Predictors of Quality of Life and Other Patient-Reported Outcomes in the PANORAMA Multinational Study of People With Type 2 Diabetes

Clare Bradley,[1] Eveline Eschwège,[2] Pedro de Pablos-Velasco,[3] Klaus G. Parhofer,[4] Dominique Simon,[5,6] Hans Vandenberghe,[7] and Linda Gönder-Frederick[8]

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OBJECTIVE

PANORAMA, a nine-country cross-sectional type 2 diabetes study, investigated factors associated with quality of life (QoL), health status, and other patient-reported outcome measures (PROMs).

RESEARCH DESIGN AND METHODS

Patients were randomly or consecutively selected from primary/secondary care. PROMs included the Audit of Diabetes-Dependent Quality of Life (ADDQoL) (generic QoL item and average weighted impact [AWI] scores), Diabetes Treatment Satisfaction Questionnaire (DTSQ) (patient- and physician-completed), Hypoglycemia Fear Survey-II worry subscale, and the EuroQoL–5 Dimension visual analog scale (EQ-VAS) measuring patient-reported health. Multivariable linear regression analyses determined predictors of each PROM including patient characteristics, physician-reported adherence, complications, and glycosylated hemoglobin.

RESULTS

In 5,813 patients, mean PROM scores indicated that generic QoL approximated "good" (0.93); perceived impact of diabetes on QoL was negative (AWI –1.69). Treatment satisfaction exceeded physicians' estimates (patient-reported: 29.76; physician-estimated: 27.75), but so did patients' perceived frequency of hypo-/hyperglycemia. Worry about hypoglycemia (13.27) was apparent. Intensifying treatments to three oral agents or insulin regimens predicted worse QoL (AWI $P < 0.01$). Insulin alone use predicted worse QoL (generic $P < 0.02$; AWI $P < 0.001$) and hypoglycemia worry ($P < 0.007$). No treatment had significant associations with EQ-VAS health status.

CONCLUSIONS

Predictors for different PROMs differed markedly and provided insights for understanding and improving these important outcomes. Intensive treatment regimens had significant negative associations with all PROMs, except the EQ-VAS health status measure. The findings demonstrate the importance of measuring QoL alongside health status and other patient-reported outcomes when evaluating diabetes treatments with a view to protecting QoL and facilitating adherence and long-term glycemic control.

[1]Health Psychology Research Unit, Royal Holloway, University of London, Egham, U.K.
[2]INSERM, Paris, France
[3]Dr. Negrin Hospital, Research Institute of Biomedical and Health Sciences (IUIBS), University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain
[4]Medical Department 4, Grosshadern, Klinikum der Universität München, Munich, Germany
[5]Institute of Cardiometabolism and Nutrition, Hôpital de la Pitié-Salpêtrière, Paris, France
[6]Diabetes Department, Hôpital de la Pitié-Salpêtrière, Paris, France
[7]AstraZeneca, Uccle, Belgium
[8]University of Virginia Health System, Charlottesville, VA

Corresponding author: Clare Bradley, c.bradley@rhul.ac.uk.

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Long-term type 2 diabetes management usually involves diet and lifestyle changes as well as medication, with consequences for quality of life (QoL) and other patient-reported outcomes (PROs). When QoL and/or treatment satisfaction is damaged by a treatment regimen, treatment adherence may be compromised, with adverse consequences for glycosylated hemoglobin (HbA_{1c}) and complication risk. Insulin use and complications are usually associated with QoL impairment (1,2). Intensive treatment can result in weight gain and increased hypoglycemia and/or involve dietary restrictions, which may damage PROs. Such problems may be avoidable in patients with type 1 and type 2 diabetes when the importance of dietary freedom for QoL is recognized, protected, and measured (3–5).

Studies comparing different treatments have assessed various PRO measures (PROMs). The UK Prospective Diabetes Study (UKPDS) interpreted the finding that the EuroQoL–5 Dimension (EQ-5D) health status questionnaire did not differ between intensified treatment and conventional treatment groups to mean that intensifying treatment did not damage QoL (6). However, QoL was not measured (7). The EQ-5D actually showed that patient-reported health did not improve with intensified treatment. Although efforts have been made to distinguish between health status and QoL (7–9), health status measures are often inaccurately referred to and interpreted as "health-related QoL" or "QoL." (For example, see ref. 10.)

"QoL" is often used as an umbrella term to refer to any PROM, including satisfaction and symptom measures. However, when the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Audit of Diabetes-Dependent Quality of Life (ADDQoL) are both included, high treatment satisfaction may be found alongside a marked negative impact of diabetes on QoL (11). To appreciate the importance of differentiating between PROMs and to understand their differential interaction with biomedical outcomes, it is useful to examine predictors of a range of PROMs. Sundaram et al. (1) led the way in investigating predictors of both diabetes-related QoL (measured by ADDQoL) and health status (Short-Form 12-Item Health Survey [SF-12]). Others followed, using the ADDQoL alone or with a health status tool (12,13). However, the small number of PROMs examined and selective samples (e.g., those within 5 years of diagnosis [14], from a specific clinic [1], or from one country [13]) limit the finding's generalizability.

PANORAMA, a multinational, real-world, cross-sectional study (NCT00916513), aimed to fill the gap in the literature by assessing a range of well-validated and/or widely used PROMs simultaneously in a larger, more representative sample of patients with type 2 diabetes. An earlier study reported univariate associations between hypoglycemia frequency and PROMs (14). Here, we report a different picture obtained from multivariable analyses investigating the contributions of treatment intensity, glycemic control, hypoglycemia, and other variables as predictors of PROMs. This is the first time that health status, QoL, diabetes-specific QoL, diabetes treatment satisfaction, and fear of hypoglycemia as a particular selection of PROMs have been used simultaneously and the first time that their predictors have been examined. Predictors of the various PROMs measuring distinct constructs were expected to differ (15).

RESEARCH DESIGN AND METHODS

Study Design

The PANORAMA study design has previously been published (15). Patients were enrolled from nine countries: Belgium, France, Germany, Greece, Italy, the Netherlands, Spain, Turkey, and the U.K. The primary objective was to investigate PROMs (ADDQoL, DTSQ, the Hypoglycemic Fear Survey-II [HFS-II] worry subscale, and EQ-5D) in patients with type 2 diabetes with multivariable analyses to examine demographic and clinical predictors of each PROM.

Study Population

Study Site Selection

Physicians and patients were recruited between May 2009 and February 2010. In each country, physicians managing type 2 diabetes were randomly selected. In seven countries, primary care physicians were recruited, but in Italy and Greece, hospital diabetologists were selected to reflect country-specific practice.

Patient Selection

Eligible patients with type 2 diabetes were randomly (in the Netherlands, Spain, and U.K.) or consecutively (in Belgium, France, Germany, Greece, Italy, and Turkey—countries without electronic health records) selected from primary care or specialist clinics. Inclusion criteria were as follows: age ≥40 years, diagnosis of type 2 diabetes for ≥1 year plus medical records available for ≥1 year. All patients received diet/exercise advice: most were treated with oral antidiabetes drugs (OADs), insulin, and/or glucagon-like peptide 1 receptor agonist (GLP-1) analogs. Treatment was unchanged for 3 months.

Key exclusion criteria included the following: type 1 diabetes and/or history of diabetic ketoacidosis or secondary diabetes (including exocrine-pancreas disease, endocrinopathies) and pregnancy.

Good Clinical Practice was followed throughout.

Data Collected

At the single study visit, participating patients and their physicians completed the study questionnaires; medical records' data were collected as previously described, including diabetes-related complications, comorbidities, and presence or history of depression (15). No information was collected on how depression was diagnosed or whether it was documented by a mental health provider. HbA_{1c} levels were measured using the A1CNow SELFCHECK, a point of care–certified device (Bayer Diabetes Care, now manufactured by PTS Diagnostics) (16). Physicians reported hypoglycemia frequency and severity, with severe hypoglycemia defined as symptomatic episodes requiring external assistance owing to severe impairment and recovery after glucose/glucagon administration. Physicians classified patient adherence to medication and lifestyle recommendations as "poor," "moderate," or "good." If patients were not at their HbA_{1c} target, physicians were asked why: options included "resistance/reluctance of patient to intensify their medication regimen (adding agent or increasing dose)" and "reluctance of physician to intensify treatment." Subcategories of reasons for physician reluctance were provided, e.g., 'fear of hypoglycemia.'

Patients completed PROM questionnaires, including ADDQoL (2,17), DTSQ (18,19), the HFS-II worry subscale (20), and EQ-5D (21–23). Linguistically validated (24) PROMs were available in the preferred language. Questionnaires can be accessed as follows: for ADDQoL and DTSQ, go to www.healthpsychologyresearch.com; for EQ-5D, go to www.euroqol.org; and for HFS-II, e-mail lag3g@hscmail.mcc.virginia.edu.

ADDQoL

The widely used ADDQoL measures the impact of diabetes on QoL. Two overview

items measure generic QoL (7-point scale from excellent [+3] to extremely bad [−3]) and diabetes-dependent QoL (In response to "If I did not have diabetes, my QoL would be:" the answers correspond to a 5-point scale from very much better [−3] to worse [+1]). Five-point impact scale scores relating to 19 specific life domains (e.g., very much better/greater [−3] to worse/less [+1]) are multiplied by related 4-point importance ratings (very important [+3] to not at all important [0]) to produce a weighted impact (WI) score (−9 to +3). For five life domains, preliminary questions determined applicability. Averaging WI scores over applicable domains produce an average weighted impact (AWI) score (−9, maximum negative impact of diabetes, to +3, maximum positive impact).

DTSQ

Recommended by the World Health Organization and International Diabetes Federation to assess diabetes care, the treatment satisfaction score is the sum of six items rated on 7-point scales (6, very satisfied, to 0, very dissatisfied). Two further items, analyzed separately, measure perceived frequency of hyperglycemia/hypoglycemia, (6, most of the time, to 0, none of the time). Physicians also independently completed the DTSQ as if they were each individual patient (see Supplementary Data and Supplementary Table 1 for psychometric properties).

HFS-II Worry Subscale

The widely used HFS-II worry subscale measures patient concern about hypoglycemia and its consequences. The 18 items are rated on 5-point Likert scales (0, never, to 4, almost always) which, summed, range from 0, least worry, to 72, most worry.

EQ-5D

EQ-5D is a generic measure of health status commonly used in cost-effectiveness analyses and recommended by the National Institute for Health and Care Excellence (NICE) (25). EQ-5D comprises a visual analog scale (EQ-VAS) plus five further questions. Only the EQ-VAS score is reported here.

Statistical Analyses

A sample size of 753 patients per country was determined to provide sufficient precision for the primary outcome in terms of the 95% CIs around each of the country-specific means, given the expected SD (15).

Episodes of nonsevere hypoglycemia were recorded per month; episodes of severe hypoglycemia were recorded per year. Patients with diabetic nephropathy were categorized by the most severe subcategory reported. As in previous PANORAMA articles, patients receiving GLP-1 analogs plus insulin and/or OADs were included in the "on insulin with OADs" (n = 3) or the "on insulin alone" (n = 3) treatment groups; patients on GLP-1 analogs alone (n = 48) were excluded from analyses.

Bivariate Pearson correlations were conducted on the ADDQoL overview items and AWI scores.

Mixed-model linear regression was used to analyze variables associated with PROM scores (change in PROM scores with 1-unit change in the independent variable), including physician as a random effect; this model takes account of any clustering of patient and treatment characteristics by physician. Multivariable analyses were adjusted for potential confounding by the other variables included (e.g., patient characteristics, clinical/biological measures), by physician, and physician characteristics. For continuous variables, average differences (95% CIs) were given per additional year (age and diabetes duration), per additional 0.1% (target HbA_{1c}), per additional kg/m^2 (BMI), per additional mmHg (systolic/diastolic blood pressure [BP]), and per visit (to general practitioners/specialists). For categorical variables, "yes" was compared with "no," except for HbA_{1c} ($\geq$7% vs. $<$7%) and physician-rated adherence to medication/lifestyle ("good" vs. "moderate"/"poor" adherence); treatment categories were compared with diet/exercise alone.

The multivariable analyses were repeated without treatment covariates to determine whether intensified treatment (including increased propensity for hypoglycemia) was masking effects of hypoglycemia more specifically.

RESULTS

Patients were recruited by 390 physicians, 77.4% of whom (298 of 390) were general practitioners. On average, physicians saw 37.8 patients with diabetes weekly.

PANORAMA enrolled 5,817 patients. Four participants with data-reporting errors, identified after database lock, were excluded from analysis. Overall, the 5,813 patients had a mean age of 65.9 years and diabetes duration of 8.9 years (Table 1). Mean HbA_{1c} at study visit was 6.9% (52 mmol/mol). The majority was treated with OADs alone (68.9% [3,959 of 5,750]). Microvascular complications were recorded for 35.9% of patients; incidence was higher (P = 0.028) in countries recruiting sequentially (36.9% [1,456 of 3,951]) rather than randomly (33.9% [631 of 1,862]).

PROMs

ADDQoL: Generic QoL and Diabetes-Related QoL

Overview item 1 responses gave a mean generic QoL score of 0.93 approximating to "good" (1) as opposed to "very good" (2) or "neither good nor bad" (0) (Table 2; Fig. 1*A*). However, mean diabetes-related QoL (overview item 2) was −1.26, indicating QoL would be better without diabetes (Fig. 1*B*). Among the 19 domain-specific items, respondents rated "freedom to eat as I wish" as the most negatively impacted/important (WI score = −3.35)—substantially more so than other items (Fig. 1*C*). Mean AWI score for the domain-specific items was −1.69, indicating substantial perceived negative impact of diabetes on QoL. AWI correlated more highly (r = 0.60; $P < 0.001$) with the diabetes-specific overview item, as expected, than with the generic QoL item (r = 0.21; $P < 0.001$).

DTSQ: Treatment Satisfaction and Perceived Frequency of Hyper- and Hypoglycemia

The DTSQ score was generally high, as assessed by patients (mean 29.76) and their respective physicians (27.75) (Table 2). Mean physician ratings were lower than mean patient ratings, indicating that physicians rated patients as less satisfied than patients rated themselves (6-item score $P < 0.001$). However, physicians significantly underestimated hyper- and hypoglycemia compared with their patients ($P < 0.001$) (Table 2).

HFS-II Worry Subscale: Concern About Hypoglycemia

The mean HFS-II worry subscale score was 13.27, indicating generally low worry about hypoglycemia (Table 2).

EQ-5D (EQ-VAS): Health Status

Mean patient-reported health status on the EQ-VAS was 70.55, where 100 is best imaginable health and 0 is worst (Table 2).

Multivariable Analysis of Factors Associated With PROMs

ADDQoL AWI Score: Diabetes-Related QoL

Age was significantly associated with ADDQoL AWI score showing less negative

Table 1—Patient and disease characteristics (*N* = 5,813)

	Total population
Patient characteristics	
Age (years), *N* = 5,812, mean (SD)	65.9 (10.4)
Male, *N* = 5,812	53.7 (3,121)
Unemployed, *N* = 5,789	4.3 (250)
Living alone, *N* = 5,809	22.1 (1,286)
Clinical and biological measures	
HbA_{1c} at index visit (%), *N* = 5,811, mean (SD)	6.9 (1.1)
HbA_{1c} <7%	62.6 (3,640)
HbA_{1c} ≥7%	37.4 (2,171)
BMI (kg/m^2), *N* = 5,811	
≤30	54.4 (3,163)
Mean (SD)	30.3 (6.1)
Systolic BP <130 and diastolic BP <80 mmHg, *N* = 5,811	19.7 (1,145)
Patients SMBG, *N* = 5,807	48.0 (2,789)
Hypoglycemia†	
Patients who experienced at least one episode of severe hypoglycemia, *N* = 5,688‡	4.4 (252)
Patients who experienced at least one episode of nonsevere hypoglycemia, *N* = 5,431	15.7 (854)
Medical conditions, symptoms, and difficulties	
Diabetes duration in years, *N* = 5,813, mean (SD)	8.9 (7.1)
Microvascular complications, *N* = 5,813	35.9 (2,087)
Chronic diabetic polyneuropathy	14.3 (833)
Autonomic neuropathy	3.6 (212)
Peripheral vascular disease	7.1 (414)
Erectile dysfunction among men, *N* = 3,121	23.8 (742)
Diabetic retinopathy	9.8 (571)
Prior treatment with photocoagulation	3.0 (173)
Diabetic nephropathy§	11.1 (642)
Microalbuminuria‡	6.4 (372)
Proteinuria‡	1.8 (102)
Renal insufficiency‡	2.8 (162)
Dialysis‡	0.1 (6)
Macrovascular complications, *N* = 5,813	24.5 (1,425)
Coronary heart disease	17.0 (987)
Peripheral vascular disease	7.1 (414)
Cerebrovascular disease	4.7 (272)
Congestive heart failure	3.6 (207)
Amputation	0.5 (27)
Experiencing abdominal pain, *N* = 5,759†	10.6 (611)
Having peripheral edema, *N* = 5,757†	6.5 (374)
Depressive disorders, *N* = 5,813	13.7 (799)
Sleep disorders, *N* = 5,813	14.3 (833)
Struggling with weight gain since starting diabetes medication, *N* = 5,760	30.9 (1,779)
Current smoker, *N* = 5,812	14.3 (833)
Physician-reported adherence	
Good adherence to medication, *N* = 5,686	70.1 (3,984)
Good adherence to lifestyle, *N* = 5,796	38.9 (2,252)
Treatment intensification, *N* = 5,812	
Physician reluctance to intensify treatment	0.2 (10)
Patient reluctance to intensify treatment	11.0 (638)
Target HbA_{1c} (%), *N* = 5,812, mean (SD)	6.6 (0.4)
Treatment, *N* = 5,750‖	
On diet/exercise alone	9.9 (571)
On only 1 OAD	32.6 (1,874)
On only 2 OADs	27.2 (1,566)
On only 3 OADs	9.0 (519)
On insulin with OADs	13.3 (765)
On insulin alone	7.1 (407)

Data are represented as % (*N*) unless otherwise indicated. Note: When the denominator for a variable differs from the overall patient population, this is the result of missing data. Percentages are based strictly on nonmissing data within any of the subsets of variables considered. †Episodes of nonsevere hypoglycemia were recorded per month, while episodes of severe hypoglycemia were recorded per year owing to the higher incidence of nonsevere hypoglycemia. ‡Severe hypoglycemia defined as an episode requiring external assistance as a result of severe impairment in consciousness or behavior, with prompt recovery after glucose or glucagon administration. §Patients categorized by the most severe subcategory of diabetic nephropathy reported. ‖As in previous articles on PANORAMA, patients receiving GLP-1 analogs plus insulin and/or OADs were included in the "on insulin with OADs" (*n* = 3) or the "on insulin alone" (*n* = 3) treatment groups, and patients on GLP-1 analogs and no insulin (*n* = 48) were excluded from the analysis.

perceived impact of diabetes on QoL with increasing age (average difference of AWI score changed 0.01 per year of age [95% CI 0.01–0.02; $P < 0.001$]) (Table 3; Supplementary Fig. 1*A*). The strongest negative association with AWI scores was insulin treatment alone (vs. diet/exercise alone), with an average difference of −0.58 (95% CI −0.84 to −0.33; $P < 0.001$). The two next most intensive treatments, insulin + OADs and three OADs without insulin, were also significantly associated with worse AWI scores. Other associations with worse AWI scores included HbA_{1c} ≥7%, microvascular complications (but not macrovascular), and depression. Neither measure of hypoglycemia (any "severe"/"nonsevere" episodes) showed any significant relationship with AWI scores in this multivariable analysis, which controlled for other variables, including treatment.

ADDQoL Generic QoL Score

The ADDQoL Generic QoL score had nearly twice as many significant associations as the AWI score (Table 3; Supplementary Fig. 1*B* vs. *A*). Although lower HbA_{1c} was significantly associated with higher (better) AWI score, it had no significant relationship with generic QoL. Several factors were significantly associated with higher (better) ADDQoL generic QoL scores: the strongest was male sex (average difference was 0.16 [95% CI 0.11–0.22; $P < 0.001$), followed by physician-reported good adherence and self-monitoring of blood glucose (SMBG). The strongest negative association was having depression, average difference −0.38 (95% CI −0.46 to −0.30; $P < 0.001$), followed by sleep disorders, −0.18 (95% CI −0.26 to −0.10; $P < 0.001$), and being on insulin with OADs −0.21 (95% CI −0.37 to −0.06; $P = 0.005$) or without (vs. diet/exercise)—but not being on three OADs (significant for the ADDQoL AWI score). Being unemployed (vs. not unemployed) predicted generic QoL but not AWI score (−0.20 [95% CI −0.33 to −0.07]; $P = 0.002$). Other factors negatively associated with ADDQoL Generic QoL scores included increasing age (positively associated with AWI scores), living alone, higher BMI (unrelated to AWI scores), macrovascular (but not microvascular) complications, comorbidities, and more physician visits. Whereas neither hypoglycemia nor BP was related to AWI score, any nonsevere (but not severe) hypoglycemia was associated with worse generic QoL,

Table 2—PROs

	N	Mean (SD)	Median (range)
ADDQoL			
Overview items			
Generic ADDQoL QoL score, overview item 1 (+3, excellent, to −3, extremely bad)	5,649	0.93 (1.02)	1.00 (−3.00, 3.00)
Diabetes-specific QoL score, overview item 2 (−3, very much better [if I did not have diabetes], to +1, worse)	5,641	−1.26 (1.00)	−1.00 (−3.00, 1.00)
AWI score†			
19 domain-specific items (−9, maximum perceived negative impact of diabetes, to +3, maximum perceived positive impact of diabetes)	5,679	−1.69 (1.78)	−1.06 (−9.00, 0.35)
DTSQ			
Treatment satisfaction, DTSQ pooled 6 items (0, very dissatisfied, to 36, very satisfied)‡			
Patient	5,296	29.76 (6.15)	31.00 (0, 36.00)
Physician	5,635	27.75 (5.89)	29.00 (0, 36.00)
Perceived frequency of hyperglycemia, item 2 (6, most of the time, to 0, none of the time)			
Patient	5,432	2.02 (1.89)	2.00 (0, 6.00)
Physician	5,671	1.82 (1.71)	1.00 (0, 6.00)
Perceived frequency of hypoglycemia, item 3 (6, most of the time, to 0, none of the time)			
Patient	5,358	1.35 (1.67)	1.00 (0, 6.00)
Physician	5,664	1.17 (1.40)	1.00 (0, 6.00)
Fear of hypoglycemia§			
HFS-II worry subscale score (0, least worry, to 72, most worry)	4,866	13.27 (15.44)	8.00 (0, 72.00)
EQ-5D‖			
Self-rated health status: EQ-5D VAS score (100, best imaginable health, to 0, worst imaginable health)	5,397	70.55 (17.75)	70 (0, 100.00)

†ADDQoL scoring: 19 specific life domains, including social life and working life, scored on a 5-point impact of diabetes scale and multiplied by a related 4-point importance rating scale to produce a WI score, which can then be averaged across all applicable domains to produce an AWI score ranging from −9 (maximum perceived negative impact of diabetes) to +3 (maximum perceived positive impact of diabetes). Generic QoL ranged from −3 (extremely bad) to +3 (excellent). ‡DTSQ scoring: The treatment satisfaction score is the sum of six items rated on a 6 to 0 scale (where 6 is very satisfied and 0 is very dissatisfied). Two additional items (considered separately) measure perceived frequency of hyperglycemia/hypoglycemia, also on a 7-point scale (6: most of the time; 0: none of the time). Physicians completed the DTSQ as if they were each individual patient, without having seen the patient's DTSQ responses. §HFS-II scoring: The 18 items of the HFS-II worry subscale are rated using a 5-point Likert scale (from 0 = never to 4 = almost always). Total scores range from 0 (least worry) to 72 (most worry). ‖EQ-5D scoring: EQ-5D is a measure of health status. Here, we report the patient-rated EQ-VAS scores only.

and higher systolic (but not diastolic) BP was associated with better generic QoL.

DTSQ: Treatment Satisfaction

Lower HbA_{1c} was associated with greater satisfaction measured by the DTSQ 6-item score: having $HbA_{1c} \geq 7\%$ (vs. $<7\%$) was most strongly associated with worse DTSQ patient scores (−1.25 [95% CI −1.63 to −0.87]; $P < 0.001$) (Table 3; Supplementary Fig. 1*C*). Other factors associated with less treatment satisfaction included depression, weight gain, abdominal pain, physician-reported patient reluctance to intensify treatment, and treatment with insulin + OADs. The strongest positive association with patients' treatment satisfaction was physician-reported good medication adherence (vs. moderate/poor adherence) (1.07 [95% CI 0.66–1.48]; $P < 0.001$), followed by physician-reported good adherence to lifestyle changes. Unlike ADDQoL scores, no patient characteristics (including age) significantly predicted DTSQ scores.

HFS-II Hypoglycemia Worry Subscale

Fear of hypoglycemia was most strongly predicted by reported hypoglycemia: those experiencing any severe or nonsevere hypoglycemia reported greater hypoglycemia worry (Table 3; Supplementary Fig. 1*D*). Another strong predictor was being on insulin treatment alone (vs. diet/exercise alone), with a difference of 3.35 (95% CI 0.92–5.79; $P = 0.007$). Other factors associated with increased worry about hypoglycemia included depression and SMBG use. Men worried less about hypoglycemia than women (−2.56 [95% CI −3.45 to −1.67]; $P < 0.001$), as did those with higher HbA_{1c} targets (−1.29 [95% CI −2.52 to −0.07]; $P = 0.039$) and older people (−0.11 [95% CI −0.16 to −0.07]; $P < 0.001$). HbA_{1c} did not predict hypoglycemia worry.

EQ-5D (EQ-VAS): Health Status

Depression was the strongest predictor of lower EQ-VAS scores (worse self-rated health), with a difference of −6.44 (95% CI −7.85 to −5.03; $P < 0.001$). EQ-VAS health status scores, like generic QoL scores, were worse with age and better in men, while ADDQoL AWI scores improved with age without sex associations. HbA_{1c} had no association with EQ-VAS. Physician-reported good adherence to lifestyle (2.84 [95% CI 1.70 to 3.97]; $P < 0.001$) and medication were associated with better EQ-VAS scores. All medical disorders examined, including micro- and macrovascular complications, were associated with worse health status, as were higher BMI and increased visits to physicians. However, higher systolic BP was marginally associated with *better* health status (Table 3; Supplementary Fig. 1*E*). No treatment variable was associated with health status.

Association of Treatment With PROMs

Multivariable regression analysis without treatment covariates found small changes in the average difference and 95% CI of the PROMs.

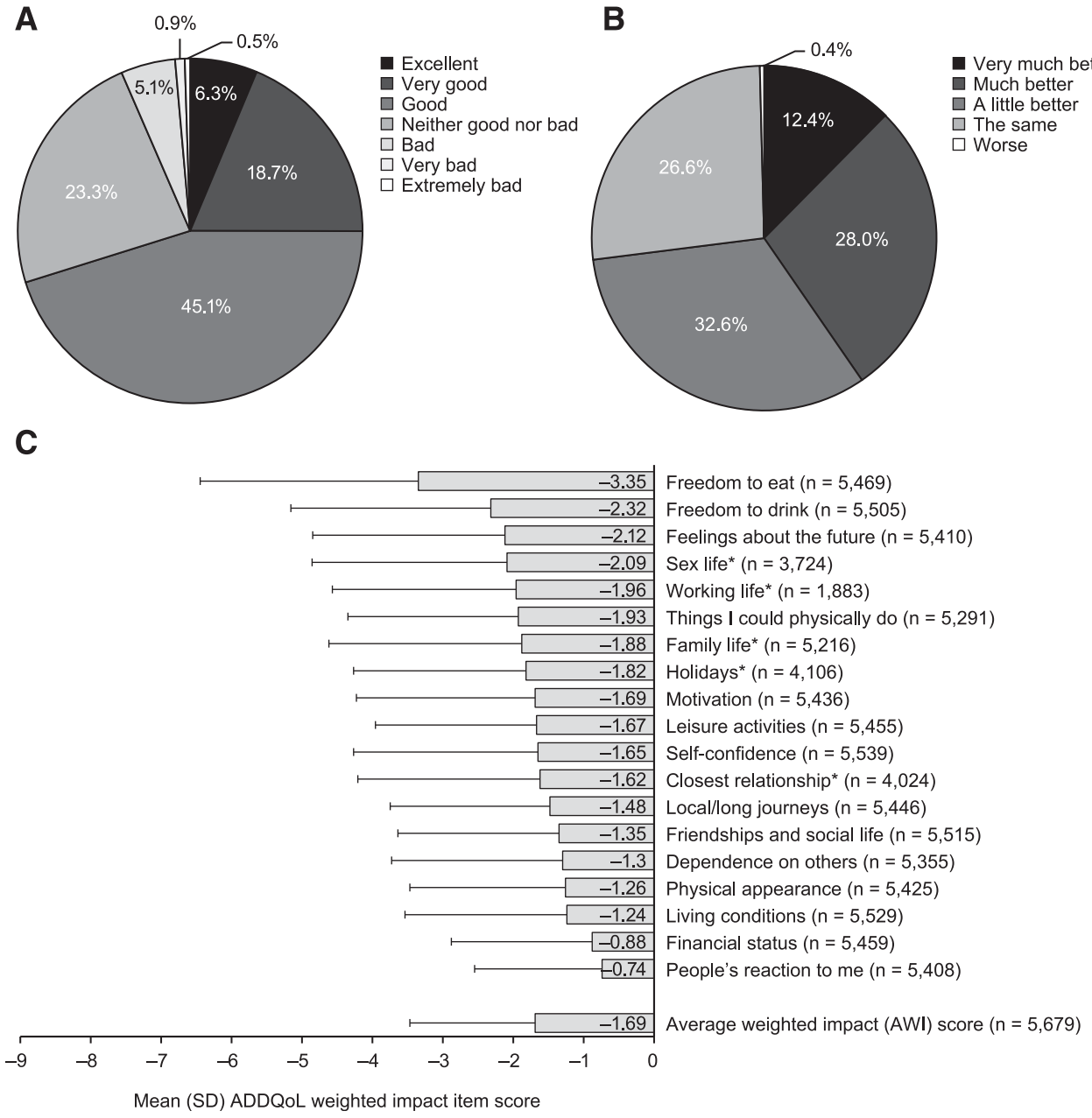

Figure 1—Mean ADDQoL scores. *A*: Answers to the first overview item of ADDQoL generic QoL: "In general, my present quality of life is. . . ." *B*: Answers to the second overview item of ADDQoL: "If I did not have diabetes my quality of life would be . . ." (*n* = 5,641). *C*: Perceived impact of diabetes on the individual domain WI scores and the AWI score of the ADDQoL questionnaire [mean (SD)]. *These items offer a not-applicable option, as they are not relevant to everyone.

Few associations changed in significance; nonsevere hypoglycemia became associated with less treatment satisfaction (−0.57 [95% CI −1.04 to −0.10]; *P* = 0.018), and its association with greater perceived negative impact of diabetes on QoL became close to significant (−0.13 [95% CI −0.26 to −0.00]; *P* = 0.050).

CONCLUSIONS

PANORAMA provided an overview across nine countries of five PROMs validated and widely used in diabetes. Simultaneous collection of PROMs and clinical data allowed exploratory analyses to identify predictors of outcomes that matter to patients. Numbers and patterns of predictors for different PROMs supported the hypothesis that they would differ in important ways (Table 3).

Nearly three-quarters of patients indicated that their QoL would be better without diabetes. The overall mean ADDQoL AWI score (−1.69) showed that QoL was impaired by diabetes to a degree similar to that found in other unselected samples (1,11,12). In the ADDITION Europe study (Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen-Detected Diabetes in Primary Care), patients reported lesser negative impact of screen-detected type 2 diabetes 5 years postdiagnosis (median AWI −0.32) (13). As in most other studies using the ADDQoL, the item reflecting the greatest negative impact of diabetes on QoL was "freedom to eat as I wish" (WI −3.35) and higher HbA_{1c} levels were associated with greater negative impact of diabetes on QoL (ADDQoL AWI score) (1,2,12,13,17).

AWI score was significantly and negatively associated with other important

Table 3—Summary of multivariable analysis (mixed-model linear regression) of variables associated with PROM scores

		PROM†				
Variable	Reference variable‡	ADDQol AWI: less negative impact of diabetes on QoL	ADDQoL generic QoL: better QoL	DTSQ: better treatment satisfaction	HFS-II: greater fear of hypoglycemia	EQ-VAS: better health status
Patient characteristics						
Age§		Older***	Younger**		Younger***	Younger***
Sex	Female		Male***		Female***	Male***
Living alone	No		Not living alone*			
Unemployed	No		Not unemployed**			
Clinical and biological measures						
HbA_{1c} ≥7% (53 mmol/mol)	<7%	HbA_{1c} <7%***		HbA_{1c} <7%***		
BMI‖			Lower BMI***			Lower BMI***
Systolic BP¶			Higher systolic BP*			Higher systolic BP*
SMBG	No		SMBG*		SMBG*	
Hypoglycemia						
Any severe hypoglycemia episodes	No				"Severe" hypoglycemia***	
Any nonsevere hypoglycemia episodes	No		No "nonsevere" hypoglycemia***		"Nonsevere" hypoglycemia***	No "nonsevere" hypoglycemia***
Medical conditions, symptoms, and difficulties						
Microvascular complications	No	No microvascular complications***				No microvascular complications*
Macrovascular complications	No		No macrovascular complications**			No macrovascular complications**
Genitourinary infections	No					No genitourinary infections*
Abdominal pain	No	No abdominal pain*		No abdominal pain**		No abdominal pain*
Peripheral edema	No		No peripheral edema**		Peripheral edema***	No peripheral edema**
Depression	No	No depression***	No depression***	No depression***	Depression***	No depression***
Sleep disorders	No	No sleep disorders*	No sleep disorders***		Sleep disorders*	No sleep disorders***
Struggling with weight gain	No	Not struggling with weight gain**	Not struggling with weight gain*	Not struggling with weight gain***		
Current smoker	No		Nonsmoker*			
Health care provided						
Visits to PCP#		Fewer visits to PCP*	Fewer visits to PCP***			Fewer visits to PCP*
Visits to specialist#			Fewer visits to specialist***		More visits to specialist*	Fewer visits to specialist***
Target HbA_{1c}††					Lower target HbA_{1c}*	
Physician-reported adherence/ reluctance						
Adherence to medication	Moderate/ poor		Good adherence to medication***	Good adherence to medication***		Good adherence to medication**
Adherence to lifestyle	Moderate/ poor		Good adherence to lifestyle***	Good adherence to lifestyle***		Good adherence to lifestyle***

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Table 3—Continued

Variable	Reference variable‡	PROM†				
		ADDQol AWI: less negative impact of diabetes on QoL	ADDQoL generic QoL: better QoL	DTSQ: better treatment satisfaction	HFS-II: greater fear of hypoglycemia	EQ-VAS: better health status
Patient reluctance to intensify treatment	No			No patient reluctance to intensify treatment**		
Treatment						
Only 3 OADs	Diet/exercise alone	Diet/exercise alone**				
On insulin with OADs	Diet/exercise alone	Diet/exercise alone**	Diet/exercise alone*	Diet/exercise alone*		
On insulin alone	Diet/exercise alone	Diet/exercise alone***	Diet/exercise alone**		Insulin alone**	

Significant variables only are presented here. Full data available in Supplementary Fig. 1. Adjusted for potential confounding by the other variables presented (patient characteristics; clinical and biological measures; hypoglycemia; medical conditions, symptoms, and difficulties; health care provided; physician-reported adherence/reluctance; and treatment) as well as by physician and physician characteristics. †The meaning of a higher score is indicated below the name of the PROM variable: a higher (less negative) ADDQoL AWI score indicates less negative impact of diabetes on QoL, a higher generic QoL score (on first overview item of the ADDQoL) indicates better QoL, a higher DTSQ score indicates greater treatment satisfaction, a higher HFS-II score indicates greater fear of hypoglycemia, and a higher EQ-VAS score indicates better perceived health status. ‡Categorical variables only. §Per additional year. ‖Per additional kg/m^2. ¶Per additional mmHg. #Per visit. ††Per additional 0.1% HbA_{1c}. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. PCP, primary care physician.

variables such as presence of microvascular complications, depression, and sleep disorders, as well as by more intensive treatments. As found previously (1,2,11–13,17), insulin use was associated with more negative impact of diabetes on QoL versus oral treatment or diet/exercise alone. Treatment with three OADs without insulin was also significantly associated with more negative AWI scores. These findings suggest that intensifying treatment for type 2 diabetes above two OADs is likely to damage QoL and, given that "freedom to eat as I wish" is the item most negatively impacted by diabetes, greater damage can be expected when dietary freedom (including having to eat when not wanting to) is limited. Future research would usefully categorize treatments by their dietary restrictions to test this hypothesis and highlight treatments that protect QoL.

Univariate analyses of the PANORAMA data had indicated a relationship between nonsevere hypoglycemia and impact of diabetes on QoL. However, this relationship was no longer present when multivariable analyses controlled for treatment, suggesting that nonsevere hypoglycemia does not add further negative impact of diabetes on QoL over and above that of intensified treatments. Nonetheless, the ADDQoL generic QoL item and EQ-5D VAS were significantly associated with nonsevere hypoglycemia regardless of whether treatment variables were included in the model. Insulin treatment with or without OADs was predictive of worse generic QoL. It may be that patients attribute some symptoms of preprandial or nocturnal hypoglycemia to malaise unrelated to diabetes, which reduces their ratings of health status and generic QoL, but not their ADDQoL AWI scores. If so, hypoglycemia symptom monitoring (26) alongside SMBG would help identify and avoid hypoglycemia.

Older age was associated with a small positive difference in AWI score; however, the opposite was found for generic QoL and EQ-VAS health status, indicating that while older patients felt that diabetes impacted less negatively on QoL than younger patients did, they perceived their overall health as worse and, perhaps as a result, their overall QoL. These PROMs also differed in their associations with HbA_{1c}; higher HbA_{1c} was associated with worse diabetes-specific AWI scores but not generic QoL or health status. This may be due to difficulties and conflicts experienced by those with elevated HbA_{1c}, which are reflected in responses to ADDQoL domains, contributing to AWI scores. Health status and generic QoL are not directly associated with HbA_{1c}, only becoming related via diabetes complications.

Overall treatment satisfaction in PANORAMA, measured by the DTSQ, showed that patients were generally satisfied with their treatment; their physicians slightly but significantly underestimated this satisfaction (while underestimating patients' experience of hyper- and hypoglycemia). In PANORAMA, physician-reported adherence was a crude estimate measured on a single 3-point scale but was associated with greater patient treatment satisfaction, an association observed elsewhere using patient-reported adherence, and treatment satisfaction measures (27), suggesting that this physician rating has some validity. Physician-rated adherence was not attributable to HbA_{1c} level, which was controlled for in the multivariable analysis. However, lower HbA_{1c} predicted greater patient treatment satisfaction. Treatment satisfaction was negatively associated with insulin treatment + OADs (vs. diet/exercise),but was not significantly associated with other treatments. The treatment group definitions in PANORAMA were too broad for discernment of differences between insulin regimens, which have previously been associated with differences in treatment satisfaction and other PROMs (28), or classes of OADs, which have different tolerability profiles (29,30). Treatment satisfaction was negatively associated with physician-reported patient reluctance to intensify treatment. Perceived reluctance

(reported for 11% of patients) may be overcome if physicians share with patients research showing that satisfaction improves once individuals with suboptimal diabetes control start insulin (28).

The mean HFS-II worry score showed that hypoglycemia worry was not high, although worry was greater with use of insulin alone vs. diet/exercise. Sex associations were observed: women worried more about hypoglycemia than men, as reported in patients with type 1 diabetes (20). Hypoglycemia worry was greater in younger patients and those with physician-reported depression. Patients with sleep disorders also worried more about hypoglycemia, perhaps reflecting experience of nocturnal hypoglycemia. Having "severe" or "nonsevere" hypoglycemic episodes strongly predicted HFS-II worry scores while not predicting other diabetes-specific PROMs studied here.

Overall PANORAMA EQ-VAS health status scores were generally good (mean 70.55 and median 70). Indeed, EQ-VAS scores were higher than those recently reported for Polish patients with type 2 diabetes (54.9 for 55- to 64-year-old patients; 50.2 in those ≥65 years old) (31). A recent cross-sectional German general population study reported a mean EQ-VAS score of 84.9 in 60–69 year olds not reporting health problems; people with diabetes of all ages had a mean −24.4 reduction in EQ-VAS (32).

Depression was the strongest negative predictor of health status and the only predictor significant for all five PROMs. Despite significant negative associations of insulin treatments with other PROMs, treatment was not significantly associated with EQ-VAS health status, suggesting that this PROM is unlikely to be a good choice for inclusion in clinical trials comparing diabetes treatments. As expected, patients with macro- and/or microvascular complications reported worse health than those without, but other factors, including sleep disorders, showed greater differences. Patients rarely consider their eyes when rating their health while reporting negative impact of eye conditions on QoL using eye condition–specific QoL measures modeled on the ADDQoL (33). Retinopathy will be associated with generic and diabetes-specific QoL rather than perceived health. In PANORAMA, higher systolic BP was associated with better health status (marginally significant) and better ADDQoL generic QoL, possibly due to side effects of BP-lowering medications.

The PANORAMA study has strengths and limitations. A key strength is the use of a selection of well-validated PROMs. Use of these tools in validated translations in a very large multicountry sample of patients with type 2 diabetes increases the generalizability of the findings. However, as with all cross-sectional data, caution is needed when making causal inferences. One limitation was lack of clarity in the Case Report Form questions about why physicians were reluctant to intensify treatment. Few physicians endorsed the initial question to indicate their reluctance to intensify treatment, but many ticked subsequent reasons for reluctance suggesting that *patient* reluctance was being considered as well as/instead of their own. Responses to the initial question about physician reluctance used in the models did not significantly predict any PROM. Improving the design of this question may in the future reveal associations between PROMs and particular reasons for physician reluctance to intensify treatment. We acknowledge that sequential recruitment based on clinic attendance (in six countries), rather than randomization from eligible preselected patients (three countries), led to a small but significant bias toward patients with more microvascular complications.

Our findings in the PANORAMA population show that individual PROMs performed in much the same ways as in prior reports of each individually. However, by assessing them simultaneously in this large multinational population we confirmed the hypothesis that predictors of the various PROMs studied would vary widely. Notably, while QoL and the negative impact of diabetes on QoL (measured by the ADDQoL) were worse for patients on more intensified treatment, health status (EQ-5D VAS) was unrelated to treatment intensity. To reach conclusions about QoL we must measure QoL; health status or another PROM is no substitute. The PANORAMA findings demonstrate the importance of appreciating the differences between QoL, health status, and other PROMs and interpreting them appropriately. Genuine measures of QoL and diabetes-dependent QoL are needed, perhaps alongside other PROMs, when evaluating and choosing between diabetes treatments if we are to protect QoL, increase regimen adherence, and thereby improve glycemic control in the long term.

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References

1. Sundaram M, Kavookjian J, Patrick JH, Miller LA, Madhavan SS, Scott VG. Quality of life, health status and clinical outcomes in type 2 diabetes patients. Qual Life Res 2007;16:165–177
2. 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
3. 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
4. Speight J, Amiel SA, Bradley C, et al. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled type 1 diabetes. Diabetes Res Clin Pract 2010;89:22–29
5. Deakin TA, Cade JE, Williams R, Greenwood DC. Structured patient education: the diabetes X-PERT Programme makes a difference. Diabet Med 2006;23:944–954
6. U.K. Prospective Diabetes Study Group. 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). Diabetes Care 1999;22:1125–1136
7. Bradley C. Importance of differentiating health status from quality of life. Lancet 2001;357:7–8
8. Bradley C, Tamburini M. Not-only-a-title. Health Qual Life Outcomes 2003;1:1
9. Speight J, Reaney MD, Barnard KD. Not all roads lead to Rome-a review of quality of life measurement in adults with diabetes. Diabet Med 2009;26:315–327
10. Anderson RT, Narayan KM, Feeney P, et al.; Action to Control Cardiovascular Risk in Diabetes (ACCORD) Investigators. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care 2011;34:807–812
11. Bradley C, Speight J. Patient perceptions of diabetes and diabetes therapy: assessing quality of life. Diabetes Metab Res Rev 2002;18(Suppl. 3):S64–S69
12. Donald M, Dower J, Coll JR, Baker P, Mukandi B, Doi SA. Mental health issues decrease diabetes-specific quality of life independent of glycaemic control and complications: findings from Australia's Living With Diabetes cohort study. Health Qual Life Outcomes 2013;11:170
13. Kuznetsov L, Griffin SJ, Davies MJ, et al. Diabetes-specific quality of life but not health status is independently associated with glycaemic control among patients with type 2 diabetes: a cross-sectional analysis of the ADDITION-Europe trial cohort. Diabetes Res Clin Pract 2014;104:281–287
14. Simon D, de Pablos-Velasco P, Parhofer KG, et al. Hypoglycaemic episodes in patients with type 2 diabetes–risk factors and associations with patient-reported outcomes: the PANORAMA study. Diabetes Metab 2015;41:470–479
15. Bradley C, de Pablos-Velasco P, Parhofer KG, Eschwège E, Gönder-Frederick L, Simon D. PANORAMA: a European study to evaluate quality of life and treatment satisfaction in patients with type-2 diabetes mellitus–study design. Prim Care Diabetes 2011;5:231–239
16. National Glycohemoglobin Standardization Program [Internet], 2014. Available from www.ngsp.org/docs/methods.pdf. Accessed 17 January 2017
17. 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
18. 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
19. Bradley C. The Diabetes Treatment Satisfaction Questionnaire: (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Bradley C, Ed. Abingdon, U.K., Routledge, 1994, p. 111–132
20. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the Hypoglycemia Fear Survey-II for adults with type 1 diabetes. Diabetes Care 2011;34:801–806
21. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Med Decis Making 2002;22:340–349
22. Glasziou P, Alexander J, Beller E, Clarke P; ADVANCE Collaborative Group. Which health-related quality of life score? A comparison of alternative utility measures in patients with type 2 diabetes in the ADVANCE trial. Health Qual Life Outcomes 2007;5:21
23. Grandy S, Fox KM. EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). Health Qual Life Outcomes 2008;6:18
24. Acquadro C, Conway K, Girourdet C, Mear I. Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments. Lyon, France, MAPI Research Institute, 2009
25. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Internet], 2016. Available from https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview. Accessed 14 November 2016
26. Taylor MD, Han TS, Ward H, McBride J, Yap I, Bradley C. Evaluation of the hypoglycaemia symptom rating questionnaire ('HypoSRQ') and its relationship with hypoglycaemic episodes measured using continuous glucose monitoring (Abstract). Diabetes Technol Ther 2013;15(Suppl. 1):A23–A4
27. Hutchins V, Zhang B, Fleurence RL, Krishnarajah G, Graham J. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin 2011;27:1157–1168
28. Bradley C, Gilbride CJ. Improving treatment satisfaction and other patient-reported outcomes in people with type 2 diabetes: the role of once-daily insulin glargine. Diabetes Obes Metab 2008;10(Suppl. 2):50–65
29. Charpentier G, Fleury F, Dubroca I, Vaur L, Clerson P. Electronic pill-boxes in the evaluation of oral hypoglycemic agent compliance. Diabetes Metab 2005;31:189–195
30. Furlong NJ, Hulme SA, O'Brien SV, Hardy KJ. Repaglinide versus metformin in combination with bedtime NPH insulin in patients with type 2 diabetes established on insulin/metformin combination therapy. Diabetes Care 2002;25:1685–1690
31. Golicki D, Dudzinska M, Zwolak A, and Tarach JS. Quality of life in patients with type 2 diabetes in Poland - comparison with the general population using the EQ-5D questionnaire. Adv Clin Exp Med 2015;24:139–146
32. Huber MB, Reitmeir P, Vogelmann M, Leidl R. EQ-5D-5L in the general German population: comparison and evaluation of three yearly cross-section surveys. Int J Environ Res Public Health 2016;13:343
33. Mitchell J, Bradley C. Quality of life in age-related macular degeneration: a review of the literature. Health Qual Life Outcomes 2006;4:97