

Adding Insulin Glargine Versus Rosiglitazone

Health-related quality-of-life impact in type 2 diabetes

AARON I. VINIK, MD, PHD¹
QUANWU ZHANG, PHD²

OBJECTIVE — We sought to assess health-related quality of life (HRQOL) in patients with type 2 diabetes treated with insulin glargine or rosiglitazone as add-on therapy to sulfonylurea plus metformin.

RESEARCH DESIGN AND METHODS — HRQOL was evaluated in 217 subjects uncontrolled with sulfonylurea plus metformin, enrolled in a 24-week, multicenter, randomized, open-label, parallel-group trial of add-on insulin glargine versus rosiglitazone. A 40-item, self-administered questionnaire at baseline and at weeks 2, 6, 12, 18, and 24 was given, including the 34-item Diabetes Symptom Checklist-Revised (DSC-R), a 5-item mental health scale from the 36-item Short-Form Health Survey (SF-36), and a single-item health rating from the SF-36. These assessments do not specify route of therapy.

RESULTS — Both treatment groups showed similar improvements in glycemic control from baseline to week 24 (change in A1C: -1.66% in the insulin glargine group, -1.51% in the rosiglitazone group, $P = 0.1446$). Both groups also showed improvement in HRQOL, although subjects treated with insulin glargine experienced significantly greater improvements compared with rosiglitazone in the DSC-R total symptom score ($P = 0.005$), total symptom distress score ($P = 0.03$), individual domain scores for mood symptoms ($P = 0.007$), ophthalmologic symptoms ($P = 0.007$), ophthalmologic distress ($P = 0.013$), fatigue distress ($P = 0.033$), and SF-36 perception of general health ($P = 0.047$).

CONCLUSIONS — Although addition of insulin glargine and rosiglitazone achieved comparable improvements in glycemic control, insulin glargine was associated with greater improvements in HRQOL, indicating that other factors (e.g., safety profile and nonglycemic actions) may further enhance HRQOL in patients with type 2 diabetes.

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The Diabetes Control and Complications Trial and the UK Prospective Diabetes Study (UKPDS) have clearly demonstrated that glycemic control attained with intensive treatment of type 1 and type 2 diabetes, respectively, is associated with significant reductions in

the risk of diabetes-related complications (1,2). In patients with type 2 diabetes, achieving and maintaining this level of glycemic control over time will generally require multiple therapies, including insulin (3,4). For example, a publication from the UKPDS reported that 53% of

patients with newly diagnosed type 2 diabetes treated with sulfonylurea monotherapy required the addition of insulin therapy within 6 years to maintain fasting plasma glucose (FPG) levels <6.0 mmol/l (108 mg/dl) (4). Similarly, another UKPDS publication found that $\sim 50\%$ of patients with newly diagnosed type 2 diabetes required multiple therapies after 3 years to maintain A1C levels $<7.0\%$, a proportion that increased to 75% of patients after 9 years (3).

Unfortunately, many patients with type 2 diabetes facing the possibility of insulin being added to their treatment regimens express concerns and fears about its effect on their quality of life (QOL) (5). Patients frequently express anxiety about the pain of injections, concerns about proper technique, and fears of hypoglycemia or weight gain associated with insulin therapy. This reluctance can lead to delays in the initiation of insulin therapy, contributing to prolonged periods of poor glycemic control (5,6).

Studies assessing the impact of insulin therapy on QOL in patients with type 2 diabetes have not provided definitive answers regarding how to reduce fears related to insulin use and how to support the initiation of insulin therapy when appropriate. Improvement of glycemic control by the addition of insulin therapy may increase QOL because of a reduction in hyperglycemic symptoms and an associated reduction in morbidity. Conversely, increased hypoglycemic events or the introduction of a complex injection regimen requiring substantial lifestyle changes could potentially decrease patient QOL (7). Nevertheless, several studies of patients with type 2 diabetes switching from oral treatment to insulin therapy reported a positive effect on patient QOL in addition to improved glycemic control (7–9). However, other studies indicated a neutral or negative effect on QOL (10–12). An alternative to switching from oral to insulin therapy is adding a basal insulin to the patient's current oral regimen. Indeed, triple therapy (with two oral agents and insulin) appears to be a regimen likely to achieve good A1C levels

From the ¹Strelitz Diabetes Research Institutes, Eastern Virginia Medical School, Norfolk, Virginia; and the ²Department of Health Outcomes, Sanofi-Aventis U.S., Bridgewater, New Jersey.

Address correspondence and reprint requests to Aaron I. Vinik, MD, PhD, Director, Strelitz Diabetes Research Institutes, Eastern Virginia Medical School, 855 W. Brambleton Ave., Norfolk, VA 23510. E-mail: vinikai@evms.edu.

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A list of the investigators in the Insulin Glargine 4014 Quality of Life Study Group can be found in the APPENDIX.

Abbreviations: DSC-R, Diabetes Symptom Checklist-Revised; FPG, fasting plasma glucose; HRQOL, health-related quality of life; QOL, quality of life; SF-36, 36-item Short-Form Health Survey; UKPDS, UK Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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(13). The earlier introduction of insulin may have advantages in terms of metabolic memory (14), but it is not clear that “triple therapy” that included insulin would have beneficial effects on QOL compared with oral therapy alone. Introducing insulin therapy with a long-acting, once-daily analog may be less disruptive to lifestyle than multiple daily dosing with conventional insulin.

We report here that in a 24-week, randomized trial of add-on insulin glargine versus add-on rosiglitazone to sulfonylurea and metformin in 217 patients whose type 2 diabetes was inadequately controlled with oral agents (15), addition of insulin improved QOL, despite equivalent improvement in glycemic control.

RESEARCH DESIGN AND METHODS

Health-related quality of life (HRQOL) was assessed in subjects (age range for inclusion was 18–80 years) whose diabetes was uncontrolled (A1C between 7.5 and 11%), despite oral sulfonylurea plus metformin therapy, and who were enrolled in a 24-week, randomized, open-label, parallel-group trial evaluating the addition of insulin glargine versus rosiglitazone at 44 U.S. centers. Details of the main study are reported elsewhere (15). All subjects gave signed informed consent.

Study medications

During the screening phase, patients on 1,000 or 1,500 mg/day metformin had their doses titrated up to 2,000 mg/day (or the maximum tolerated dose) with a stabilization period of at least 2 weeks before randomization. Both sulfonylurea and metformin doses remained unchanged throughout the remainder of the study (15). At the start of the treatment phase, subjects were randomized 1:1 to receive either insulin glargine or rosiglitazone as add-on therapy through a randomization code for each study site. Insulin glargine was administered as a single daily subcutaneous injection at bedtime at a starting dose of 10 IU/day for 7 days, which was titrated weekly to achieve a target FPG value of <100 mg/dl. The starting dose of rosiglitazone was 4 mg once daily for 6 weeks, increased to a maximum of 8 mg (administered either once daily or as 4 mg b.i.d.) if FPG values were >100 mg/dl after 6 weeks (15). Study medication accountability logs for insulin glargine and rosiglitazone were collected and evaluated for assessment of compliance.

Outcome measures

The primary outcome measure for this analysis was the change in HRQOL from baseline to follow-up assessments, compared between patients randomized to insulin glargine or rosiglitazone.

HRQOL measurement

HRQOL assessment in this study evaluated patients' perception of their state of health and the impact on their lifestyle. HRQOL was assessed using a 40-item, self-administered questionnaire at baseline and at weeks 2, 6, 12, 18, and 24. Subjects were provided with instructions on how to answer items and were asked to complete the questionnaire before randomization. This questionnaire included the Diabetes Symptom Checklist-Revised (DSC-R) to assess diabetes-related symptoms and symptom distress (16,9). The DSC-R consists of 34 items grouped into eight symptom subscales: hyperglycemia, hypoglycemia, psychological cognitive functioning, psychological fatigue, cardiovascular functioning, neuropathic pain, neuropathic sensory, and ophthalmologic functioning. In reviewing the instrument, we found it more appropriate to label hypoglycemia as “mood symptoms” for purposes of this report (not in the actual questionnaire administered to patients) because this symptom subscale of the DSC-R comprises three items that assess whether in the past month the patient experienced 1) moodiness, 2) irritability just before a meal, and 3) irritation or annoyance not necessarily related to hypoglycemia; this symptom subscale, therefore, will be referred to as “mood symptoms” throughout the remainder of this report. Patients responded either “yes” or “no” regarding whether they experienced each of the listed symptoms. For the symptoms to which they responded “yes,” follow-up questions were asked about the extent to which the patient was bothered by the symptoms using a 5-point anchored scale ranging from a low of 1 (“not at all bothered”) to a high of 5 (“extremely bothered”). Thus, higher scores on this measure indicated greater psychological and/or physical distress. The raw score (sum of all item scores) for each of the eight symptom subscales was converted to a scale ranging from 0 to 100 (result divided by the possible score range and multiplied by 100). A total symptom score and a total distress score were calculated from responses to all 34 items (16). The 40-item HRQOL questionnaire also contained the 5-item mental health

scale from the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) to assess general emotional well-being and the single-item rating of health from the SF-36 to assess general health perceptions (17).

Statistical analysis

Psychometric evaluation. The psychometric properties of the measure were established using principal component analysis and confirmatory factor analysis (using Mplus). Factor structures for the measure were produced and found to have adequate goodness of fit: Tucker-Lewis index >0.95, comparative fit index >0.95, root mean square error of approximation <0.06, and standardized root mean square residual <0.08 (18). Modification indexes were used to revise the measurement structures based on improvement of goodness of fit. Intraclass correlations were estimated based on the ratio of within- to between-subject variances derived from mixed-effects models by using the SAS Proc Mixed program. Construct validity of domain scores was evaluated by regressing each of the domain scores on A1C, incidence of hypoglycemia, and early withdrawal. Considering temporal relationships between DSC-R domain scores and the three clinical measures, these regression models used time-varying A1C and hypoglycemia measures across all visits. Single items of each domain were regressed on the three clinical measures to determine content specificity of patient-reported outcomes using the DSC-R.

Evaluation of patient-reported physical and psychological outcomes. Eight pairs of symptom and psychological distress scores, general perception of health, and emotional well-being scores were compared between treatment groups at the end of the study. Repeated-measures analysis was used to evaluate both within- and between-group changes from baseline. Because of correlation among patient-reported outcomes, multivariate mixed-effects models were used to assess treatment effects on the domain scores to enhance statistical efficiency. Domain scores after normalization are reported to reduce undue influence of outliers.

RESULTS— Subjects ($n = 217$) were randomized, and a total of 214 completed baseline HRQOL questionnaires ($n = 104$ on insulin glargine, $n = 110$ on rosiglitazone).

Table 1 shows the baseline demo-

Table 1—Baseline demographics and disease characteristics (intent-to-treat population)

Characteristic	Insulin glargine	Rosiglitazone
n	104	112
Age (years)	55.9 ± 10.5	55.3 ± 11.4
Sex (male/female)	45/55	58/42
Race		
White	70.2	76.8
African American	14.4	12.5
Asian	1.9	0.9
Hispanic	11.5	8.9
Other	1.9	0.9
BMI (kg/m ²)	34.6 ± 7.0	33.6 ± 6.3
Duration of diabetes (years)	8.5 ± 5.8	8.1 ± 5.1
A1C (%)	8.8 ± 1.0	8.7 ± 1.0
FPG [mmol/l (mg/dl)]	10.4 ± 3.1 (187.2 ± 55.8)	10.6 ± 3.3 (190.8 ± 59.4)
HRQOL scores		
Hyperglycemia symptoms	42.8 ± 36.1	35.7 ± 34.4
Hyperglycemia distress	33.8 ± 16.3	32.2 ± 16.1
Mood symptoms	34.3 ± 38.2	27.4 ± 35.9
Mood distress	30.6 ± 14.2	28.8 ± 14.2
Cardiovascular symptoms	23.1 ± 29.8	19.5 ± 24.8
Cardiovascular distress	27.5 ± 10.9	26.0 ± 8.9
Neuropathic sensory symptoms	30.9 ± 31.2	29.5 ± 32.1
Neuropathic sensory distress	29.7 ± 12.1	29.2 ± 12.3
Neuropathic pain symptoms	19.3 ± 31.1	15.6 ± 24.1
Neuropathic pain distress	27.1 ± 14.0	25.2 ± 8.8
Fatigue symptoms	55.5 ± 39.9	47.8 ± 37.0
Fatigue distress†	42.5 ± 21.2	36.2 ± 17.1
Cognitive symptoms	35.8 ± 35.9	30.8 ± 32.9
Cognitive distress	32.5 ± 15.7	29.4 ± 12.5
Ophthalmologic symptoms	26.9 ± 31.0	21.9 ± 27.8
Ophthalmologic distress	27.9 ± 11.6	25.6 ± 7.9
Total symptoms	33.3 ± 23.8	28.4 ± 21.4
Total distress	31.3 ± 10.5	29.0 ± 8.7
Perception of general health	46.3 ± 21.6	50.5 ± 21.0
Emotional well-being	74.1 ± 18.4	76.7 ± 18.4

Data are % or means ± SD. * $P = 0.0646$; † $P = 0.017$. Between-group P values for all other characteristics and HRQOL scores were not statistically significant.

graphics and disease characteristics for the intent-to-treat population. Treatment groups were comparable with respect to all demographic and baseline disease characteristics, except for a trend toward more female subjects in the insulin glargine group and more male subjects in the rosiglitazone group ($P = 0.0646$); this difference did not significantly affect the results.

Glycemic control

As previously reported (15), FPG decreased significantly from baseline to end point in both treatment groups, with greater reductions experienced by the insulin glargine group (-3.60 ± 0.23 vs. -2.57 ± 0.22 mmol/l [-64.9 ± 4.14 vs. -46.3 ± 4.0 mg/dl], $P = 0.001$) (15). FPG values at end point were 6.78 ± 2.12

mmol/l (123.05 ± 38.2 mg/dl) for insulin glargine and 7.81 ± 2.55 mmol/l (141.74 ± 45.9 mg/dl) for rosiglitazone. Change from baseline in A1C was similar between the two treatment groups at study end point (-1.66% in the insulin glargine group, -1.51% in the rosiglitazone group, $P = 0.1446$). However, patients with baseline A1C values $\geq 9.5\%$ experienced significantly greater reductions when treated with insulin glargine versus rosiglitazone ($P < 0.05$) (15). End-of-study A1C values were 7.11% for insulin glargine and 7.21% for rosiglitazone.

HRQOL outcomes

Intra-class correlations of the 16 symptom and distress subscales, total symptom and distress scores, and perception of general

health and emotional well-being ranged from 0.64 for cardiovascular symptoms to 0.81 for total distress with an average of 0.70, indicating very high test-retest or within-individual reliability. Confirmatory factor analysis on baseline data supported the factor structures of the eight symptom subscales with minor modifications to the original instrument domains. (Details will be furnished from the authors upon request. Goodness-of-fit tests: Tucker-Lewis index = 0.94, comparative fit index = 0.95, root mean square error of approximation = 0.045, and standardized root mean square residual = 0.058.)

At baseline, subjects in the insulin glargine group had higher scores (indicating poorer HRQOL at baseline) than subjects in the rosiglitazone group in all DSC-R symptom and symptom distress domains. Patients in the insulin glargine group scored 33.28 in total symptoms relative to 28.99 in the rosiglitazone group; baseline total symptom distress score was 31.29 versus 29.20, respectively. These differences were, however, not statistically significant.

As shown in Fig. 1, HRQOL improved for subjects in both treatment groups over the 24-week study. Subjects treated with insulin glargine experienced significantly greater improvements from baseline compared with rosiglitazone-treated subjects in total symptom score (adjusted difference in change from baseline at week 24, 7.59; $P = 0.005$ [Fig. 1A]) and total symptom distress score (adjusted difference in change from baseline at week 24, 1.92; $P = 0.03$ [Fig. 1B]). For individual domain scores of the DSC-R (Fig. 2), subjects treated with insulin glargine experienced greater improvement from baseline than rosiglitazone-treated subjects in mood symptoms ($P = 0.007$), ophthalmologic symptoms ($P = 0.007$), ophthalmologic distress ($P = 0.013$), and fatigue distress ($P = 0.033$). The differences between treatment groups were not statistically significant for the remaining symptom and symptom distress scores. However, with the exception of cardiovascular symptoms and hyperglycemia distress, the remaining domain scores all favored the insulin glargine group.

In addition to the DSC-R items, adjusted patients' perception of general health (where higher scores indicate better health perception) improved more strongly from baseline to end of study with insulin glargine than rosiglitazone (difference between groups in change,

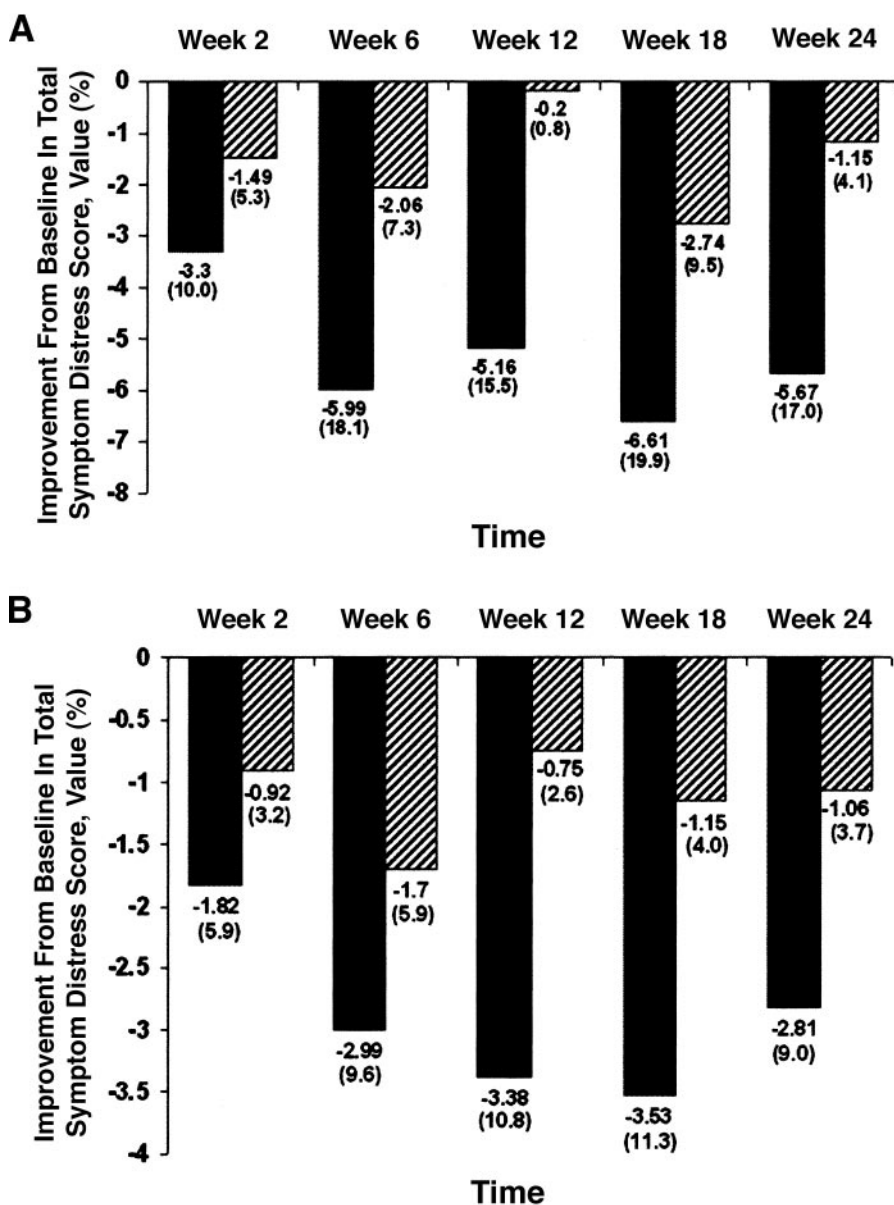


Figure 1—Unadjusted improvement from baseline in total symptom and symptom distress scores. A: Adjusted difference in change from baseline at week 24, 7.59. $P = 0.005$. B: Adjusted difference in change from baseline at week 24, 1.92. $P = 0.03$. ■, insulin glargine; ▨, rosiglitazone.

5.38; $P = 0.047$). The insulin glargine group showed improvement in unadjusted scores for the perception of general health from 46.29 at baseline to 53.09 at study end point, compared with improvement in the rosiglitazone group from 50.46 at baseline to 52.66 at study end point.

Association between HRQOL results and clinical outcomes

Changes in HRQOL domains were compared with clinical outcomes. Within individuals over the study visits, higher A1C values, even when controlled for the

incidence of hypoglycemic events and early termination, were associated with poorer general health ($P = 0.0272$) and worse scores for total distress ($P = 0.03$), hyperglycemia distress ($P < 0.0001$), fatigue distress ($P = 0.0008$), visual symptoms ($P = 0.0098$), fatigue symptoms ($P = 0.0202$), and hyperglycemia symptoms ($P = 0.0001$). Study completion was associated with improved emotional well-being ($P = 0.0434$) and lower (improved) scores for cognitive distress ($P = 0.0219$), cognitive symptoms ($P = 0.026$), and mood symptoms ($P = 0.0234$), even controlling for the change

in A1C. More subjects in the rosiglitazone group than in the insulin glargine group discontinued the study early (21 [18.8%] vs. 8 [7.6%] subjects; $P = 0.0104$). Generally, subjects who completed the study had better HRQOL scores than subjects who withdrew from the study early.

CONCLUSIONS— This study demonstrates that in a randomized trial in which subjects with uncontrolled type 2 diabetes on oral therapy (sulfonylurea plus metformin) achieved comparable improvements in glycemic control with the addition of either insulin glargine or rosiglitazone, subjects treated with insulin glargine reported greater improvements in certain elements of HRQOL than subjects treated with rosiglitazone. The finding that injectable therapy demonstrated improvements in QOL relative to oral therapy even when similar levels of glycemic control were achieved suggests that the relationship between glycemic control and QOL is complex.

Several previous studies (7,9,10) have similarly not found a simple independent association between A1C levels and QOL. For example, Fischer et al. (9) assessed HRQOL using the same instruments as those in the current study in 50 patients initiating insulin glargine. A significant 1.47% A1C reduction in 16 weeks was reported along with significant improvements in total symptoms, total symptom distress, emotional well-being, and general health perception; however, there was no significant correlation between A1C and HRQOL. In a 1-year study of 94 consecutive patients with type 2 diabetes referred to an outpatient clinic for consideration of insulin therapy (twice-daily insulin; type not specified), a mean reduction of 2.6% in A1C was accompanied by improvement in QOL, but the degree of improvement was not dependent on changes in A1C (7). Presence of hyperglycemic symptoms at baseline was the main determinant of QOL improvements; psychosocial patient characteristics or treatment satisfaction may also have been intermediate factors between A1C and QOL. Patients switched to twice-daily injections of insulin therapy (65%) experienced similar overall improvements in QOL compared with those remaining on oral therapy but reported more problems with social functioning and more pain compared with non-insulin-treated patients (7).

In the current study, insulin glargine was administered once daily; therefore,

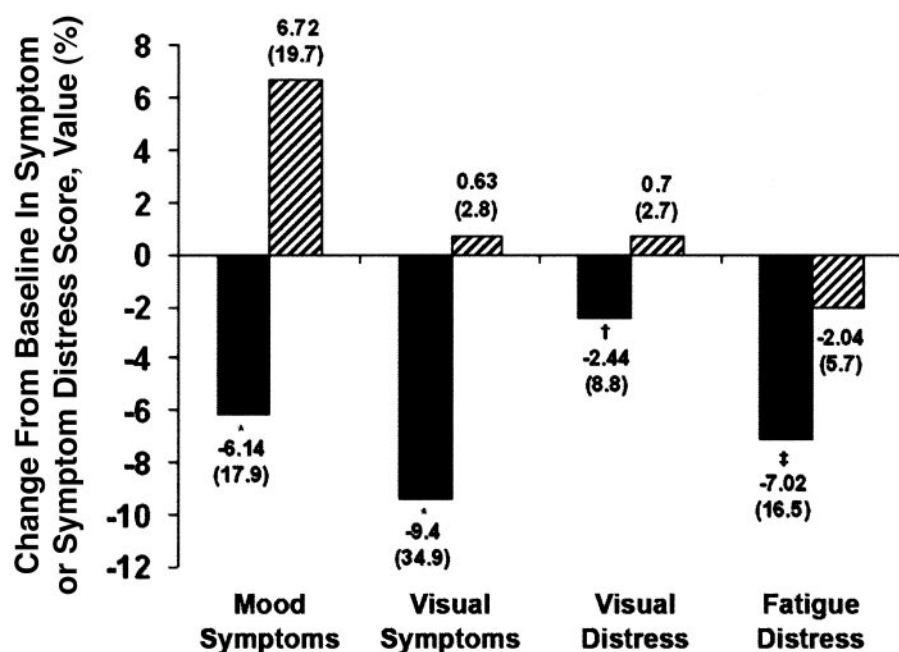


Figure 2—Change from baseline in unadjusted symptom or symptom distress score. * $P = 0.007$, † $P = 0.013$, ‡ $P = 0.033$ compared with rosiglitazone. ■, insulin glargine; ▨, rosiglitazone.

the potential negative aspects of injectable therapy relative to oral therapy may have had relatively less impact on overall QOL. The comparable glycemic control between the study groups suggests that improved HRQOL in patients treated with insulin glargine may in part be due to adverse events possibly related to study medication occurring in fewer patients treated with insulin glargine than with rosiglitazone (6.7 vs. 28.6%; $P < 0.0001$). Future studies addressing HRQOL and degree of glycemic control should include follow-up questions to the patients that address self-management, monitoring, and patient expectations, among others. There were no occurrences of edema (vs. 12.5% in the rosiglitazone group; $P = 0.001$ between groups) and less weight gain in the insulin glargine versus the rosiglitazone group (1.7 vs. 3.0 kg; $P = 0.02$) (15). Hypoglycemia was not a factor in the differences in HRQOL. The overall incidence of hypoglycemia was similar between treatment groups, and severe hypoglycemic events were rare ($n = 6$ in the rosiglitazone group; $n = 3$ in the insulin glargine group) (15). The more favorable side-effect profile in the insulin glargine group was likely a factor contributing to the significantly lower withdrawal rate in this group compared with the rosiglitazone group ($P = 0.0104$) (15). In addition, study completion was associated with improved HRQOL.

In studies involving patients with di-

abetes, the type of instrument used to measure QOL can affect outcomes. For example, use of diabetes-specific, patient-rated, validated instruments, such as the Norfolk Quality of Life Questionnaire—Diabetic Neuropathy, can identify the impact of conditions, such as diabetic neuropathy, which may affect QOL in subtle ways but may go unnoticed by the clinician (19). A potential limitation of the current study comparing the impact of an oral antidiabetes agent with insulin injection on QOL is the use of the DSC-R, which does not contain any questions directly related to different routes of administration. However, the mental health scale and general health perception items from the SF-36, also included in this study, may have been able to reflect any anxiety or other negative feelings associated with use of injectable therapy. Analyses of the DSC-R suggest that this is an instrument capable of discerning differences in certain aspects of HRQOL, but development of specific instruments to address these unanswered questions would be helpful. Alternatively, a double-dummy study design, in which patients who received oral agents only also received an injectable placebo and patients who received insulin injection also received an oral placebo, would have helped to reduce patient-perceived treatment bias.

In summary, despite equivalent gly-

combination failures, introduction of triple therapy with insulin glargine enhanced HRQOL compared with rosiglitazone. Given the negative perceptions of insulin therapy in the past and concerns that initiation of insulin therapy in patients with type 2 diabetes could potentially decrease QOL, the improvements from baseline in HRQOL associated with insulin glargine therapy in this study are particularly reassuring.

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APPENDIX

The following are investigators in the Insulin Glargine 4014 Quality of Life Study Group: P. Cleary, J. Edelsberg, G. Harding, G. Oster, J. Rosenstock, S. Vietas, and D. Weycher.

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