Risk Factors for Nocturnal Hypoglycemia in Insulin-treated Patients With Type 2 Diabetes: A Secondary Analysis of Observational Data Derived From an Integrated Clinical Trial Database

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ABSTRACT

Purpose: A trade-off exists in most diabetes therapies between the benefits of good glycemic control and the morbidity of hypoglycemia. Balancing these factors to achieve desired outcomes is a key consideration for personalized diabetes therapy. Hypoglycemia at night (nocturnal hypoglycemia [NH]) is a common but often under-reported problem in insulin-treated patients with type 2 diabetes. To better understand the risk for NH, we pooled data from multiple clinical trials of insulin treatment and specifically examined NH risk factors in relation to glycemic goals.

Methods: Of 53 randomized trials involving insulin treatment, 18 trials that collected NH data were included. Risk factors associated with NH were identified by using gradient-boosting methods. A proportional hazards model was used to quantify the hazard ratio (HR) for risk factors. By modeling with individual patient data, a patient-level NH risk score distribution was created. Finally, results of the model were used to quantify an adjustment to the glycemic goal that would fully offset each risk factor, all other factors being equal.

Findings: Data pooling resulted in the inclusion of 7341 patients with type 2 diabetes from 18 randomized clinical trials. In the mean 6-month treatment period, 43% of patients experienced at least 1 episode of NH (mean [SD], 1.1 [1.5] events/month). Reduction of glycosylated hemoglobin (HbA_{1c}) levels during the trial was a risk factor for NH (HR, 1.40 [95% CI, 1.38-1.43] per –1% of HbA_{1c}). Higher baseline HbA_{1c} level was a protective factor against NH (HR, 0.76 [95% CI, 0.74–0.77] per +1% of HbA_{1c}); and the adjustment to HbA_{1c} goal required to offset 1% higher baseline HbA_{1c} was –0.825%. Patient characteristics for risk of NH included older age (HR, 1.02 [95% CI, 1.01–1.02]) per 1-year increase), female sex (HR, 1.18 [95% CI, 1.15–1.22]), black or African-American race (HR, 1.41 [95% CI, 1.33–1.50] vs white race), longer diabetes duration (HR, 1.02 [95% CI, 1.01–1.02] per 1-year increase), diabetic nephropathy (HR, 1.40 [95% CI, 1.27–1.54]), and concomitant sulfonylurea use (HR, 1.10 [95% CI, 1.05–1.15]). Asian race was associated with a lower risk of NH (HR, 0.50 [95% CI, 0.48–0.53] vs white race); this finding could be offset with a 2.03% adjustment to the HbA_{1c} goal.

Implications: Data on NH are scarce. By pooling multiple clinical trials, this study was able to evaluate patient-level data. A quantitative understanding of the trade-off between individual risk factors for NH and glycemic reduction may help clinicians to personalize patients' glycemic goals, while effectively managing NH risk. Limitations of the study include that patients were selected through inclusion/exclusion criteria and that patient compliance may be better in a trial setting. Validating the findings in the real world will be helpful. (*Clin Ther*. 2017;39:1790–1798) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: database research, glycemic control, insulin therapy, nocturnal hypoglycemia, type 2 diabetes.

INTRODUCTION

For patients with type 2 diabetes, maintenance of an optimal glycosylated hemoglobin (HbA_{1c}) level is

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associated with decreased complications, improved quality of life, and reduced health care costs.[1,2] However, achievement of normoglycemia or near normoglycemia must be balanced with avoidance of hypoglycemia,[3–5] an adverse event that can reduce quality of life, increase health care costs, and adversely affect treatment adherence.[6] The importance of hypoglycemia risk when selecting each patient's glycemic goal is well recognized. This emphasis was highlighted in a recent publication in which the opinions of expert diabetologists were used to construct an algorithm for estimation of individualized glycemic targets based on patient characteristics[7]; involvement of >140 opinion-leading physicians led to the conclusion that "risk of hypoglycemia from treatment" was the most important factor in determining a patient's glycemic target.

Despite the awareness of hypoglycemia as the limiting factor in glycemic control, evidence to help clinicians manage the risk is limited[8] because hypoglycemic events are often undetected, under-reported, or unreported except in severe cases. Nocturnal hypoglycemia (NH) may be defined as any hypoglycemic event that is experienced while asleep[9] or during a specific time period (eg, between the hours of 10:00 PM and 6:00 AM).[10] NH is common, affecting up to one quarter of all patients with type 2 diabetes.[11] NH diminishes a patient's quality of life, functioning, and sleep, and it negatively affects management of diabetes.[9,12,13] Although some risk factors for NH have been identified previously,[14,15] the relative contributions of each factor to the risk of NH are still unknown.

The objective of the present study was to use high-quality data from randomized clinical trials to identify clinical and demographic factors that are associated with increased risk of NH in insulin-treated patients with type 2 diabetes. We created a large pooled clinical database from 18 insulin trials. The associations between the identified clinical and demographic factors and NH risk were quantified, and the magnitude of each risk factor was reported as an adjustment to the HbA_{1c} goal that would exactly offset the risk of NH. This method was used so that clinicians may understand the trade-off between each risk factor and the glycemic goal.

MATERIALS AND METHODS

Studies and Patients

All 53 randomized clinical trials using commercially approved insulin treatments in patients with type 2 diabetes, conducted by Eli Lilly and Company from 2000 to 2014, were considered for inclusion. Exclusion criteria were trials in patients with type 1 diabetes only, trials not reporting blood glucose data, trials not monitoring NH or the signs and symptoms of hypoglycemia, use of investigational agents, and trials designed primarily for insulin pumps or other devices (see **Supplemental Figure 1** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.07.037 for details regarding the trial selection process). Trials in patients with type 1 diabetes were excluded because there were too few patients in the database. The resulting 18 trials were pooled for analysis by using patient-level data (see **Supplemental Table I** for trial descriptions in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.07.037).

The protocol definition of NH differed among trials, reflecting changing or evolving standards in clinical diabetes management over the 14-year period; however, reporting of NH was comparable. The NH events were systematically captured in the case report files in all studies from the patient diaries.

Patients were divided into 2 groups: those who experienced at least 1 NH event during the trials and those who did not. Descriptive statistics for demographic and baseline characteristics were generated for the 2 groups as well as for the total analysis population. In addition to the common comorbidities, 2 clusters of frequently observed diagnosis codes recorded at baseline were considered as categorical variables ("the presence of other vascular complications" and "the presence of other conditions possibly associated with NH") and included in the regression. Percentages were calculated for categorical variables and means (SDs) for continuous variables. A χ^2 test was used to compare categorical variables between patients with and without NH, and a t test was used to compare continuous variables.

Model Development

First, we searched for core risk factors for NH among all variables (see **Supplemental Table II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.07.037) using a machine learning technique with