Insulin Detemir Versus Insulin Glargine in the Hospital: Do Hypoglycemia Rates Differ?

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IN BRIEF Several studies have compared the safety and efficacy of insulin detemir and insulin glargine; however, most have been conducted in the ambulatory care setting. This retrospective cohort study compared hypoglycemia rates between the two basal insulin analogs in hospitalized patients with diabetes. No difference was found between the two insulin cohorts in the proportion of patients who experienced hypoglycemic events.

In 2015, it was estimated that ~30.3 million Americans were living with type 1 or type 2 diabetes (1). Common long-term complications of uncontrolled diabetes include end-stage renal disease, diabetic retinopathy, amputations, and increased hospitalizations (2,3). In the inpatient setting, hyperglycemia, hypoglycemia, and blood glucose variability can lead to increased costs, lengths of stay, and mortality (4,5). Long-acting insulin analogs remain one of the mainstays of therapy in the management of blood glucose in patients with diabetes (5). Two commonly used basal insulin analogs are insulin glargine and insulin detemir.

Detemir and glargine exhibit similar pharmacokinetic and pharmacodynamic profiles, which make them appropriate for basal therapy. Both demonstrate a peakless time-action profile and a long duration of action, although they achieve this through different absorption mechanisms (6,7). Glargine is derived using recombinant technology and forms a precipitate that dissolves slowly at physiologic pH, thus delaying absorption. This delayed absorption allows for a duration of action that ranges from 10 to 24 hours, reaching up to ~30 hours in a few studies (6,8). Detemir is also derived using recombinant technology and, when injected, forms a soluble depot. In addition, acylation and self-association properties of detemir allow for reversible binding to albumin, which results in its prolonged duration of action. Detemir's duration of action on blood glucose varies from 6 to 23 hours and is largely dose dependent, with longer duration observed as dosage increases (6,9). Glargine and detemir may be administered once or twice daily depending on medication and patient considerations (8,9). These can include basal insulin dose, prandial insulin use, glycemic target, patient preference, and endogenous insulin reserve (10–12).

Studies comparing the safety and efficacy of detemir and glargine have been done mostly in the ambulatory care setting and have demonstrated similar glycemic control when added to mealtime insulin or oral medications in patients with type 2 diabetes (13,14). In contrast, a subgroup of the PREDICTIVE study (15) found improvements in glycemic control and a reduction of hypoglycemic events when switching patients with type 1 or type 2 diabetes from glargine to detemir at routinely scheduled clinic visits (15).

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Despite the breadth of comparative literature surrounding basal insulin therapy in the ambulatory care environment, there is a paucity of evidence comparing the safety and efficacy of glargine and detemir in hospitalized patients. Galindo et al. (16) performed a retrospective database analysis of glargine and detemir use in hospitalized patients who had either type 1 or type 2 diabetes. No difference in average blood glucose values was noted between the two insulin cohorts throughout the hospital stay. Similarly, there were no differences in maximum blood glucose or number of patients with severe hyperglycemia. Interestingly, there was an increase in hypoglycemic events in the detemir cohort. Patients who received detemir also received higher total daily doses (TDDs) of insulin, as well as more daily injections. In contrast, Zhang et al. (17) performed a prospective randomized crossover trial comparing glargine and detemir in hospitalized patients with type 2 diabetes. The authors concluded that the two insulins demonstrated similar time to fasting blood glucose target and similar TDDs. Hypoglycemic events occurred in three of the patients switched to detemir. However, this analysis was limited to 42 patients, thus restricting its power to detect safety events of statistical significance.

More evidence comparing glargine and detemir in the inpatient environment is necessary. The purpose of this study was to compare the efficacy and safety profiles of glargine and detemir by exploring the incidence of both hypoglycemia and hyperglycemia in hospitalized patients with diabetes.

Design and Methods

Sample Selection

This retrospective cohort study was conducted at a 772-bed community teaching hospital in patients with a diagnosis of type 1 or type 2 diabetes between January 2010 to November 2017. Data from the month of December 2013 were not collected because a transition of preferred formulary agent (from glargine to detemir) occurred during this time. Patients were identified via active orders for either detemir or glargine within the electronic medical record (EMR) system. EMRs of adult patients with a diagnosis of diabetes and an order for detemir or glargine were reviewed for inclusion. Patients were excluded if they were pregnant, had received a continuous insulin infusion, had received detemir or glargine for <72 hours, were admitted to an intensive care unit (ICU), or had missing data needed for analysis (missing both height and weight, having no blood glucose measurements, or missing serum creatinine [SCr] values) within 72 hours of initiation of either detemir or glargine. Institutional review board approval was obtained before the study commenced.

Data Collection

Data were electronically abstracted from the EMR system using Access 2016 software (Microsoft Corp., Redmond, Wash.) to extract *International Classification of Diseases,* 9th or 10th revision, codes and Excel 2016 software (Microsoft Corp., Redmond, Wash.) to extract all other data. Authors M.A.C. and C.A.G. organized the extracted data. Data collected within 72 hours of detemir or glargine initiation included highest and lowest creatinine clearance, all blood glucose values, short-acting insulin, sliding scale type, insulin TDD, nothing-by-mouth status, acute kidney injury, chronic kidney disease, corticosteroids, beta-blockers, total parenteral nutrition, enteral nutrition, and specific infections, including urinary tract infection, pneumonia, bacteremia, and diabetic foot infection. Data collected outside of 72 hours included baseline demographics, length of stay, long-acting insulin taken before admission, and most recent A1C. Electronically abstracted data were manually validated by examining 50 patients per cohort.

Outcomes

The primary outcome was the proportion of patients who experienced hypoglycemia within 72 hours of initiating detemir or glargine. Hypoglycemia was defined as a blood glucose value <70 mg/dL. Secondary outcomes included the proportion of patients who experienced hyperglycemic events, the total number of hypoglycemic events, and total insulin requirements within 72 hours of detemir or glargine initiation. Hyperglycemia was defined as a blood glucose value >180 mg/dL.

Data Analysis

Our sample size was based on an overall rate of hypoglycemia in the detemir group of 33.5% compared to 29% for the glargine group, with an alpha error rate of 0.05 and 80% power (16). To find this difference, a sample size of 1,659 patients per group was needed, for a total of 3,318 patients. Data were analyzed using SPSS version 25.0 software (IBM Corp., Armonk, N.Y.). Descriptive data were expressed as mean ± SD, median ± interquartile range, or frequency and percentage. Univariate analysis was performed using a Student t test, a Mann-Whitney U test, or a χ^2 test for continuous, ordinal, and categorical data, respectively. Multivariate logistic regression was performed using hypoglycemia as the dependent variable. Variables were initially considered for inclusion into the model if there was a difference between the detemir and glargine groups and there was an association with hypoglycemia (P <0.1).

Results

Of the 5,200 patients initially screened, 3,726 were identified for inclusion. A total of 3,318 patients (1,659 in each cohort) were randomly selected for the final data analysis. The most common reason for exclusion was no diagnosis of diabetes. Figure 1 shows an inclusion and exclusion flowchart. Baseline characteristics are summarized in Table 1 and were mostly similar between the two cohorts. The detemir cohort includ-

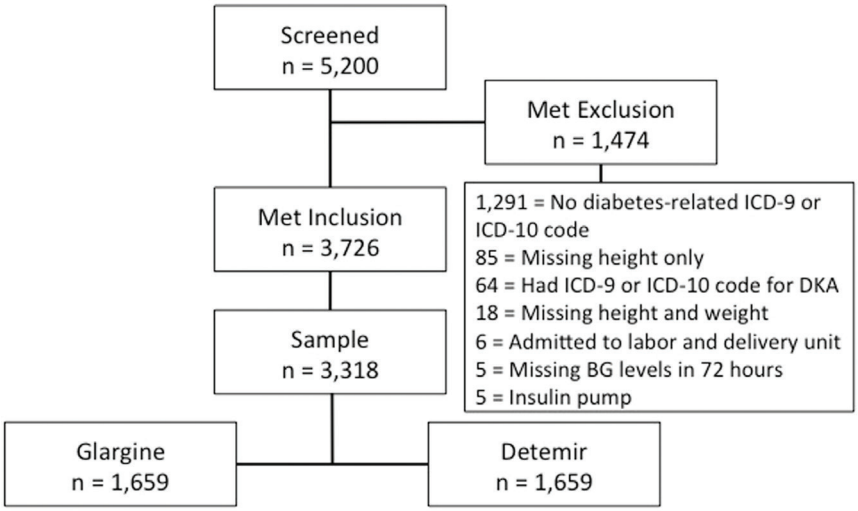

FIGURE 1. Flowchart of inclusion and exclusion criteria. BG, blood glucose; DKA, diabetic ketoacidosis; ICD, *International Classification of Diseases*.

ed more patients with a diagnosis of bacteremia and included more patients who received the high-intensity insulin scale, beta-blockers, and corticosteroids.

No difference was found in the proportion of patients with hypoglycemic events between the two cohorts (24.2% glargine vs. 25.5% detemir, P = 0.356). To assess for potential confounders, multivariate regression analysis was performed (Table 2). Age, baseline SCr, high-intensity insulin scale, and concomitant corticosteroid use all met criteria to be included in the final model. When controlling for these factors, there was no difference in hypoglycemia occurrence with detemir or glargine. No difference was seen in the proportion of patients with hyperglycemic events in the glargine versus detemir group (92.7 vs. 91.1%, P = 0.086). The median number of hypoglycemic events was 0 (range 0–0) for the glargine group versus 0 (range 0–1) in the detemir group (P = 0.257). No difference in insulin TDD was observed between the two cohorts: 34 ± 32 units for glargine versus 35 ± 33 units for detemir (P = 0.606).

TABLE 1. Baseline Characteristics

	Glargine Group (n = 1,659)	Detemir Group (n = 1,659)	P
Age, years*	64 ± 14.7	63 ± 14.3	0.019
Male sex, *n* (%)	774 (46.7)	779 (47.0)	0.862
Race, *n* (%)			0.076
African American	870 (52.4)	852 (51.4)	
Asian	4 (0.2)	9 (0.5)	
Caucasian	649 (39.1)	691 (41.7)	
Other	136 (8.2)	107 (6.4)	
BMI, kg/m^2*	31.2 ± 11.2	31.7 ± 12.2	0.214
Baseline SCr, mg/dL*	1.4 ± 1.4	1.5 ± 1.7	0.081
A1C, %*	8.5 ± 2.3	8.6 ± 2.2	0.326
Initial blood glucose, mg/dL*	213.0 ± 93.2	211.1 ± 91.7	0.555
Bacteremia, *n* (%)	10 (0.6)	51 (3.1)	<0.001
Insulin scale, *n* (%)			
High intensity	292 (17.6)	357 (21.5)	0.004
Medium intensity	747 (45.0)	1101 (66.4)	<0.001
Low intensity	418 (25.2)	529 (31.9)	<0.001
ICU	10 (0.6)	19 (1.1)	0.093
Custom	221 (13.3)	121 (7.3)	<0.001
Beta-blocker, *n* (%)	968 (58.3)	1122 (67.6)	<0.001
Steroid, *n* (%)	263 (15.9)	324 (19.5)	0.006

**Mean ± SD.*

Discussion

Data comparing the use of glargine and detemir are mostly derived from the ambulatory care setting, with very few studies dedicated to hospitalized patients. In our study, we found no difference between the detemir and glargine cohorts in the proportions of patients who experienced hypoglycemic events. Additionally, there were no differences found in the proportion of patients with hyperglycemic events, overall number of hypoglycemic events, and insulin TDD. These results suggest that either agent is appropriate for the management of diabetes in hospitalized patients. However, our results also highlight that blood glucose is difficult to manage; ~25% of the patients in this study experienced hypoglycemia, and >90% experienced hyperglycemia.

Our results differ from those of Galindo et al. (16), who found an increase in both hypoglycemic events and insulin TDD in patients receiving detemir, which may be a result of different methods used for data collection. Data in the study by Galindo et al. relating to potential confounders were collected throughout the entire hospital stay. These potential confounders may not have been temporally related to the occurrence

TABLE 2. Multiple Logistic Regression for Long-Acting Insulin as a Predictor of Hypoglycemia

Variable	Odds Ratio (95% CI)	*P*
Glargine versus detemir	0.911 (0.777–1.069)	0.255
Age, years	1.011 (1.005–1.016)	<0.001
Baseline SCr, mg/dL	1.152 (1.099–1.207)	<0.001
Insulin TDD, units	1.005 (1.003–1.008)	<0.001
High-intensity insulin scale	0.715 (0.572–0.893)	0.003
Concomitant steroid	0.709 (0.565–0.889)	0.003

of hypoglycemia or to the initiation of long-acting insulin therapy. Additionally, confounding bias may have been introduced by a longer length of stay, which would have been difficult to control for. We collected data within 72 hours of initiation of long-acting insulin to attempt to address these issues. Collecting data for the first 72 hours is similar to the strategy employed prospectively in the study by Zhang et al. (17), in which hypoglycemic outcomes were followed for 3 days after long-acting insulin initiation.

The results of this study suggest that a therapeutic interchange between glargine and detemir could be appropriate. Although these agents are similar in price per vial, institutions could select the insulin with the smallest negotiated price. However, there are a few unanswered questions that could be explored in future studies. First, we did not compare patients who came in on detemir or glargine and were switched to the alternate agent versus those who stayed on the same agent. Second, we did not evaluate glycemic variability with glargine or detemir. Additionally, we did not perform a regression on hyperglycemia to evaluate the effect of potential confounding factors because our primary outcome focused on hypoglycemia. We chose hypoglycemia as our primary outcome because of its association with mortality in hospitalized patients (5).

This study has limitations. First, it was observational in design, and data were acquired electronically, which could have led to information bias. To decrease the likelihood of information bias, we performed manual validation of electronically collected data. Second, practice changes may have occurred during the timeframes in which data were collected, although insulin TDDs were similar between the groups. Third, this study excluded patients admitted to the ICU, and results cannot be directly applied to this patient population. Finally, we excluded patients who received long-acting insulin but did not have a diagnosis of diabetes.

In conclusion, this study found similar rates of hypoglycemia in patients receiving insulin glargine and those receiving insulin detemir. Both insulins appear to be appropriate options in hospitalized patients with diabetes. Further research is warranted to pursue a similar comparison in critically ill patients, as well as to evaluate overall glycemic variability using these two long-acting insulin analogs.

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Duality of Interest

No potential conflicts of interest relevant to this article were reported.

Author Contributions

M.A.C., C.A.G., and C.L.H. developed the project protocol. M.A.C. and C.A.G. collected and organized data. M.A.C. wrote the first draft of the manuscript. C.A.G. and C.L.H. reviewed and edited the manuscript. All authors reviewed the final version of the manuscript. C.A.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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