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Demonstrating the Burden of Hypoglycemia on Patients' Quality of Life in Diabetes Clinical Trials: Measurement Considerations for Hypoglycemia

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ABSTRACT

Objectives: To evaluate the association between hypoglycemia and health-related quality of life (HRQoL) in the context of a clinical trial using both an objectively confirmed and a patient-reported measure of hypoglycemia. **Methods:** During a phase III, double-arm, randomized study, patients completed the short form 36 health survey (SF-36), a generic HRQoL questionnaire, at baseline and at weeks 24, 52, and 104. The objectively confirmed measure of hypoglycemia was based on a combination of plasma glucose measure and presence of hypoglycemia-related symptoms. The patient-reported frequency of hypoglycemia was defined as the following item: "How often have you felt that your blood sugars have been unacceptably low recently?" The association between hypoglycemia and HRQoL was evaluated in intent-to-treat patients (N = 3059) by using repeated-measurements analyses, with SF-36 scores used as explained variables and baseline SF-36 score, age, sex, country, time, and either number of objectively confirmed hypoglycemic events (0, ≥1) or patient-reported frequency of hypoglycemia (continuous variable 0–6) as explanatory variables. **Results:** During study duration, less than 6% of patients experienced at least one objectively confirmed hypoglycemic event and about half the patients reported unacceptably low blood sugars "none of the time." The association between the number of objectively confirmed hypoglycemic events and HRQoL was not statistically significant, while the patient-reported frequency of hypoglycemia was statistically significantly related to all SF-36 scores ($P < 0.001$), except physical functioning; patients reporting greater perceived frequency of hypoglycemia had worse HRQoL. **Conclusions:** Using a patient-reported measure of hypoglycemia in the context of a clinical trial could enable the burden of hypoglycemia for patients to be demonstrated.

Keywords: clinical trial, diabetes, health-related quality of life, hypoglycemia, measurement.

Introduction

Type 2 diabetes is a chronic, progressive disease characterized by hyperglycemia resulting from multiple abnormalities including impaired insulin secretion and peripheral insulin resistance. Type 2 diabetes is associated with serious long-term microvascular and macrovascular complications such as cardiovascular disease, neuropathy, and diseases of the eyes, which, in turn, increase morbidity, mortality, and health care costs [1–4]. Treatments can include oral medications for hyperglycemia and for other conditions often associated with diabetes such as hypertension and dyslipidemia, or insulin therapy. However, treatments require above all a lifelong commitment of patients to blood sugar monitoring, healthy eating, regular physical exercise, and weight control, thus making diabetes management very restrictive. In addition, certain diabetes treatments are associated with side effects such as hypoglycemia and weight gain [5,6]. In particular, sulfonylureas are typically known to cause hypoglycemia, with older sulfonylureas such as glyburide associated with a higher risk of events [7,8]. Hypoglycemia can be a major barrier in achieving treatment goals and has been shown to be linked to an increased risk of cardiovascular events [9] and dementia [10] and by "defensive eating" can contribute to weight gain [11].

Even though it is agreed that a hypoglycemic event should be characterized by a combination of a symptomatic episode and the measure of plasma glucose, defining hypoglycemic events remains difficult as no consensus exists on the plasma glucose threshold to be used. For the EMA, a symptomatic episode with plasma glucose level lower than 54 mg/dL (3 mmol/L) can be qualified as a hypoglycemic event [12], while for the Food and Drug Administration (FDA), a hypoglycemic event is defined as an event combining typical symptoms of hypoglycemia and plasma glucose level lower than 70 mg/dL (3.9 mmol/L) [13]. In addition, the reporting of hypoglycemic events is challenging not only because of hypoglycemia unawareness [14] but also because patients often do not measure their blood glucose level on a regular basis [15,16] and hypoglycemic events commonly occur during the night when the patient is not aware of them [17,18]. Thus, only a small proportion of the true hypoglycemic events can be captured.

In observational studies, a wide range of any hypoglycemic event rates were observed: 38% in the Real-Life Effectiveness and Care Patterns of Diabetes Management study in patients with a sulfonylurea or thiazolidinedione added to ongoing metformin therapy [19], 63% in a US Internet-based survey in patients taking

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oral antihyperglycemic medications [20], and between 10% and 28% in the first decade of the UK Prospective Diabetes Study in patients treated with diet alone and insulin, respectively [21]. In randomized clinical trials, rates of any hypoglycemic events were 10% for patients treated with rosiglitazone compared with 12% for patients treated with metformin and 39% for patients treated with glyburide in A Diabetes Outcomes Progression Trial [22], and 28% for patients treated with pioglitazone compared with 20% for placebo in the PROspective pioglitAzone Clinical Trial in macroVascular Events study [23]. Establishing one estimation of the incidence of hypoglycemia based on the literature, however, is not feasible because of a wide variety in the definitions of hypoglycemia, type of study, type of treatment, and characteristics of the population used in studies reporting hypoglycemic event rates [24].

Because diabetes patients face many issues related to the disease and its treatment, separating the direct benefit of the treatment on patients' health-related quality of life (HRQoL) from all other elements involved is often challenging in clinical trials despite improvements on primary clinical outcomes [25–28]. The particular impact of hypoglycemia on HRQoL has often been demonstrated in observational studies [20,29–33], suggesting that the potential indirect benefit of a diabetes treatment on HRQoL could be demonstrated through the burden of hypoglycemia. Randomized clinical trials, however, generally focus only on the direct impact of a treatment on HRQoL, and it is not clear whether the impact of hypoglycemia on HRQoL demonstrated in observational studies could be shown in the monitored context of a randomized clinical trial. The objective of this study was to evaluate the association between hypoglycemia and HRQoL in the context of a clinical trial using different measures of hypoglycemia, including both objectively confirmed and patient-reported measures of hypoglycemia.

Methods

Study design

The CLAF237-2308 study was a phase III, double-arm, multicenter, randomized, double-blind, active controlled study evaluating the long-term efficacy of treatment with vildagliptin as add-on therapy compared with glimepiride in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Patients included were diagnosed with type 2 diabetes, male or female, aged between 18 and 73 years, had a hemoglobin A_{1c} (HbA1c) level higher than 6.5% and lower than or equal to 8.5%, and were inadequately controlled with metformin. In this study, vildagliptin has demonstrated efficacy on HbA1c comparable to that of glimepiride after 2 years of add-on treatment with markedly reduced hypoglycemia risk (2.3% vs. 18.2%) [34].

The short form 36 health survey

The short form 36 health survey (SF-36) [35–37] is a widely used, validated generic questionnaire measuring patients' HRQoL. It includes eight dimension scores (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) and two summary scores (Physical Component Scale and Mental Component Scale). Dimension scores range from 0 to 100, and summary scores are US-norm based with a mean of 50 and an SD of 10. For all dimension and summary scores, higher scores indicate better HRQoL. In the study, patients were asked to complete the SF-36 at baseline and at weeks 24, 52, and 104.

Measures of hypoglycemia

Objectively confirmed hypoglycemia

Patients were considered to have a hypoglycemic event when they had plasma glucose level lower than 56 mg/dL (3.1 mmol/L) and presence of symptoms suggestive of hypoglycemia among a list of 44 symptoms (anxiety, asthenia, dizziness, hyperhidrosis, tremor, etc.). The number of objectively measured hypoglycemic events was assessed both in the 1-month and 6-month periods immediately preceding SF-36 questionnaire completion.

Perceived frequency of hypoglycemia

The patients' perceived hypoglycemia was assessed through the single-item score "How often have you felt that your blood sugars have been unacceptably low recently?" of the Diabetes Treatment Satisfaction Questionnaire (DTSQ), as defined by the authors of the questionnaire [38,39]. The response scale for this item ranges from 0 (none of the time) to 6 (most of the time). As the SF-36, patients were asked to complete the DTSQ in the study at baseline and at weeks 24, 52, and 104.

Statistical analysis

Analysis of the association between hypoglycemia and HRQoL

The association between hypoglycemia and HRQoL was evaluated by using repeated-measurements analyses. For each SF-36 score, two repeated-measurements mixed models were performed: one to evaluate the impact of the number of objectively confirmed hypoglycemic events on HRQoL and one to evaluate the impact of the perceived frequency of hypoglycemia on HRQoL. In each model, the explained variable was the SF-36 score and the explanatory variables were the baseline value of the considered SF-36 score, age, sex, country, time (in weeks), and either the number of objectively confirmed hypoglycemic events (0, $\geq$1) or the perceived frequency of hypoglycemic events (continuous variable ranging from 0 to 6). All models included data from weeks 24, 52, and 104. The analysis was conducted on pooled treatment groups of the intent-to-treat (ITT) population, including all subjects who received at least one dose of the study drug and had at least one postbaseline assessment of the primary or secondary efficacy variables while on dual-therapy treatment (i.e., assessments while on rescue medication were not considered).

Statistical tests, level of significance, and software

Because of the multiplicity of tests to be performed, a weak threshold for statistical significance (1%) was used for each test to decrease the risk of having a statistically significant test by chance. All analyses were performed with SAS software for Windows (Version 9.2, SAS Institute, Inc., Cary, NC).

Results

Demographic and clinical characteristics of the study population

The ITT population included 3059 patients among the 3118 randomized patients (Fig. 1). Of patients who attended the visits, 94%, 93%, 93%, and 92% of the patients completed the SF-36 at baseline and at week 24, 52, and 104, respectively. Patients' mean age was 58 years, with a majority of men and most patients coming from Western Europe (Table 1).

Regardless of the follow-up visit, about 1% of the patients experienced at least one objectively confirmed hypoglycemic event in a 1-month period prior to SF-36 completion and less than 6% of the patients experienced at least one objectively confirmed hypo-