is more reason than ever for monitoring PROs in clinical practice at annual review or before and after a change of treatment. Distressing symptoms, dissatisfaction with treatment and unwanted effects on aspects of life important for QoL are all important reasons for changing treatment even if HbA$_{1c}$ is reaching target. HbA$_{1c}$ targets will be more likely to be maintained in the long term if patients are free of symptoms and satisfied with a treatment, which is having as little negative impact as possible on their QoL.

## CONCLUSION

In summary, the studies discussed here demonstrate that insulin glargine is associated with greater improvements in treatment satisfaction and other PROs compared with intensified oral therapy or alternative insulin types. Improved treatment satisfaction with insulin glargine may be associated with its simplicity (once-daily dosing, once-daily self-monitoring of blood glucose to guide titration), low risk of hypoglycaemia and other adverse events, and the relative lack of dietary restrictions. Exenatide may be a useful option in the majority who do not experience distressing side effects or for whom they are sufficiently temporary. As type 2 diabetes progresses with increasing loss of endogenous insulin activity and homeostatic control of blood glucose levels, once-daily insulin glargine with OHAs may become insufficient to maintain glycaemic control. Twice-daily premix insulins may be a preferred option when further intensification of treatment is needed by patients who choose anyway to lead routine lives with set mealtimes. However, for the majority of people, protecting their QoL is likely to need a more flexible regimen that avoids the restrictions to meal times and content required with premix insulin treatments, if hypoglycaemia and hyperglycaemia are to be avoided. The addition of prandial insulin one meal at a time to basal insulin glargine, together with training in carbohydrate counting and insulin adjustment, will help to preserve dietary freedom with meals missed or delayed as needed, carbohydrate content varied and occasional feasts enjoyed with valuable consequences for the QoL of people with diabetes as well as their families, friends and colleagues.

## ACKNOWLEDGEMENTS

## REFERENCES

1    Stratton IM, Adler AI, Neil HA *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321**: 405-412.

2    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). (UK Prospective Diabetes Study Group). Lancet 1998; **352**: 837-853.

3    Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. Qual Life Res 1999; **8**: 79-91.

4    Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. Diabetes Metab Res Rev 2002; **18 Suppl 3**: S64-69.

5    Wee HL, Tan CE, Goh SY, Li SC. Usefulness of the Audit of Diabetes-Dependent Quality-of-Life (ADDQoL) questionnaire in patients with diabetes in a multi-ethnic Asian country. PharmacoEconomics 2006; **24**: 673-682.

6    Nathan DM, Buse JB, Davidson MB *et al.* Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy : A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006; **49**: 1711-1721.

7    Polonsky WH, Fisher L, Guzman S, Villa-Caballero L, Edelman SV. Psychological insulin resistance in patients with type 2 diabetes: the scope of the problem. Diabetes Care 2005; **28**: 2543-2545.

8    Rubino A, McQuay LJ, Gough SC, Kvasz M, Tennis P. Delayed initiation of subcutaneous insulin therapy after failure of oral glucose-lowering agents in patients with Type 2 diabetes: a population-based analysis in the UK. Diabet Med 2007; **24**: 1412-1418.

9    Yki-Jarvinen H, Juurinen L, Alvarsson M *et al.* INITIATE (INITiate Insulin by Aggressive Titration and Education). A randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007.

10    Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia 2002; **45**: 937-948.

11    Morris AD. Addressing dosing frequency in diabetes: a simple approach to improving adherence to therapy and clinical outcomes. Diabetes Educ 2003; **29**: 440-446, 448, 450-443.

12    Polonsky WH. Emotional and quality-of-life aspects of diabetes management. Curr Diab Rep 2002; **2**: 153-159.

13    Speight J, Bradley C. The Dose Adjustment For Normal Eating (DAFNE) Trail: What makes people with Type 1 diabetes agree/decline to participate? Diabet Med 2001; **18**: 129.

14    Garratt AM, Schmidt L, Fitzpatrick R. Patient-assessed health outcome measures for diabetes: a structured review. Diabet Med 2002; **19**: 1-11.

15    Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In: Bradley C, ed. *Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers 1994.

16    Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. Diabet Med 1990; **7**: 445-451.

17    Anderson RT, Skovlund SE, Marrero D *et al*. Development and validation of the insulin treatment satisfaction questionnaire. Clin Ther 2004; **26**: 565-578.

18    Grootenhuis PA, Snoek FJ, Heine RJ, Bouter LM. Development of a type 2 diabetes symptom checklist: a measure of symptom severity. Diabet Med 1994; **11**: 253-261.

19    Bradley C. The Well-being Questionnaire. In: Bradley C, ed. *Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers 1994.

20    Bradley C, Gamsu DS. Guidelines for encouraging psychological well-being: report of a Working Group of the World Health Organization Regional Office for Europe and International Diabetes Federation European Region St Vincent Declaration Action Programme for Diabetes. Diabet Med 1994; **11**: 510-516.

21    Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD. Randomized trial comparing continuous subcutaneous insulin infusion and conventional insulin therapy in type II diabetic patients poorly controlled with sulfonylureas. Diabetes Care 1991; **14**: 738-744.

22    Taylor R, Foster B, Kyne-Grzebalski D, Vanderpump M. Insulin regimens for the non-insulin dependent: impact on diurnal metabolic state and quality of life. Diabet Med 1994; **11**: 551-557.

23    Wilson M, Moore MP, Lunt H. Treatment satisfaction after commencement of insulin in Type 2 diabetes. Diabetes Res Clin Pract 2004; **66**: 263-267.

24    Howorka K, Pumprla J, Schlusche C, Wagner-Nosiska D, Schabmann A, Bradley C. Dealing with ceiling baseline treatment satisfaction level in patients with diabetes under flexible, functional insulin treatment: assessment of improvements in treatment satisfaction with a new insulin analogue. Qual Life Res 2000; **9**: 915-930.

25    Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. Diabetes Care 1999; **22**: 530-532.

26    Bradley C, Plowright R, Stewart J, Valentine J, Witthaus E. The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health Qual Life Outcomes 2007; **5**: 57.

27    Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabet Med 2006; **23**: 736-742.

28    Houlden R, Ross S, Harris S, Yale JF, Sauriol L, Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral therapy in the management of Type 2 diabetes: the Canadian INSIGHT Study. Diabetes Res Clin Pract 2007; **78**: 254-258.

29    Mitchell J, Wolffsohn JS, Woodcock A *et al*. +Psychometric evaluation of the MacDQoL individualised measure of the impact of macular degeneration on quality of life. Health Qual Life Outcomes 2005; **3**: 25.

30    Woodcock A, Bradley C, Plowright R, ffytche T, Kennedy-Martin T, Hirsch A. The influence of diabetic retinopathy on quality of life: interviews to guide the design of a condition-specific, individualised questionnaire: the RetDQoL. Patient Educ Couns 2004; **53**: 365-383.

31    Shen W, Kotsanos JG, Huster WJ, Mathias SD, Andrejasich CM, Patrick DL. Development and validation of the Diabetes Quality of Life Clinical Trial Questionnaire. Medical care 1999; **37**: AS45-66.

32    Hayes R, Bowman L. Reliability and validity of the Treatment Flexibility Scale. Qual Life Res 2003; **12**: 863.

33    Riazi A, Ishii H, Barendse S, Bradley C. Well-being questionnaire (W-BQ): translation and psychometric development of a short form (W-BQ12) in Japanese. Proc Brit Psychol Soc 1999; **7 (Suppl 1)** 34A.

34    Riazi A, Bradley C, Barendse S, Ishii H. Development of the Well-being questionnaire short-form in Japanese: the W-BQ12. Health Qual Life Outcomes 2006; **4**: 40.

35    Witthaus E, Stewart J, Bradley C. Treatment satisfaction and psychological well-being with insulin glargine compared with NPH in patients with Type 1 diabetes. Diabet Med 2001; **18**: 619-625.

36    Pouwer F, Snoek FJ, van der Ploeg HM, Ader HJ, Heine RJ. The well-being questionnaire: evidence for a three-factor structure with 12 items (W-BQ12). Psychol Med 2000; **30**: 455-462.

37    Mitchell J, Bradley C. Psychometric evaluation of the 12-item Well-being Questionnaire for use with people with macular disease. Qual Life Res 2001; **10**: 465-473.

38    McMillan CV, Bradley C, Gibney J, Russell-Jones DL, Sonksen PH. Psychometric properties of two measures of psychological well-being in adult growth hormone deficiency. Health Qual Life Outcomes 2006; **4**: 16.

39    Weisbord SD, Fried LF, Arnold RM *et al.* Development of a symptom assessment instrument for chronic hemodialysis patients: the Dialysis Symptom Index. Journal of pain and symptom management 2004; **27**: 226-240.

40    Vinik AI, Zhang Q. Adding Insulin Glargine Versus Rosiglitazone: Health-related quality-of-life impact in type 2 diabetes. Diabetes Care 2007; **30**: 795-800.

41   Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005; **143**: 559-569.

42   Secnik Boye K, Matza LS, Oglesby A *et al*. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. Health Qual Life Outcomes 2006; **4**: 80.

43   Bradley C. Importance of differentiating health status from quality of life. Lancet 2001; **357**: 7-8.

44   Mitchell J, Bradley C. Measuring quality of life in macular disease: what use are utilities? Proceedings of vision 2005; International congress series 2005; **1282**: 654-658.

45   Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992; **30**: 473-483.

46   Woodcock AJ, Julious SA, Kinmonth AL, Campbell MJ. Problems with the performance of the SF-36 among people with type 2 diabetes in general practice. Qual Life Res 2001; **10**: 661-670.

47   Meneghini LF, Schwartz S, Rak ES, Harris A, Strange P. Improved glycemic control with insulin glargine (GLAR) vs pioglitazone (PIO) as add-on therapy in patients with type 2 diabetes (T2D) uncontrolled on sulfonylurea (SU) or metformin (MET) monotherapy. Diabetes 2005; **54 (Suppl 1)**: Abstrast 10-LB.

48   Fischer JS, McLaughlin T, Loza L, Beauchamp R, Schwartz S, Kipnes M. The impact of insulin glargine on clinical and humanistic outcomes in patients uncontrolled on other insulin and oral agents: an office-based naturalistic study. Curr Med Res Opin 2004; **20**: 1703-1710.

49   Witthaus E, Stewart J, Bradley C. Improved psychological outcomes after initiation of insulin treatment in patients with Type II diabetes. Diabetologia 2000; **43 (Suppl 1)**: A205.

50   Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006; **29**: 554-559.

51   Meneghini LF, Schwartz S, Strange P, Oster G. Health-related quality of life and costs of receiving add-on therapy with insulin glargine or pioglitazone in patients with type 2 diabetes. Diabetologia 2006; **49 (Suppl 1)**: 543 (Abstrast 0894).

52   Vinik AI, Zhang Q. Health-related quality of life (HRQOL) and early study termination in patients adding insulin vs a thiazolidinedione to one or two oral agents. Diabetes 2006; **55 (Suppl 1)**: A137 (Abstract 576-P).

53   Massi Benedetti M, Humburg E, Dressler A, Ziemen M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. Horm Metab Res 2003; **35**: 189-196.

54   Bretzel RG, Nuber, U., Wolfgang, Landgraf., Owens, David., Bradley, C., Linn, T.,. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008; **371**: 1073-1084.

55   DAFNE study group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ 2002; **325**: 746.

56   Raskin P, Allen E, Hollander P *et al*. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005; **28**: 260-265.

57   Brod M, Cobden D, Lammert M, Bushnell D, Raskin P. Examining correlates of treatment satisfaction for injectable insulin in type 2 diabetes: lessons learned from a clinical trial comparing biphasic and basal analogues. Health Qual Life Outcomes 2007; **5**: 8.

58   Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005; **28**: 254-259.

59   Bradley C, El-Haschimi K. Treatment satisfaction in patients with type 2 diabetes: basal insulin plus oral agents versus twice-daily premixed insulin alone – analyses by country. Diabet Med 2006; **23 (Suppl 1)**: 361 (Abstract P1010).

60   Yoo BK, Triller DM, Yoo DJ. Exenatide: a new option for the treatment of type 2 diabetes. Ann Pharmacother 2006; **40**: 1777-1784.

61  Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin 2006; **22**: 1523-1534.

62  Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J. Fear of hypoglycemia: quantification, validation, and utilization. Diabetes Care 1987; **10**: 617-621.

63  Irvine A, Cox D, Gonder-Frederick L. The Fear of Hypoglycaemia Scale. In: Bradley C, ed. *Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers 1994.

64  de Luis DA, Aller R, Cuellar L *et al*. Effect on quality of life with a new insulin injection device in elderly patients with diabetes mellitus type 2. J Diabetes Complications 2004; **18**: 216-219.

65  Korytkowski M, Bell D, Jacobsen C, Suwannasari R. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clin Ther 2003; **25**: 2836-2848.

66  Rubin RR, Peyrot M. Quality of life, treatment satisfaction, and treatment preference associated with use of a pen device delivering a premixed 70/30 insulin aspart suspension (aspart protamine suspension/soluble aspart) versus alternative treatment strategies. Diabetes Care 2004; **27**: 2495-2497.

67  Stockl K, Ory C, Vanderplas A *et al*. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Curr Med Res Opin 2007; **23**: 133-146.

68  Summers KH, Szeinbach SL, Lenox SM. Preference for insulin delivery systems among current insulin users and nonusers. Clin Ther 2004; **26**: 1498-1505.

69  Jacobsen AM, DCCT Research Group. The Diabetes Quality of Life Measure. In: Bradley C, ed. *Handbook of psychology and diabetes: a guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers 1994.

70    Davis TM, Clifford RM, Davis WA. Effect of insulin therapy on quality of life in Type 2 diabetes mellitus: The Fremantle Diabetes Study. Diabetes Res Clin Pract 2001; **52**: 63-71.

71    UKPDS. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). U.K. Prospective Diabetes Study Group. Diabetes Care 1999; **22**: 1125-1136.