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Predictors of hypoglycaemia in insulin-treated type 2 diabetes patients in primary care: A retrospective database analysis

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ABSTRACT

Aims: To investigate the frequency and predictors (diabetes care and treatment, comorbidity) of documented hypoglycaemia in primary care patients with insulin-treated type 2 diabetes.
Methods: Data from 32,545 patients (mean age: 70 (SD 11) years, 50.3% males) from 1072 practices were retrospectively analyzed (Disease Analyzer database Germany: 09/2011–08/2012). Logistic regression (≥1 documented hypoglyemia) was used to adjust for confounders (age, sex, practice characteristics, diabetes treatment regimen).
Results: The prevalence of patients (12 months) with at least one reported hypoglycaemia was 2.2% (95% CI: 2.0–2.4%). The adjusted odds of having hypoglycemia were increased for renal failure (OR; 95% CI: 1.26; 1.16–1.37), autonomic neuropathy (1.34; 1.20–1.49), and adrenocortical insufficiency (3.08; 1.35–7.05). Patients with mental disorders including dementia (1.49; 1.31–1.69), depression (1.24; 1.13–1.35), anxiety (1.18; 1.01–1.37), and affective disorders (1.80; 1.36–2.38) also showed an increased odds of having hypoglycemia. Location of the practice in an urban area was associated with a lower odds ratio (0.74; 0.68–0.80).
Conclusions: Both individual patient characteristics (e.g. comorbidity) and regional factors (practice location) have a substantial impact on hypoglycaemia in primary care patients with insulin therapy.

1. Introduction

Hypoglycemia is a common side effect of insulin therapy in type 2 diabetes, and has a negative impact on mortality, morbidity and quality of life [1]. Risk factors for hypoglycaemia in insulin-treated type 2 diabetes as reported in the literature [2] and listed in the summary of product characteristics of established insulin formulations [3] include behavioral (e.g. missed meals, exercise, alcohol), physiological (e.g. older age, longer diabetes duration, renal impairment) and therapeutic factors (e.g. concomitant medication). However, much of this evidence results from randomized controlled trials (RCT), which often exclude patients with an increased risk of hypoglycemia [4]. Although most patients with type 2 diabetes are treated in primary care, there is a lack of data on prevalence

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and predictors of hypoglycemia in type 2 diabetes patients under real-life conditions [5]. In particular, the role of comorbidity and the impact of practice characteristics have not often been evaluated.

Thus, the aim of the current analysis was to investigate the frequency and predictors of hypoglycemia in insulin-treated type 2 diabetes in general and internal medicine practices throughout Germany.

2. Patients and methods

The Disease Analyzer database (IMS HEALTH) assembles drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the practice computer system of general practitioners [6]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System) and the validity of reported data were monitored by IMS based on a number of quality criteria (e.g. completeness of documentation, linkage of diagnoses and prescriptions).

The analyzed database period was September 2011 to August 2012 (1072 practices), however, for the assessment of diabetes duration and comorbidity the whole patient history in the practice was considered (median: 6.8 years, range: 1.0–20.6 years). All patients with type 2 diabetes (ICD-10 E11) and/or regular prescriptions of oral anti-diabetics in the past were eligible for the analysis. To ensure continuous insulin treatment, only those patients were selected who received at least one insulin prescription during the first (09/2011–02/2012) and the second (03/2012–08/2012) study half-year. Further inclusion criteria were age above 40 years and membership of a statutory health insurance company (no privately insurance patients).

Patients with hypoglycaemia were identified by specific ICD-10 codings (E16.0, E16.1 and E16.2). The choice of possible predictors was based on a literature search and expert opinions (personal communication with diabetologists). Potential predictors of hypoglycemia considered in the present analysis were older age (>75 years), longer diabetes duration (>5 years), renal impairment (ICD: E112, E142, N18, N19, Z49), autonomic neuropathy (ICD: G909, G629), mental disorders such as dementia (ICD: F01, F03, G30), depression (ICD: F32, F33), anxiety (ICD: F41) and affective disorders (ICD F30, F31, F34-F39), hyperthyreosis (ICD: E05) and adrenocortical insufficiency (ICD: E271, E272, E273, E274). Furthermore, the association of the following specific co-medication with hypoglycemia was assessed based on ATC codes: ACE inhibitors (C09A, C09B) and beta blockers (C07).

Demographic data included patient age, sex, practice region (East/West Germany; rural/urban region) and specialization (diabetologist). Furthermore, type of insulin treatment regimen (basal supported oral therapy, BOT; basal-bolus therapy, ICT; conventional therapy with premixed insulin, CT; prandial insulin therapy, SIT; continuous subcutaneous insulin infusion, CSII), co-medication with oral antidiabetic drugs, lipid disorders and hypertension were assessed. In addition, the Charlson co-morbidity index was used as general marker of co-morbidity. The Charlson index is a weighted index that accounts for the number and severity of co-morbidities in administrative database studies [7]. The conditions included in the Charlson index cover a wide range of co-morbidities (macrovascular diseases, dementia, pulmonary diseases, gastrointestinal, liver and renal diseases, diabetes, tumors and AIDS). Data on HbA1c, fasting glucose measurements and body mass index, which were only available in a subgroup, were also analyzed. Poor glycemic control was defined according to the German guideline as HbA1c > 6.5% [8]. Rapid improvement of glycemic control was also considered as a predictor of hypoglycemia defined as HbA1c difference $\geq$ 1.5% and last HbA1c $\leq$ 6.5% or fasting glucose (FG) difference $\geq$ 50 mg/dl and last FG $\leq$ 100 mg/dl.

Descriptive statistics (means, standard deviations, median and interquartile range, proportions) are given for the above mentioned variables. The proportion of patients with at least one documented hypoglycemia was calculated. Univariate logistic regression models were fitted with hypoglycemia ($\geq$1 during 12 months) as dependent variable and the potential predictors. Potential confounders (age, sex, referral to diabetologist care) and co-morbidity (hypertension, lipid disorders, Charlson index) were included as independent variables. Covariates that were significant in the univariate analyses ($p < 0.05$) were considered in a multivariate logistic regression. The variables that were automatically selected by the backward stepwise regression were included in the final model. Two sided tests were used and a p-value of <0.05 was considered as statistically significant. All analyses were carried out using SAS 9.3. (SAS Institute, Cary, USA). The analysis was carried out following established national [9] and international good practice recommendations of secondary data analysis [10].

3. Results

The clinical characteristics of the 32,545 insulin-treated type 2 diabetes patients in the primary care practices are shown in Table 1. As expected, most of these older patients had a diabetes duration longer than five years, were obese (BMI >30 kg/m^2) and had poor glycemic control. About 60% were on ICT (basal–bolus therapy) followed by 22% on CT (premixed insulin). Supported oral therapy (BOT), continuous subcutaneous insulin infusion (CSII) and supplementary insulin therapy (SIT) were of minor importance. Comorbid conditions including hypertension, lipid disorders, renal insufficiency, and depression were frequently observed.

Overall, 3221 patients (9.9%) experienced at least one documented hypoglycemic event during the total observational period in the practices (median: 6.8 years). The prevalence of patients with at least one reported hypoglycaemia during the study period (12 months) was 2.2% (95% CI: 2.0–2.4%). The results of the univariate analyses showed that the odds of having a documented hypoglycemia (12 months) was significantly increased for longer diabetes duration (>5 years), autonomic neuropathy, impaired renal function, dementia, depression, affective disorders, and adrenocortical insufficiency (data not shown). No significant association was found for improved glycemic control and hyperthyreosis. Overall, 25,615 patients (78.7%) had at least one predictor that was significantly related to hypoglycemia. Furthermore, 13,127 patients (40.3%) and

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