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Abstract: To explore the frequency of hypoglycaemic episodes, their risk factors, and associations with patient-reported outcomes in patients with type 2 diabetes enrolled in the PANORAMA cross-sectional study.

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Hypoglycaemic episodes in patients with type 2 diabetes –risk factors and associations with patient-reported outcomes: The PANORAMA Study

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ABSTRACT

Aim: To explore the frequency of hypoglycaemic episodes, their risk factors, and associations with patient-reported outcomes in patients with type 2 diabetesenrolled in the PANORAMA cross-sectionalstudy.

Methods: 5,783 patients aged≥40 years with type 2 diabetes duration≥1 year were recruited in nine European countries. Patients reported severe and non-severe hypoglycaemic episodes during the past year at a single study visit. Patient-reported outcomes were measured by the Audit of Diabetes-Dependent Quality of Life, Diabetes Treatment Satisfaction Questionnaires, Hypoglycaemia Fear Survey-II, and EQ-5D Visual Analog Scale.

Results: During the previous year, 4.4% of the patients experienced ≥1 severe hypoglycaemic episode; among those without severe hypoglycaemia, 15.7% experienced ≥1 non-severe episode. Patients experiencing any hypoglycaemic episode reported a greater negative impact of diabetes on quality of life, greater fear of hypoglycaemia, less treatment satisfaction and worse health status than those with no episodes. In multivariate analyses hypoglycaemia was significantly associated with longer diabetes duration; presence of microvascular and, to a lesser extent, macrovascular complications; treatment with insulin, glinides or sulfonylureas; and use of self-monitoring of blood glucose.

Conclusion: In patients with type 2 diabetes, severe hypoglycaemic episodes were not uncommon and onein fiveexperienced some form of hypoglycaemiaduring the previous year. Hypoglycaemia was associated with more negative patient-reported outcomes. The risk of hypoglycaemia increased with diabetes duration, presence of diabetes-related complications, use of self-monitoring blood glucose, insulin secretagogues, and insulin treatment.

Key words: Type 2 diabetes, Hypoglycaemia, Glucose-lowering treatments, Patient-reported outcomes, Quality of life

Introduction

Hypoglycaemia is a common side effect of some glucose lowering treatments and is associated with increased morbidity and mortality, as well as increased healthcare costs and lost productivity (1–5). The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement on hyperglycaemia management in patients with type 2 diabetes, recommends that in patients with a high risk of hypoglycaemia, advanced complications, and extensive comorbid conditions, initiation of treatments likely to induce hypoglycaemia should be delayed as long as possible. In addition, blood glucose targets may need to be moderated (6).

Episodes of hypoglycaemia can produce physical and psychological effects including sweating, palpitations, shaking, hunger, confusion, drowsiness, odd behaviour, speech difficulty, loss of coordination, and headaches(7). The clinical consequences of hypoglycaemia can be serious, including seizures, loss of consciousness, injury (5, 7), cardiac ischemia (8), cardiac arrhythmias (9)and other cardiovascular events (10, 11), hospitalization, or death (12). In the USA, adverse drug reactions to insulin and oral antidiabetes drugs (OADs) accounted for an estimated 22,726 emergency hospitalizations nationally per year between 2007 and 2009, in people aged ≥65 years, with 94.6% attributed to hypoglycaemia(3). Overall, the second most common drug class associated with emergency hospitalizations was insulin (13.9%), and the fourth most common was OADs (10.7%) (3). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, severe hypoglycaemia was associated with increased mortality in both standard and intensive treatment groups but mortality risk was nothigher in the intensive than in the standard treatmentgroup (1)and it has been suggested that hypoglycaemia, which was three times more frequent in the intensively treated group, could have been a contributory factor in some of the deaths (4, 10, 13, 14).

Even mild hypoglycaemia can be a psychological burden to patients, and fear of hypoglycaemia may inhibit adherence to treatment (15). In the UK Prospective Diabetes Study (UKPDS), patients treated by insulin with ≥2 episodes of hypoglycaemia in the previous year had worse scores for psychological tension and overall mood disturbance, and reported lower work satisfaction than patients with no hypoglycaemia(16). Nevertheless, there is a paucity of studies investigating associations between hypoglycaemia and patient-reported outcomes (PROs).

The PANORAMA study was designed to assess the quality of type 2 diabetes care in Europe with a large sample of patients with type 2 diabetes recruited in nine countries, managed mainly in primary care (NCT00916513). A previous analysis from PANORAMA evaluated glycaemic control in Europe (17). This paper aims to assess the frequency and risk factors of severe and non-severe hypoglycaemic episodes and the PROs associated with them.

Materials and Methods

Study design

The PANORAMA study design has been detailed elsewhere (18). Briefly, PANORAMA was an observational, cross-sectional study of people with type 2 diabetes, designed to be representative of the population of these patients in nine countries: Belgium, France, Germany, Greece, Italy, the Netherlands, Spain, Turkey, and the United Kingdom.

Study population

In each country, a random selection procedure was applied to databases of physicians managing patients with type 2 diabetes. Specialist or primary care physicians involved in each country were recruited to reflect country-specific practice. Therefore, in most countries primary care physicians were recruited, but in Italy and Greece diabetologists were selected. The study was conducted between April 2009 and April 2010.

In the Netherlands, Spain and the UK, where electronic health records were available, patients were randomly selected for inclusion. Centres in Belgium, France, Germany, Greece, Italy and Turkey were asked to enrol consecutive patients. Patients aged ≥40 years were eligible if they had type 2 diabetes diagnosed ≥1 year before study entry with medical records available for ≥1 year, and no change in drug treatment (except for dose) within the previous 3 months. All patients received diet and exercise advice; most were also treated with OADs and/or insulin. Patients were excluded if they had type 1 diabetes and/or a history of diabetic ketoacidosis or secondary diabetes, were pregnant, or receiving systemic glucocorticoid treatment.

The study was performed in accordance with the ethical principles of the Declaration of Helsinki, consistent with International Conference on Harmonisation/Good Clinical Practice and the AstraZeneca policy on Bioethics. All patients gave written informed consent.

Data collected

Data were collected at the study visit by the physician via medical record review, patient interview, and patient-self-completed questionnaires. HbA_{1c} was measured by each physician during the study visit using an identical point-of-care device (A1Cnow®, Bayer) certified by the US National Glycohemoglobin Standardization Program (19).

All episodes of hypoglycaemia reported by the patient in the last year were recorded by physicians: the number of severe hypoglycaemic episodes and the average number of non-severe episodes of hypoglycaemia per month, or, if fewer than one per month, the approximate average number per year. Frequencies of hypoglycaemic episodes were presented for the past year. Severe hypoglycaemia was defined as an episode requiring external assistance, with prompt recovery after glucose or glucagon administration. All other episodes of hypoglycaemia were classified as non-severe.

Physicians recorded their assessment of each patient's adherence to lifestyle recommendations (eg, diet, exercise) and diabetes medication; these were rated as 'poor', 'moderate', or 'good'. Physicians also recorded the presence of microvascular and macrovascular diabetes-related complications, depressive disorders, sleep disorders, and whether patients had used self-monitoring blood glucose (SMBG) in the previous 3 months.

Patients completed PRO questionnaires in their own language at the study visit. Linguistic validation procedures were used for translations.PRO measurement relied on four different questionnaires: the Audit of Diabetes-Dependent Quality of Life (ADDQoL), the Diabetes Treatment Satisfaction Questionnaire (DTSQ), the Hypoglycemia Fear Survey-II (HFS-II), and the EQ-5D. The ADDQoL is a self-administered questionnaire providing an individualized measure of the impact of diabetes on quality of life (QoL) using 19 specific life domains, each rated on a 5-point impact scale and a 4-point importance scale (20). The impact rating for each domain is multiplied by the corresponding importance rating to give a weighted impact (WI) score ranging from -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes). An overall average WI (AWI) score is calculated from the WI scores from all applicable domains (-9 to 3). In addition, an overview item measures present QoL (from excellent 3, to extremely bad -3) and another overall item estimates the impact of diabetes on QoL (-3 to +1). The DTSQ is a self-administered 8-item questionnaire that has demonstrated validity and reliability in patients with type 2 diabetes (21). Each item is scored on a 7-point scale from 6 (eg, very satisfied, very convenient) to 0 (eg, very dissatisfied, very inconvenient). Six items are summed to form the DTSQ 6-item

treatment satisfaction score (0 to 36). The remaining two items measure perceived frequency of hyperglycaemia and hypoglycaemia (worded as 'how often have blood sugars been unacceptably high [low] recently') and scored from 6 (most of the time) to 0 (none of the time). The DTSQ was also completed by physicians as if they were the patient, while blinded to patient responses. The HFS-II worry subscale consists of 18 items rated from 0 (never) to 4 (almost always), with a total score ranging from 0 (least worry) to 72 (most worry) (22). Each item addresses a concern that people with diabetes may have about low blood sugar and its potential negative consequences. The EQ-5DVisual Analog Scale (EQ-5D VAS), ranging from 0 to 100,was also used to assess health status (better health status when score is higher)(23).

Statistical analyses

Patient socio-demographic characteristics, clinical and biological measures, treatment, glycaemic control, physician-reported outcomes, and PRO scores were compared between patients with and without episodes of severe hypoglycaemia in the past year, and, among patients who experienced no severe hypoglycaemia, between those with and without non-severe hypoglycaemia in the past year. Patients were categorized into treatment groups according to their current treatment at the study visit: diet and exercise alone (DE only); OADs without insulin secretagogues and insulin (OADs -S-I); OADs with sulfonylureas and no insulin (OADs +SU-I); OADs with glinides and no insulin (OADs +G-I); and insulin with or without OADs(insulin ±OADs). Patients receiving both sulfonylureas and glinides were excluded. Biguanides, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists could be added to any of the four groups as they have a low inherent risk for hypoglycaemia. Subgroup comparisons used Chi-square tests for categorical variables, t-tests for continuous variables, both presented as mean (standard deviation), and non-parametric Wilcoxon rank-sum tests for PROs, presented as medians (quartiles). In a post-hoc analysis, the rate of renal insufficiency and/or dialysis treatment was compared between the OADs +SU-I and OADs +G-I groups.

Multivariate analyses used logistic regression to calculate odds ratios (ORs), their 95% confidence intervals (CIs) and associated *P*-values for hypoglycaemic episodes in the past 12 months, by applying a stepwise selection algorithm to a model containing variables that might be expected to affect risk of hypoglycaemia. The continuous variables (increments used) were: age (1 year), BMI (1 kg/m^2), diabetes duration (1 year), and HbA_{1c} (1% [11 mmol/mol]), and the categorical variables were: antidiabetes treatment, gender, current

smoker, living alone, left education after age 18 years, unemployed, macrovascular and microvascular complications, poor adherence to lifestyle or medication, SMBG, depressive disorder and sleep disorder. PROs were not included in the multivariate analyses. The reference group for treatment combined the DE only and OADs -S-I treatment groups, as both had very few patients.

Results

A total of 5,817 patients were enrolled in PANORAMA. Four participants with data-reporting errorsidentified after database lock, were excluded from the current investigation. Fourteen patients had no data on episodes of severe hypoglycaemia, and 16 patients had taken both sulfonylureas and glinides in the previous year, giving a sample size of 5,783 patients. Of the data reported in univariate analyses, 81.5% of variables had <5% missing data.

During the previous year, 254/5,783 (4.4%) patients experienced ≥1 episode of severe hypoglycaemia. A further five patients had no data on non-severe hypoglycaemia, so 5,524 patients were analysed for non-severe hypoglycaemia and, among patients who did not experience severe hypoglycaemia, 868/5,524 (15.7%) experienced ≥1 episode of non-severe hypoglycaemia.

Concerning clinical and biological parameters, compared with patients without any severe hypoglycaemia in the past year, those who experienced ≥1 severe hypoglycaemic episode had a longer diabetes duration and poorer glycaemic control and more diabetes-related complications (micro- and macrovascular), although they were more likely to use SMBG. They were also less likely to live alone and were more frequently current smokers. They had a poorer physician-reported adherence to diabetes medication and lifestyle recommendations. They were also more likely to have depressive and sleep disorders(Tables 1 and 2).

Patients who reported non-severe hypoglycaemia in the past year, compared with those who did not report any hypoglycaemia, also had a longer diabetes duration, poorer glycaemic control, and more frequent diabetes-related complications in spite of more frequent use of SMBG. They also had a poorer physician-reported adherence to lifestyle recommendations (but not to diabetes medication) and more depressive and sleep disorders.

In addition, they had lower diastolic blood pressure and were more frequently female (Tables 3 and 4).

Rates of both severe and non-severe hypoglycaemic events were highest in patients treated with insulin ±OADs (14.2% and 39.3%, respectively) and lower in patients treated with DE only (0.0% and 1.1%, respectively) and OADS -S-I (1.3% and 8.6%, respectively), and intermediary with OADs +SU-I (2.6% and 14.4%, respectively) and OADs +G-I (5.4% and 22.1%, respectively) (Tables 2 and 4). Rates of renal insufficiency and/or dialysis were 40/1675 (2.4%) in the OADs +SU-I group and 18/296 (6.1%) in the OADs +G-I group ($P = 0.0005$). Of the 40 patients with renal insufficiency in the OADs +SU-I group, two patients reported severe hypoglycaemia and four reported non-severe hypoglycaemia. Of the 18 patients in the OADs +G-I group, no one reported severe hypoglycaemia and five patients reported non-severe hypoglycaemia.

All the PRO measures indicated significantly poorer outcomes ($P < 0.001$) in patients who experienced severe hypoglycaemia versus no severe hypoglycaemia, and also in those who experienced non-severe hypoglycaemia versus no hypoglycaemia in the last year (Tables 2 and 4). The DTSQ 6-item score was consistently lower when assessed by physicians than by patients, even more when patients reported any hypoglycaemia, severe (4.0 vs 2.0) or non-severe (2.0 vs 1.0) (Tables 2 and 4). DTSQ item 3, assessing the frequency of recent unacceptably low blood sugar, was lower when rated by physicians than by patients, except for severe hypoglycaemia (Tables 2 and 4).

Multivariate analysis showed that the risk of severe hypoglycaemia in the past year was significantly associated with treatment with insulin ±OADs (OR 6.49; $P < 0.001$), OADs +G-I (OR 3.10; $P = 0.003$), compared with DE only/OADs -S-I treatment, while the association with OADs +SU-I (OR 1.68; $P = 0.076$) was not significant. Risk of severe hypoglycaemia was also significantly associated with longer diabetes duration, lower BMI, macrovascular and even more so with microvascular complications and SMBG use, but no significant association was found with glycaemic control (Table 5). Risk of non-severe hypoglycaemia was also significantly associated with treatment with insulin ±OADs (OR 5.04; $P < 0.001$), OADs +G-I (OR 2.95; $P < 0.001$), and OADs +SU-I (OR 2.23; $P < 0.001$) compared with DE only/OADs -S-I treatment, and with female gender, longer diabetes duration, better glycaemic control, microvascular complications, and SMBG use, with a trend close to significance for macrovascular complications (Table 6).

Discussion

The PANORAMA study found that a bit more than20% of patients with type 2 diabetes reported hypoglycaemic events (including 4.4% severe hypoglycaemia) during the past year. Hypoglycaemic episodes mostly occurred in patients treated by insulin (among this group, 14.2% experienced severe and 39.3% non-severe hypoglycaemia) and insulin secretagogues (glinides [5.4% and 22.1%] and sulfonylureas [2.6% and 14.4%]). In comparison, rates of severe hypoglycaemia for patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) varied from 18.5% per year (27% in the intensive and 10% in the conventional treatment groups, respectively) (24) to 31.5% per year in the EURODIAB study (25). The findings of the current study are in accordance with an earlier observation that insulin and OADs were common causes of emergency hospitalization due to adverse drug effects in elderly people in the USA (3). However, the observed frequency of hypoglycaemia in type 2 diabetes populations varies considerably across different studies and severe hypoglycaemic episodes have been reported in 0.8% to 10.8% of patients (26–29).Methodological differences may explain some variation in the frequencies recorded in these studies, and also differences in antidiabetes treatment: the recent meta-analysis showing the lowest frequency (0.8%) of severe hypoglycaemia included 22 studies of patients with type 2 diabetes treated with sulfonylureas, without insulin treatment (29); in the three other studies, episodes of severe hypoglycaemia varied between 4.0% and 10.8%, indicating that severe hypoglycaemia is not uncommon in patients with type 2 diabetes. This is an important clinical consideration not only because hypoglycaemia results in greater use of health service resources with a corresponding financial impact (3, 30), but mainly because it may have consequences as serious as fatal cardiovascular events (4, 8, 10–12).

The PANORAMA study also demonstrated in univariate analysis the impact of hypoglycaemic episodes on PROs. ADDQoL AWI scores were significantly more negative in patients with severe and/or non-severe hypoglycaemia compared with patients reporting no hypoglycaemia. Not surprisingly, treatment satisfaction increased gradually from severe hypoglycaemia to no hypoglycaemia groups. Poorer health status and greater hypoglycaemiaworry have been found in other type 2 diabetes studies(26, 31–33). In these studies, it should be noted that macro- and microvascular complications were more frequent in patients who experienced hypoglycaemia and were not controlled for, while they may have intervened as confounding factors in the association between hypoglycaemia and PROs.

In addition, in a less expected finding, physician-reported DTSQ treatment satisfaction scores were consistently lower (ie, less treatment satisfaction) than patient-reported treatment satisfaction scores, and this discrepancy was even larger for patients reporting hypoglycaemia, and especially severe hypoglycaemia. However, physicians underestimated the frequency of unacceptably low blood glucose values(item 3 on the DTSQ) for all groups except the group reporting severe hypoglycaemia, suggesting that physicians may be more worried about severe hypoglycaemia than patients, but less aware of non-severe hypoglycaemia. Recent recommendations highlight the importance of hypoglycaemia prevention, particularly in frail patients (6). Ideally, physicians should support their patients appropriately and reinforce their self-confidence without communicating excessive anxiety about hypoglycaemia, to achieve a fair glucose control, defined in terms of both low HbA_{1c} and low risk of significant hypoglycaemia, and reduce the risk of diabetes-related complications (15).

In the PANORAMA study, multivariate analyses confirmed the role of sulfonylureas, glinides, and insulin treatments in increasing the risk of severe as well as non-severe hypoglycaemia with a higher risk for insulin versus insulin secretagogues and, within this last group, a higher risk for glinides versus sulfonylureas. These findings are well established (15), except for the higher risk of hypoglycaemia with glinides compared with sulfonylureas, in contrast to some studies that included small numbers of patients with short follow-up periods(34, 35). Indeed, a meta-analysis of antidiabetes drugs added to metformin found that glinides were associated with a higher risk of hypoglycaemia than sulfonylureas: relative risk 7.50 (95% CI: 2.12, 41.52) versus 4.57 (95% CI: 2.11, 11.45), with placebo as a reference (36). In the PANORAMA study the higher risk of hypoglycaemia on glinides compared with sulfonylureas does not seem to be explained by the higher rate of renal insufficiency in the glinides group, and the rates of hypoglycaemia in the two groups with renal insufficiency suggest that other factors may be involved.

Our study also indicated that patients with longer diabetes duration and macrovascular and, even more so, microvascular complications, were at increased risk of hypoglycaemia. These associations may be linked: a longer time of exposure to hyperglycaemia will lead to a higher risk of diabetes-related complications, and a longer duration of diabetes also results in decreasing β-cell function, leading to intensification of antidiabetes treatment. In the PANORAMA study, the other factor associated with hypoglycaemia of any severity was the use of SMBG. Reverse causality may explain this association, though unexpected at first

consideration: patients who experienced hypoglycaemia are more likely to be encouraged to use SMBG, and will more readily accept it. In addition, SMBG use can detect asymptomatic hypoglycaemia and thus increase the recording of non-severe hypoglycaemia episodes. Reimbursement regulations may also have influenced this association, as in many countries reimbursement of SMBG for patients with type 2 diabetes is restricted to patients treated with sulfonylureas or insulin. Three other factors were associated with only one type of hypoglycaemia: lower BMI was a risk factor for severe hypoglycaemia, while female gender and lower HbA_{1c} were associated with higher risk for non-severe hypoglycaemia. In a post-hoc epidemiological analysis of the ACCORD study, lower BMI and female gender were also identified as risk factors for severe hypoglycaemia(37). Lower BMI was also a risk factor in the RECAP-DMstudy (31), while female gender was a risk factor for severe hypoglycaemia in the Edinburgh type 2 diabetesstudy (38). In the PANORAMA study, HbA_{1c} and risk of hypoglycaemia were associated in opposite directions in both univariate and multivariate analyses. The multivariate analyses showing a significantly higher risk of non-severe hypoglycaemia and a non-significant trend for severe hypoglycaemia with a lower level of HbA_{1c} are likely to be more reliable than univariate analyses, as many confounders can intervenein this relationship.

The PANORAMA study collected a large quantity of data on hypoglycaemia in patients with type 2 diabetes. Strengths of the study were recruitment of a representative sample of Europeans with type 2 diabetes. In France where consecutive recruitment was used, the PANORAMA population had characteristics similar to the randomized sample recruited for the ENTRED study using the national Health Insurance database: same age (66 years), and similar diabetes duration and HbA_{1c} values (10 years vs 11 years and 7.0% vs 7.1% in PANORAMA and ENTREDstudies, respectively) (39). This suggests that recruitment biases may be minimal. Other strengths were to have measured HbA_{1c} using the same standardized device for all the patients across the nine European countries, and to have used informative, well-validated and widely used questionnaires to assess PROs, such as ADDQoL and DTSQ. Nevertheless, hypoglycaemia can be challenging to recognize in a patient interview during a consultation and physicians may be reluctant to discuss hypoglycaemia with their patients to avoid causing concern.Nonetheless, the data collected in the present study from patient interview and physician records remain a useful resource, even if memory bias cannot be eliminated. A limitation of the study design is that patients were categorized according to their current treatment as recorded at the single study visit, which

may not always reflect their treatment in the past 12 months, as the inclusion criteria required a stable treatment for the last 3 months only. This could explain why 27 patients receiving OADs -S-I at inclusion reported experiencing severe hypoglycaemia in the last year. It was likely they had received insulin or insulin secretagogue treatment in the past year, which was interrupted before the last 3 months preceding inclusion. Another limitation of the present analysis is the use of univariate analyses only for between-group comparisons on PRO measures. As diabetes-related complications were more frequent in those who experienced hypoglycaemia, multivariate analyses are needed to adjust for confounders in assessing the association between hypoglycaemiaand PROs. The data will be presented in another report.

In conclusion, the PANORAMA study indicates that severe and non-severe hypoglycaemia are not uncommon in patients with type 2 diabetes when treated with insulin, sulfonylureas, and glinides. It also showed an association between hypoglycaemia risk and longer diabetes duration, microvascular complications, and use of SMBG, while the negative impact of hypoglycaemia on patient QoL, satisfaction with antidiabetes treatment, worry about hypoglycaemia, and health status remain to be confirmed. Clinicians mightconsider an individualized treatment for their patients with type 2 diabetes, and choose a multipronged approach using newer therapies to decrease the use of insulin secretagogues and insulin tominimize the risk of hypoglycaemia (15, 40).

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Beverley Balkau, PhD, reviewed the prefinal version of the manuscript.

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Conflicts of interest

The PANORAMA study was sponsored by AstraZeneca and Bristol-Myers Squibb, who were involved in: the design and conduct of the study; data collection, analysis and interpretation; preparation and review of the manuscript, and decision to submit the manuscript for publication. C.B., D.S., and P.d.P. are co-chairs of the PANORAMA steering committee. All non-company authors have received honoraria/consulting fees for their participation on the PANORAMA Study Advisory Committee. All non-company authors received honoraria and expenses for attending steering group meetings and conferences where PANORAMA results were presented. D.S. has served on speakers' bureaus for Lifescan, Lilly-France, and sanofi-aventis, and has served on advisory panels for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Janssen, Merck Sharp and Dohme, Novartis, and Takeda, has received sponsorship to organize scientific meetings from GlaxoSmithKline, Janssen, Merck Sharp and Dohme, Novartis, sanofi-aventis and Takeda, and has participated as an investigator in studies conducted by Lilly-France, Novartis, and Novo-Nordisk.

P.d.P. has received speaker fees from Bristol-Myers Squibb, Novartis, sanofi-aventis and Takeda, and has served as an advisory board member for Boehringer-Ingelheim. K.G.P. has received consulting fees and/or speaker fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb and Merck Sharp and Dohme. L.G.F. is co-copyright owner of the Hypoglycemia Fear Survey (HFS) and receives licensing fees, which support research programmes in hypoglycaemia at the University of Virginia, from corporations who use the survey in their research. The study sponsors (AstraZeneca and Bristol-Myers Squibb) licensed the HFS from the University of Virginia. L.G.F. has also received honoraria and expenses for consulting from AstraZeneca, Bristol-Myers Squibb, Johnson and Johnson, Abbott Diabetes Lab, and Dexcom Inc. I.D.L. is a full-time employee of Bristol-Myers Squibb. H.V. is a full-time employee of AstraZeneca. E.E. has no further disclosures. C.B. is copyright owner of the ADDQoL and DTSQ used in the PANORAMA study, a Director and majority shareholder in the spin-off company, Health Psychology Research (HPR) Ltd, which licenses C.B.'s questionnaires. C.B. receives royalties when the questionnaires are licensed to commercial companies and advises others on the use of the questionnaires. HPR Ltd pays C.B.'s university for a percentage of her time at full economic costs. HPR Ltd licenses C.B.'s questionnaires for others to use and supports the linguistic validation and further development of her questionnaires. C.B. has received research funding from ViiV Healthcare. The study sponsors (AstraZeneca and Bristol-Myers Squibb) licensed the ADDQoL and DTSQ from HPR Ltd. C.B. has also received honoraria and expenses for speaking about the measurement of patient-reported outcomes at meetings organized by AstraZeneca and Bristol-Myers Squibb and by other pharmaceutical companies including Lilly Global and Novo Nordisk. C.B. has received consultancy fees from GlaxoSmithKline and ViiV Healthcare and is a member of the advisory committee of Novo Nordisk.

Clinical Trials Registration Number: NCT00916513

Table 1. Clinical and Biological Characteristics of Patients with or without Severe HypoglycaemicEpisodes in the Past Year

	None (n = 5,529)	At Least One Severe Hypoglycaemic Episode (n = 254)	*P* Value[a]
Age, years	65.9 (10.3)	65.2 (10.7)	0.298
Gender, male	2,979 (53.9)	127 (50.0)	0.224
Employment status, unemployed	239 (4.3)	11 (4.3)	0.993
Leaving full-time education ≥18 years	1,302 (29.9)	64 (33.3)	0.309
Living alone	1,237 (22.4)	41 (16.1)	0.019
Current smoker	776 (14.0)	48 (18.9)	0.030
Diabetes duration	8.7 (6.9)	13.4 (8.8)	<0.001
Macrovascular complications	1,315 (23.8)	101 (39.8)	<0.001
Microvascular complications	1,472 (26.6)	166 (65.4)	<0.001
Depressive disorders	736 (13.3)	62 (24.4)	<0.001
Sleep disorders	772 (14.0)	60 (23.6)	<0.001
BMI	30.3 (6.2)	29.7 (5.4)	0.075
Systolic blood pressure (mm Hg)	134.6 (15.4)	134.6 (15.3)	0.954
Diastolic blood pressure (mm Hg)	78.3 (9.0)	77.9 (12.0)	0.616
Self-monitoring blood glucose use	2,562 (46.4)	208 (81.9)	<0.001
LDL-c (mmol/l)	2.7 (0.9)	2.7 (1.0)	0.760
HbA_{1c} at index visit (%)	6.9 (1.1)	7.4 (1.2)	<0.001
(mmol/mol)	52 (12)	57 (13.1)	

Data are presented as number (%) ormean (standard deviation).

BMI, body mass index; LDL-c, low-density lipoprotein cholesterol

[a]*P*-value for comparison between group with no episodes of severe hypoglycaemia and groupwith at least one episode of severe hypoglycaemia.

Table 2. Physician-reported Patient Adherence, Patient-reported Outcome Measures and Antidiabetes TreatmentCharacteristics of Patients with or without Severe Hypoglycaemic Episodes in the Past Year

	None (n = 5,529)	At Least One Severe Hypoglycaemic Episode (n = 254)	*P* Value[a]
Physician-reported patient adherence			
Poor adherence to medication	270 (5.0)	31 (12.2)	<0.001
Poor adherence to lifestyle	1,116 (20.2)	77 (30.3)	<0.001
Patient-reported outcome measures			
AWI ADDQoL	-1.00 (-2.4, -0.3)	-2.56 (-4.0, -0.9)	<0.001
DTSQ 6 items (patient)	31.0 (27, 35)	29.0 (24, 33)	<0.001
Item 3 (patient): perceived frequency of hypoglycaemia	1.3 (1.7)	2.4 (1.8)	<0.001
DTSQ 6 items (physician)	29.0 (24, 32)	25.0 (22, 29)	<0.001
Item 3 (physician): perceived frequency of hypoglycaemia	1.1 (1.4)	2.6 (1.6)	<0.001
HFS-ws score	7.0 (1, 19)	22.0 (11, 36)	<0.001
EQ-5D VAS	71.0 (60, 81)	62.5 (50, 77)	<0.001
Treatment			
Diet and exercise alone	571 (100.0)	0 (0.0)	
OADs -S-I	1,985 (98.7)	27 (1.3)	
OADs +SU-I	1,631 (97.4)	44 (2.6)	<0.001[b]
OADs +G-I	280 (94.6)	16 (5.4)	
Insulin ±OADs	1,000 (85.8)	166 (14.2)	

Data are presented as number (%), mean (standard deviation) or median (Q1, Q3).

AWI ADDQoL, average weighted impact Audit of Diabetes-Dependent Quality of Life; DTSQ, Diabetes Treatment Satisfaction Questionnaire; +G, with glinides; HFS-ws, Hypoglycaemia Fear Survey worry subscale; -I, no insulin; ±OADs, with or without

OADs; OAD, oral antidiabetes drugs; -S, no secretagogues; +SU, with sulfonylureas; VAS, Visual Analog Scale.

[a]*P*-value for comparison between group with no episodes of severe hypoglycaemia and group with at least one episode of severe hypoglycaemia.

[b]*P*-value for comparison between all treatment groups.

Table 3. Clinical and Biological Characteristics of Patients with or without Non-severe Hypoglycaemic Episodes (Excluding Patients with Severe Hypoglycaemia) in the Past Year

	None (n = 4,656)	At Least One Non-severe Hypoglycaemic Episode (n = 868)	*P* Value[a]
Age, years	65.9 (10.4)	65.9 (10.1)	0.897
Gender, male	2,547 (54.7)	429 (49.4)	0.004
Employment status, unemployed	205 (4.4)	34 (3.9)	0.524
Leaving full-time education ≥18 years	1,091 (30.2)	206 (28.1)	0.278
Living alone	1,049 (22.5)	186 (21.4)	0.469
Current smoker	662 (14.2)	113 (13.0)	0.356
Diabetes duration	8.0 (6.4)	12.1 (8.1)	<0.001
Macrovascular complications	1,027 (22.1)	284 (32.7)	<0.001
Microvascular complications	1,094 (23.5)	376 (43.3)	<0.001
Depressive disorders	578 (12.4)	158 (18.2)	<0.001
Sleep disorders	594 (12.8)	177 (20.4)	<0.001
BMI	30.3 (6.2)	30.4 (5.8)	0.536
Systolic blood pressure (mm Hg)	134.7 (15.3)	134.1 (15.8)	0.310
Diastolic blood pressure (mm Hg)	78.5 (9.0)	77.2 (9.3)	<0.001
Self-monitoring blood glucose use	1,893 (40.7)	667 (76.9)	<0.001
LDL-c (mmol/l)	2.7 (0.9)	2.6 (0.9)	0.189
HbA_{1c} at index visit (%)	6.8 (1.1)	7.1 (1.1)	<0.001
(mmol/mol)	51 (12)	54 (12)	

Data are presented as number (%) or mean (standard deviation).

BMI, body mass index; LDL-c, low-density lipoprotein cholesterol

[a]*P*-value for comparison between group with no episodes of non-severe hypoglycaemia and group with at least one episode of non-severe hypoglycaemia.

Table 4. Physician-reported Patient Adherence, Patient-reported Outcome Measures and Antidiabetes Treatment Characteristics of Patients with or without Non-severe Hypoglycaemic Episodes (Excluding Patients with Severe Hypoglycaemia) in the Past Year

	None (n = 4,656)	At Least One Non-severe Hypoglycaemic Episode (n = 868)	*P* Value[a]
Physician-reported patient adherence			
Poor adherence to medication	225 (5.0)	45 (5.2)	0.762
Poor adherence to lifestyle	914 (19.7)	202 (23.3)	0.016
Patient-reported outcome measures			
AWI ADDQoL	-0.94 (-2.3, -0.3)	-1.61 (-3.1, -0.6)	<0.001
DTSQ 6 items (patient)	31.0 (27, 35)	30.0 (25, 34)	<0.001
Item 3 (patient): perceived frequency of hypoglycaemia	1.2 (1.6)	1.9 (1.6)	<0.001
DTSQ 6 items (physician)	29.0 (25, 32)	27.0 (23, 30)	<0.001
Item 3 (physician): perceived frequency of hypoglycaemia	1.0 (1.3)	1.7 (1.4)	<0.001
HFS-ws score	6.0 (0, 18)	13.0 (6, 26)	<0.001
EQ-5D VAS	74.0 (60, 84)	70.0 (50, 80)	<0.001
Treatment			
Diet and exercise alone	565 (98.9)	6 (1.1)	
OADs -S-I	1,813 (91.4)	170 (8.6)	
OADs +SU-I	1,395 (85.6)	234 (14.4)	<0.001[b]
OADs +G-I	218 (77.9)	62 (22.1)	
Insulin ±OADs	606 (60.7)	393 (39.3)	

Data are presented as number (%), mean (standard deviation) or median (Q1, Q3).

AWI ADDQoL, average weighted impact Audit of Diabetes-Dependent Quality of Life; DTSQ, Diabetes Treatment Satisfaction Questionnaire; +G, with glinides; HFS-ws,

Hypoglycaemia Fear Survey worry subscale; -I, no insulin;±OADs, with or without OADs; OAD, oral antidiabetes drugs; -S, no secretagogues; +SU, with sulfonylureas; VAS, Visual Analog Scale.

[a]*P*-value for comparison between group with no episodes of non-severe hypoglycaemia and group with at least one episode of non-severe hypoglycaemia.

[b]*P*-value for comparison between all treatment groups.

Table 5. Multivariate Logistic Regression Analysis of Patient and Treatment Factors with Severe Hypoglycaemia as the Independent Variable

Variable	Odds Ratio (95% CI)	*P*Value
Age, years	0.98 (0.97, 1.00)	0.075
Male[a]	0.84 (0.61, 1.17)	0.315
Living alone	0.76 (0.50, 1.15)	0.192
Unemployed	0.86 (0.40, 1.87)	0.701
Leaving full-time education >18 years	1.33 (0.95, 1.87)	0.096
Current smoker	1.27 (0.83, 1.94)	0.266
Diabetes duration, years	1.02 (1.00, 1.04)	0.037
Macrovascular complications	1.44 (1.03, 2.03)	0.035
Microvascular complications	2.78 (1.96, 3.96)	<0.001
Depressive disorders	1.18 (0.79, 1.76)	0.423
Sleep disorders	1.24 (0.84, 1.84)	0.281
BMI, kg/m^2	0.96 (0.93, 0.99)	0.007
Self-monitoring blood glucose use	1.64 (1.07, 2.53)	0.024
HbA_{1c} at index visit	0.95 (0.84, 1.08)	0.459
On OADs +SU-I (vs diet and exercise or OADs -S-I)	1.68 (0.95, 2.96)	0.076
On OADs +G-I (vs diet and exercise or OADs -S-I)	3.10 (1.45, 6.63)	0.003
On insulin ±OADs (vs diet and exercise or OADs -S-I)	6.49 (3.74, 11.28)	<0.001
Physician estimate of poor adherence to medication (vs moderate or good adherence)	1.41 (0.79, 2.52)	0.248
Physician estimate of poor adherence to lifestyle (vs moderate or good adherence)	1.23 (0.83, 1.83)	0.299

BMI, body mass index; CI, confidence interval; +G, with glinides; -I, no insulin; OAD, oral antidiabetes drug; ±OADs, with or without OADs; -S, no secretagogues; +SU, with sulfonylureas.

[a]With female gender as a reference.

Table 6. Multivariate Logistic Regression Analysis of Patient and Treatment Factors, with Non-severe Hypoglycaemia as the Independent Variable (Excluding Patients with Severe Hypoglycaemia)

Variable	Odds Ratio (95% CI)	*P* Value
Age, years	0.99 (0.98, 1.00)	0.054
Male[a]	0.70 (0.58, 0.85)	<0.001
Living alone	0.90 (0.72, 1.13)	0.367
Unemployed	0.73 (0.46, 1.16)	0.185
Leaving full-time education >18 years	0.97 (0.79, 1.18)	0.749
Current smoker	0.97 (0.75, 1.27)	0.837
Diabetes duration, years	1.03 (1.02, 1.04)	<0.001
Macrovascular complications	1.22 (1.00, 1.51)	0.055
Microvascular complications	1.26 (1.02, 1.54)	0.029
Depressive disorders	1.16 (0.90, 1.49)	0.251
Sleep disorders	1.22 (0.96, 1.56)	0.104
BMI, kg/m^2	0.99 (0.98, 1.01)	0.311
Self-monitoring blood glucose	2.78 (2.25, 3.43)	<0.001
HbA_{1c} at index visit	0.88 (0.81, 0.95)	0.002
On OADs +SU-I (vs diet and exercise or OADs –S-I)	2.23 (1.75, 2.84)	<0.001
On OADs +G-I (vs diet and exercise or OADs –S-I)	2.95 (2.02, 4.30)	<0.001
On insulin ±OADs (vs diet and exercise or OADs –S-I)	5.04 (3.82, 6.65)	<0.001
Physician estimate of poor adherence to medication (vs moderate or good adherence)	1.09 (0.71, 1.66)	0.692
Physician estimate of poor adherence to lifestyle (vs moderate or good adherence)	1.04 (0.82, 1.33)	0.721

BMI, body mass index; CI, confidence interval; +G, with glinides; -I, no insulin; OAD, oral antidiabetes drug; ±OAD, with or without OADs; -S, no secretagogues; +SU, with sulfonylureas.

[a]With female gender as a reference.

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Figure

Episodes of Hypoglycaemia

How many episodes of severe hypoglycaemia did the patient have in the past 12 months? ⌊__⌋

'Severe' defined as symptomatic episodes requiring external assistance due to severe impairment in consciousness or behaviour and prompt recovery after glucose or glucagon administration.

How many episodes of hypoglycaemia (other than severe) did the patient have on average per month? ⌊__⌋

If the number above is less than 1, please state the approximate number of episodes per year instead: ⌊__⌋

Of which

⌊__⌋ were diagnosed by symptoms only (resolved by glucose intake)

⌊__⌋ were diagnosed by glucose measurement only (glucose concentration <3 mmol/L)

⌊__⌋ were diagnosed by glucose measurement (glucose concentration <3 mmol/L) and symptoms