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Clinical Research Article

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Outcomes of "Real-World" Insulin Strategies in the Management of Hospital Hyperglycemia

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Abbreviations: BB, basal bolus; BO, basal only; CHF, congestive heart failure; CKD, chronic kidney disease; DRG, diagnostic related group; ESRD, end stage renal disease; LOS, length of stay; POC, point of care; RABBIT 2, Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes; RCT, randomized clinical trial; RR, rate ratio; SS, sliding scale.

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Abstract

Context: Guidelines recommend scheduled long-acting basal and short-acting bolus insulin several times daily to manage inpatient hyperglycemia. In the "real world," insulin therapy is complicated, with limited data on the comparative effectiveness of different insulin strategies.

Objective: This work aimed to evaluate the association of different insulin strategies with glucose control and hospital outcomes after adjustment for patient and physician factors that influence choice of therapy.

Methods: This retrospective, observational study took place at an academic hospital. Participants included noncritically ill hospitalized medical/surgical patients (n = 4558) receiving subcutaneous insulin for 75% or longer during admission. Insulin therapy was grouped into 3 strategies within the first 48 hours: basal bolus (BB: scheduled long and short/rapid n = 2358), sliding scale (SS: short/rapid acting n = 1855), or basal only (BO: long only: n = 345). Main outcome measures included glucose control: hypoglycemic days, hyperglycemic days, euglycemic days, mean glucose; and hospitalization: in-hospital mortality, length of stay (LOS), and readmissions.

Results: Initial therapy with BB was associated with more hypoglycemic (2.40; CI, 2.04 to 2.82) ($P < .001$) and fewer euglycemic days (0.90; CI, 0.85 to 0.97) ($P = .003$) than SS, whereas BO was associated with fewer hyperglycemic days (0.70; CI, 0.62 to 0.79) ($P < .001$), lower mean glucose (–18.03; CI, –22.46 to –12.61) ($P < .001$), and more euglycemic days (1.22; CI, 1.09 to 1.37) ($P < .001$) compared to SS. No difference in mortality, LOS, and readmissions was found. However, decreased LOS was observed in the BB subgroup with a medical diagnostic related group (0.93; CI, 0.89 to 0.97) ($P < .001$).

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Conclusion: BO had a more favorable hyperglycemia profile than SS. BB, on the other hand, showed worse glycemic control as compared to SS. In the real-world hospital, BO may be a simpler and more effective insulin strategy.

Key Words: insulin, basal-bolus, hyperglycemia, hypoglycemia, inpatient, hospital

Inpatient hyperglycemia is prevalent in 32% to 38% of hospital admissions [1, 2] and is associated with worse outcomes in critically ill [3, 4] as well as noncritically ill patients [1, 5-7]. Not surprisingly, a diagnosis of diabetes is associated with increased hospital complications, longer length of stay (LOS), and increased mortality [3, 4, 8, 9]. However, even without a prior history of diabetes, hospital hyperglycemia is associated with higher mortality, longer LOS [5-7, 10, 11], and increased intensive care unit transfers [7]. Inpatient hyperglycemia worsens the outcome of medical conditions such as myocardial infarction [12-14], stroke [15], and community-acquired pneumonia [2, 16]. Likewise in surgical patients, perioperative hyperglycemia has a strong association with mortality, increased LOS, and hospital-associated complications (eg, infections, renal failure, myocardial infarction) [17, 18], even in patients with no previously known history of diabetes. Similarly, hypoglycemia (glucose < 70 mg/dL) is associated with increased morbidity and mortality [19-21], further highlighting the significant challenge of inpatient blood glucose management.

Historically, hospital hyperglycemia was managed by a sliding scale (SS) insulin regimen [22]. In 2012, Endocrine Society Guidelines on the management of noncritically ill hospitalized patients recommended the use of an insulin regimen with 3 components: 1) scheduled long- or intermediate-acting basal insulin, 2) scheduled rapid or short-acting insulin regimen administered before meals, and 3) as-needed correction insulin if the premeal glucose is above target, also termed the *basal bolus* (BB) insulin regimen. These guidelines were largely based on 2 trials of BB vs SS in the Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes (RABBIT 2 and RABBIT 2 Surgery Trials) [23, 24]. Both trials were prospective, randomized, multicenter, open-label trials in patients with type 2 diabetes only who were managed with oral agents prior to admission. These trials, in medical (n = 130) and in surgical (n = 211) patients, both demonstrated superior glucose control with less hyperglycemia using BB compared to SS. In both studies, mean glucose was 27 mg/dL less and more patients reached the target goal of less than 140 mg/dL [23, 24]. Additionally, in the surgical patients, there was a decrease in composite postoperative complications with BB therapy (24.3 and 8.6%; odds ratio 3.39; 95% CI, 1.50-7.65; $P = .003$) [24]; however, BB resulted in more hypoglycemia than SS in both trials [23, 24]. Although these trials were small, they affirmed that hyperglycemia is improved with a BB insulin regimen compared to SS. Subsequently, the same investigators studied the standard BB regimen vs a simplified version with basal insulin and correction scale only, (basal-plus) vs the SS. In this trial, 375 randomly assigned patients with type 2 diabetes who had been admitted to noncritical medical or surgical units were managed with oral agents or low doses of insulin (total daily requirements < 0.4 units/kg) on BB, basal-plus, or SS regimens. Surprisingly, this follow-up study demonstrated that a basal-plus insulin regimen resulted in similar glycemic control to BB regimen but again with more hypoglycemia than SS [25]. In recent years, the American Diabetes Association Standards of Medical Care in Diabetes has modified the recommendation in noncritically ill hospitalized patients to use basal and rapid or short-acting insulin before meals or a basal plus bolus correction if poor or no oral intake [26].

The RABBIT 2 and RABBIT 2 Surgery Trial were incorporated into the guidelines to support a change in the standard of practice. Although valuable and well designed, these studies were relatively small and were limited to type 2 diabetes patients without significant additional comorbidities who were managed on oral agents alone before admission. Moreover, the daily insulin management with necessary dose adjustments was performed by a skilled research team under a strict protocol. Unfortunately, in "real-world" management of inpatient hyperglycemia, there are many variables that affect the prescriber's choice of insulin therapy and the subsequent outcomes. For example, the use of corticosteroid therapy or the presence of end-organ dysfunction such as liver failure, heart failure, or kidney failure heavily influence the response to different insulin strategies. Additionally, BB is a complicated insulin regimen of 4 to 5 different insulin doses of 2 different insulin types and requires some degree of knowledge and skill to manage daily in a safe and effective manner. Therefore, the results may be dependent on the provider's education as well as expertise. Without adequate skill, all insulin regimens have the potential for harm. While these trials offered the first insight into developing protocols for managing inpatient hyperglycemia, much bigger trials are needed to address the real-life scenarios physicians often confront. Observational studies of patients in everyday

clinical settings may provide valid evidence of safety and effectiveness where large randomized clinical trial (RCT) data are limited or lacking.

Therefore, the objectives of this study were to determine patient and provider factors that influence the choice of insulin strategies to manage inpatient hyperglycemia in the real-world hospital setting, and to evaluate the outcomes of these different strategies with respect to glucose control and hospital outcomes.

Research Design and Methods

Data Source

We conducted a retrospective analysis of 4558 admissions to noncritical care medical and surgical units at Houston Methodist Hospital, a large tertiary care center, between January 2013 and September 2015. Patients 18 years or older who received subcutaneous insulin for 75% or more of their hospital stay and no intravenous insulin were included. Patients on insulin pump therapy were excluded.

Point of care (POC) glucose values were collected at the bedside with glucose meters (ACCU-CHEK Inform, Roche Diagnostics) and wirelessly downloaded to the Remote Automated Laboratory System-Plus (RALS-Plus; Medical Automation Systems), along with the electronic health record and a unique patient identifier. All data were then extracted from the hospital's electronic health record and deidentified for analysis.

This study was approved by the institutional review boards at the Houston Methodist Research Institute and the University of Houston.

Insulin Therapy

Insulin therapy was grouped into 3 strategies defined by insulin orders over the first 48 hours of hospitalization: BB (scheduled long-acting insulin with scheduled short- or rapid-acting insulin with meals, and/or correction short- or rapid-acting insulin, or insulin premix 70/30); SS (a sliding scale of short- or rapid-acting aspart, lispro, or regular insulin only), or BO (scheduled long-acting insulin glargine or neutral protamine Hagedorn [NPH] only). Patients without any insulin administration within the first 2 days of hospital stay or with a total LOS of 2 days or fewer were excluded.

Outcomes

POC glucose values were categorized into 4 measures of glucose control. For each hospital day, POC glucose values were classified as 1) hyperglycemic (mean of all POC glucose > 180 mg/dL), 2) hypoglycemic (any POC glucose < 70 mg/dL), or 3) euglycemic (no POC glucose values < 70 and a calculated mean of all POC glucose values ≤ 180 mg/dL). The fourth measure was a mean of all POC glucose values over the entire hospital stay. Hospital outcomes evaluated in this study were LOS, readmissions at 30 and 60 days, and in-hospital mortality.

Patient and Provider Covariates

Patient demographic information included age, sex, race, and marital status. Baseline clinical variables included first POC glucose value, any concurrent use of corticosteroid or oral antihyperglycemic drug, palliative care, and the presence of comorbidities including existing admission diagnoses of diabetes, hypertension, coagulopathy, cirrhosis, congestive heart failure, acute kidney injury, chronic kidney disease (CKD), and atherosclerotic cardiovascular disease. Other covariates related to hospitalization were admitting physician specialty (surgery or medicine), payer type, and diagnostic related group (DRG) type (medical or surgical). All these 20 factors were used to create a propensity score to equalize the groups based on these covariates.

Statistical Analysis

Descriptive statistics (chi-square and analysis of variance) were used for bivariate unadjusted comparisons (one characteristic at a time with treatment group) of patient and provider characteristics and clinical outcomes across the treatment groups. Multinomial logistic regression analysis [27] was used to determine the unique association of patient demographic factors, baseline clinical variables, and provider factors listed earlier with initial insulin therapy strategy. This method is a multivariable model, used for categorical outcomes with more than 2 categories. It provides the association of each factor with choice of initial treatment as an odds ratio after adjusting for the effect of all the other variables and allows a calculation of the propensity scores for receiving each type of insulin therapy. Propensity scores are the predicted probability of receiving 1 of the 3 insulin strategies, conditional on the patient demographic factors, baseline clinical variables, and provider factors; it is a powerful method to reduce the number of covariables while improving causal inference through balancing the differences in covariables across groups [28, 29]. The propensity scores thus combine all the patient and provider factors into one score. We performed a check to ensure that the propensity score is in fact balancing the differences between groups by using the inverse probability of treatment weight [30]. Using the inverse of the probability of treatment as a weighting

factor creates a weighted data set in which treatment selection is not confounded. After confirming the propensity score balances covariates, we used it as a regressor covariate in subsequent analysis to adjust the comparisons of outcomes across therapy groups, which adjusts for baseline differences between the groups. Because the glucose control measures are count variables, negative binomial regression was conducted for the hyperglycemic, hypoglycemic, and euglycemic days. Linear regression was conducted for mean POC glucose. Logistic regression was conducted for 30-day and 60-day readmission. Finally, because LOS was skewed, this outcome was log-transformed before conducting linear regression. All regression analyses were adjusted by propensity score in the overall population, and conducted with SAS version 9.4 (SAS Institute) with an α level of .05. Finally, because DRG is a major classification and is unbalanced in our population, we also conducted all analyses stratified by DRG.

Results

A total of 4558 patients were included: BB (n = 2358, 51.7%), SS (n = 1855, 40.7%), and BO (n = 345, 7.6%).

Patient and Provider Factors Associated With Treatment

Of 20 patient and provider factors, 16 differed across the 3 insulin strategy groups in bivariate analysis before propensity score adjustment (Table 1), indicating the need for case-mix adjustment using propensity score for treatment comparisons. After weighting the sample with the inverse probability of treatment weight, all covariables are now balanced across groups ($P > .05$ for all variables, last column of Table 1), allowing subsequent unbiased estimates of treatment group association with glucose control measures and hospital outcomes.

The association of each patient and provider factor with the choice of initial therapy after adjustment for all remaining factors obtained from the multinomial regression is presented in Table 2. Factors associated with increased use of BB compared to SS were higher POC glucose on admission, cirrhosis, diabetes, CKD, and end-stage renal disease. Factors associated with decreased use of BB compared to SS were race/ethnicity other than White or Black, older age, surgical admitting physician, concurrent use of oral hypoglycemic agents, and coagulopathy. Factors associated with increased use of BO compared to SS were Medicare payer, surgical DRG, congestive heart failure, CKD, and end-stage renal disease. Factors associated with decreased use of BO compared to SS were race/ethnicity other than White or Black, older age, surgical admitting physician, oral hypoglycemic use, and steroids.

Glucose Control and Hospital Outcomes (Unadjusted)

Mean POC glucose across the hospital stay (Table 3) was highest in BB (193.64 mg/dL; 46.88, and lowest in BO 158.11 mg/dL; 33.87, $F = 107.99$, $P < .001$). The average number of hyperglycemic days was highest in BB (2.90; 2.67) and lowest in BO (1.77; 2.11, $F = 26.99$, $P < .001$).

The average number of hypoglycemic days was highest in BB (0.47; 0.98) and lowest in SS (0.18; 0.64, $F = 57.99$, $P < .001$). The average number of euglycemic days was highest in BO (4.52; 4.02) and lowest in BB (2.75; 3.33, $F = 42.97$, $P < .001$). The average LOS was longest in BO (7.14; 4.77) and shortest in BB (6.40; 4.60, $P = .021$).

Given the differences of a regimen with separately scheduled basal and bolus insulin with meals compared to a regimen of premixed insulin, we performed a separate analysis of hypoglycemia with the premix insulin group within the BB group. We assessed the difference in the number of hypoglycemic days between those who received premixed insulin (n = 39) vs those in the BB group who did not receive premixed insulin (n = 2319). There was no significant difference in the mean number of hypoglycemic days (BG < 70 mg/dL) ($P = .25$), clinically significant hypoglycemic days (BG < 54 mg/dL) ($P = .71$), and severe hypoglycemic days (BG < 40 mg/dL) ($P = .28$) between the 2 groups.

Readmission within 30 and 60 days and mortality rates did not differ across treatment groups. There were 6 deaths (0.3%) in the BB group, 4 (0.2%) in the SS group, and none in the BO group ($P = .64$).

Glucose Control and Hospital Outcomes (Adjusted by Propensity Score)

All glucose measures differed across treatment groups in propensity score–adjusted analysis (Table 4). The number of hyperglycemic days was lower in BO compared to SS (rate ratio [RR] = 0.70; 95% CI, 0.62-0.79), which equates to a 30% decrease in hyperglycemic days for BO compared to SS. BB and SS did not differ in hyperglycemia control. Patients on BB had 44% more hyperglycemic days than patients on BO ($\beta = .36$, $P < .001$). The number of hypoglycemic days was higher in BB and BO compared to SS but did not differ between the BB and BO groups. The number of euglycemic days was higher in BO compared to SS (RR = 1.22; 95% CI, 1.09-1.37), and lower in BB compared to SS (RR = 0.90; 95% CI, 0.85-0.97). This equates to a 22% increase in euglycemic days for BO compared

Table 1. Differences in patient and provider factors across treatment groups before and after propensity scores adjustment

Variable	Basal bolus	Sliding scale	Basal only	*P*	
	N = 2358	N = 1855	N = 345	Unadjusted	After PS
	Mean (SD)	Mean (SD)	Mean (SD)		
Age	62.31 (13.78)	65.69 (13.64)	63.08 (14.84)	< .001	.95
First POC glucose value	208.92 (92.20)	179.05 (69.05)	157.67 (66.96)	< .001	.84
	n (%)	n (%)	n (%)		
Sex: male	1212 (51.4)	936 (59.5)	184 (53.3)	.59	.99
Ethnicity					
White	1168 (49.5)	931 (50.2)	178 (51.6)	.001	.96
African American	638 (27.1)	434 (23.4)	104 (30.1)		
Other	552 (23.4)	490 (26.4)	63 (18.3)		
Marital status					
Married	1269 (53.8)	1028 (55.4)	193 (55.9)	.030	.99
Always single	511 (21.7)	332 (17.9)	72 (20.9)		
Currently single	578 (24.5)	495 (26.7)	80 (23.2)		
Surgical physician	401 (17.0)	500 (26.9)	59 (17.1)	< .001	.88
Payer type					
Medicare	607 (25.7)	476 (25.7)	79 (22.9)	.008	.99
Commercial	1468 (62.3)	1201 (64.7)	239 (69.3)		
Medicaid	138 (5.9)	72 (3.9)	17 (4.9)		
Other	145 (6.1)	106 (5.7)	10 (2.9)		
Surgical DRG (vs medical)	605 (25.7)	619 (33.4)	123 (35.7)	< .001	.40
Received oral antidiabetic	398 (16.9)	639 (34.5)	55 (15.9)	< .001	.81
Received steroids	759 (32.2)	561 (30.2)	86 (24.9)	.018	.98
Diagnosis present on admission					
AKI	520 (22.1)	302 (16.3)	64 (18.6)	< .001	.98
ASCVD	432 (18.3)	291 (15.7)	60 (17.4)	.079	.85
CHF	681 (28.9)	467 (25.2)	114 (33.0)	.002	.88
Cirrhosis	219 (9.3)	122 (6.6)	33 (9.6)	.004	.79
CKD	665 (28.2)	419 (22.6)	114 (33.0)	< .001	.88
Coagulopathy	251 (10.6)	230 (12.4)	41 (11.9)	.20	.79
Diabetes	2055 (87.2)	1520 (81.9)	287 (83.2)	< .001	.22
ESRD	264 (11.2)	123 (6.6)	65 (18.8)	< .001	.95
Hypertension	1088 (46.1)	1004 (54.1)	122 (35.4)	< .001	.62
Palliative	23 (1.0)	17 (0.9)	0 (0)	.100	.92

Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; DRG, diagnostic related group; ESRD, end-stage renal disease; POC, point of care; PS, propensity scores.

to SS, and 10% decrease in euglycemic days for BB compared to SS. The number of euglycemic days was 21% less in BB compared to BO (β = –.23, *P* = .008). Euglycemic days were not different for BB compared to SS (*P* = .97). The mean POC glucose across hospital stay was lower in BO (β = –18.03, *P* < .001) compared to SS, and was not different between BB and SS. The mean POC glucose was higher in BB compared to BO (β = 18.29, *P* < .001). Readmission within 30 and 60 days and LOS were not different across treatment groups in the overall population.

In stratified analysis (see Table 4), results were like the overall cohort, indicating that medical and surgical DRG patients had similar outcomes, with the following 2 exceptions: LOS was lower in BB (β = –.07, *P* < .001) compared to SS in medical DRG patients (n = 3211). This equates to a 7% decrease in LOS for BB compared to SS.

Discussion

To our knowledge, this study is the first large-scale investigation to compare strategies of inpatient glucose control and hospital outcomes in a real-world setting. After accounting for more than 20 patient and provider variables with propensity score analysis, we found that patients receiving BO had the lowest hyperglycemic days, more euglycemic days, and lower mean POC glucose, but at the expense of higher hypoglycemia than SS. Contrary to the RABBIT 2 trials, BB was inferior to SS in the real-world

Table 2. Multivariable association of each patient and provider factor with initial treatment choice

Variable	Basal bolus vs sliding scale		Basal only vs sliding scale	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex: female vs male	0.97 (0.84-1.11)	.62	0.88 (0.68-1.12)	.30
Ethnicity				
African American vs White	0.89 (0.75-1.05)	.169	0.92 (0.68-1.23)	.56
Other vs White	0.77 (0.65-0.90)	.001	0.57 (0.42-0.79)	.001
Age	0.98 (0.97-0.99)	< .001	0.98 (0.97-0.99)	< .001
Marital status				
Always single vs married	0.99 (0.83-1.20)	.99	0.97 (0.70-1.35)	.85
Currently single vs married	0.97 (0.83-1.14)	.74	0.92 (0.68-1.25)	.60
First POC glucose value	1.00 (1.00-1.01)	< .001	0.99 (0.99-0.99)	< .001
Physician type at admit: surgical vs medical	0.69 (0.57-0.83)	< .001	0.56 (0.39-0.79)	.001
Payer type				
Medicare vs commercial	1.12 (0.94-1.34)	.190	1.33 (0.96-1.83)	.083
Medicaid vs commercial	1.11 (0.80-1.55)	.52	1.28 (0.70-2.35)	.43
Other vs commercial	1.10 (0.82-1.49)	.52	0.71 (0.35-1.43)	.33
DRG type: surgical vs medical	0.87 (0.74-1.02)	.090	1.40 (1.06-1.85)	.018
Received oral antidiabetic	0.40 (0.34-0.47)	< .001	0.45 (0.33-0.62)	< .001
Received steroids	1.11 (0.95-1.28)	.190	0.67 (0.51-0.90)	.007
Comorbidities present on admission				
AKI	1.14 (0.95-1.37)	.156	0.84 (0.60-1.17)	.30
ASCVD	1.10 (0.92-1.32)	.31	0.79 (0.57-1.11)	.171
CHF	1.10 (0.94-1.29)	.25	1.30 (0.98-1.71)	.067
Cirrhosis	1.35 (1.06-1.73)	.017	1.47 (0.96-2.24)	.078
CKD	1.41 (1.12-1.76)	.003	1.90 (1.26-2.87)	.002
Coagulopathy	0.75 (0.61-0.92)	.005	0.81 (0.56-1.18)	.27
Diabetes	1.84 (1.52-2.22)	< .001	1.15 (0.82-1.61)	.42
ESRD	1.71 (1.28-2.27)	< .001	2.71 (1.70-4.31)	< .001
Hypertension	1.09 (0.90-1.32)	.37	0.92 (0.63-1.33)	.64

Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; DRG, diagnostic related group; ESRD, end-stage renal disease; OR, odds ratio; POC, point of care.

Table 3. Unadjusted association of glucose control within treatment groups

Variable	Basal bolus	Sliding scale	Basal only	*P*
	N = 2358	N = 1855	N = 345	
	Mean (SD)	Mean (SD)	Mean (SD)	
Mean POC glucose	193.64 (46.88)	185.32 (38.63)	158.11 (33.87)	< .001
Hyperglycemic d	2.90 (2.67)	2.71 (2.77)	1.77 (2.11)	< .001
Hypoglycemic d	0.47 (0.98)	0.18 (0.64)	0.66 (1.11)	< .001
Euglycemic d	2.75 (3.33)	3.29 (3.55)	4.52 (4.02)	< .001
Length of stay	6.40 (4.60)	6.49 (4.67)	7.14 (4.77)	.021

Abbreviation: POC, point of care.

with no difference in hyperglycemia, less euglycemia, and increased hypoglycemia. However, despite the worse glucose control, BB did have the better outcome of a lower LOS than SS in patients admitted for a medical DRG.

Recommendations to replace the outdated and ineffective practice of SS with BB in inpatient glucose management has been advocated for more than a decade. However, there is inertia for universally adopting BB in daily practice while other strategies are being used in the real world. The type of insulin strategy used depends on the many differences we found between groups both in patients and providers. The RABBIT 2 trials that demonstrated

Table 4. Glucose control and hospital outcomes after adjustment by propensity scores[a], overall and stratified by diagnostic related group

Insulin groups	Overall (N = 4558)	Medical DRG (N = 3211)	Surgical DRG (N = 1347)
30-d readmission[b]			
BB vs SS	0.96 (0.81 to 1.13) (.62)	1.01 (0.83 to 1.23) (.90)	0.80 (0.57 to 1.13) (.20)
BO vs SS	0.96 (0.71 to 1.30) (.79)	1.10 (0.78 to 1.57) (.58)	0.66 (0.36 to 1.18) (.16)
60-d readmission[b]			
BB vs SS	0.99 (0.86 to 1.16) (.99)	1.00 (0.84-1.19) (.99)	0.98 (0.73 to 1.31) (.87)
BO vs SS	0.91 (0.70 to 1.19) (.50)	0.99 (0.72 to 1.37) (.98)	0.71 (0.43 to 1.18) (.19)
Length of stay[b]			
BB vs SS	0.96 (0.92 to 0.99) (.06)	0.93 (0.89 to 0.97) (< .001)	1.02 (0.94 to 1.09) (.69)
BO vs SS	1.06 (1.01 to 1.16) (.06)	1.05 (0.96 to 1.14) (.29)	1.07 (0.95 to 1.21) (.32)
Hyperglycemic d[b]			
BB vs SS	0.98 (0.92 to 1.04) (.56)	0.97 (0.90 to 1.04) (.32)	0.99 (0.89 to 1.10) (.85)
BO vs SS	0.70 (0.62 to 0.79) (< .001)	0.70 (0.60 to 0.82) (< .001)	0.69 (0.57 to 0.84) (< 0.001)
Hypoglycemic d[b]			
BB vs SS	2.40 (2.04 to 2.82) (< .001)	2.28 (1.88 to 2.75) (< .001)	2.76 (2.02 to 3.77) (< .001)
BO vs SS	2.80 (2.17 to 3.61) (< .001)	2.43 (1.77 to 3.33) (< .001)	3.53 (2.28 to 5.46) (< .001)
Euglycemic d[b]			
BB vs SS	0.90 (0.85 to 0.97) (.003)	0.85 (0.78 to 0.92) (< .001)	1.00 (0.88 to 1.13) (.97)
BO vs SS	1.22 (1.09 to 1.37) (< .001)	1.18 (1.02 to 1.36) (.020)	1.25 (1.03 to 1.52) (.030)
Mean glucose[c]			
BB vs SS	0.92 (–1.50 to 3.34) (.46)	1.46 (–1.50 to 4.43) (.33)	–1.14 (–5.45 to 3.16) (.60)
BO vs SS	–18.03 (–22.46 to –12.61) (< .001)	–18.78 (–24.39 to –13.16) (< .001)	–16.74 (–24.04 to –9.45) (< .001)

All results are presented as estimate (95% CI) and *P* values.

Abbreviations: BB, basal bolus; BO, long only; DRG, diagnostic related group; SS, sliding scale.

[a]Variables included in the propensity score are from Table 1.

[b]Results shown are exponentiated coefficients interpreted relative to 1.0.

[c]Results shown are coefficients interpreted as mean effects.

evidence for BB over SS were in a homogenized population of patients with only type 2 diabetes mellitus and without advanced liver, cardiac, kidney disease, or on corticosteroid therapy. In the real-world setting, the most common hospital scenario is the coexistence of diabetes with organ dysfunction that plays a significant role in choice and the outcome of insulin therapy. Furthermore, concurrent use of diabetogenic therapies also affects management. Our study is the first to outline the significant patient and provider characteristics that influence the choice of insulin therapy on admission within the first 48 hours and its impact on patient outcomes throughout the hospitalization. As a result of our findings, we propose that a universal practice of BB may be too difficult to achieve in the real-world setting and, in fact, does not result in the best outcome for all patients. Patient and provider factors must be further investigated before the widespread adoption of BB as the best practice for management of all inpatient hyperglycemia. The BB insulin regimen is complex, with 4 to 5 injections daily, and is highly dependent on coordination with nutritional intake for optimal effect. This can be a major challenge in the hospital environment where the patient can be on a rapidly changing nutrition plan for procedures or have highly variable oral intake because of illness or medication side effects. Additionally, the optimal efficacy of BB insulin therapy requires careful timing and coordination of glucose measurement with insulin administration immediately prior to meal consumption. Given that most US hospitals allow their patients to order meals on demand at various times, nursing staff may not be aware of when the patient consumes the meal. This often results in mistiming of insulin administration, which can cause harm to the patient with unintended hypoglycemia and hyperglycemia. BB must also be assessed and dosed daily, requiring close coordination and titration during frequent changes in medications, nutritional status, and physiology because of the patient's illness. While this can be achieved with the expertise of a research team in a study environment or in consultation with an endocrinologist or trained diabetes team, it may not be possible by a general admitting physician. Therefore, simplified insulin regimens such as BO may have the best compliance and glucose control when compared both to SS and BB.

Outside the 2 small, randomized, controlled RABBIT 2 trials, the advantages of BB have not been clearly established in noncritically ill patients with respect to glycemic

control and patient outcomes. In a systematic review, Colunga-Lozano and colleagues included 8 randomized, controlled trials of 1048 individuals with type 2 diabetes in noncritically ill medical and surgical adults [31]. They found increased severe hypoglycemia (defined as blood glucose < 40 mg/dL) in the BB group at a rate of 24 per 1000 people compared to 5 per 1000 people in the SS group. The SS group had a 14.8-mg/dL higher average blood glucose and 0.5-day longer hospital stay than the BB groups. However, with further analysis, the authors could not conclude a clear advantage or disadvantage of either insulin strategy and had low or very low confidence in the results because of the minimal number of studies, study participants, and imprecise results. As a larger, natural study, 10 120 noncritically ill adults with type 2 diabetes admitted to a single academic hospital and examined before and after implementation of a BB insulin therapy protocol were compared to 30 271 controls without diabetes. Despite decreasing days with hypoglycemia of less than 70 mg/dL by 32%, ($P < .01$) and days with hyperglycemia of greater than 300 mg/dL ($P < .01$) by 16%, there was no improvement in intensive care use, hospital complications, mortality, or medial LOS with BB treatment. An exception though was in a small group of 234 patients with newly diagnosed type 2 diabetes who had a decrease of 18.7% in complications ($P < .01$) [32]. To date, it is still unclear which insulin regimen and corresponding glycemic control will translate to benefits in patient outcomes of clinical significance. Moreover, these studies were all in patients identified with type 2 diabetes and do not include hyperglycemia caused by other medical therapies or conditions (eg, corticosteroids, enteral or parenteral nutrition, cystic fibrosis, organ transplantation). In the real-world practice, it is even more elusive which patients will benefit from BB vs other types of insulin regimens. Nevertheless, we do not advocate reverting to the historical use of SS, which has been proven to be ineffective for glycemic control and results in worse patient outcomes. Our findings support that on a large scale, a simpler regimen of basal insulin alone is adequate in providing the reduction in hyperglycemia and its intended benefits in patient outcomes. In fact, Umpierrez et al had similar findings in the Basal Plus study indicating that basal insulin alone is as effective and safe as BB in glucose control [25]. However, this regimen would clearly not be appropriate for the subset of patients for whom scheduled prandial insulin is necessary, such as those with type 1 diabetes or type 2 with hyperglycemia related to nutrition. Further investigation is needed in identifying the key clinical variables to guide clinicians on the optimal insulin strategy on admission. These should include historical information such as type of diabetes, A1C on admission, preadmission diabetes medications, and prior comorbidities, while also accounting for acute variables such as admission glucose, changes in organ function, nutritional status, and glycemic effects of new medications used during the hospitalization. Our study highlights the numerous factors that contribute to the choice of insulin therapy at admission and illustrates the complexity of glucose management in real-world practice in achieving the outcomes demonstrated in the limited clinical trials. A simpler regimen, such as addition of basal insulin alone without the complex regimen of basal with scheduled prandial bolus, and correction bolus may be a more effective strategy in most patients with hyperglycemia as a universal approach, at least initially.

The strengths of our study include a large sample size of more than 4500 inpatient admissions, with incorporation of more than 20 different variables commonly present in hospital patients, including patient demographics, pertinent clinical comorbidities, baseline admission glucose levels, and use of oral hypoglycemic agents and steroids. We included patients who only received insulin for 75% or more of their hospital days and excluded patients managed with intravenous insulin and in the intensive care unit. We compared several measures of glucose control and relevant hospital outcomes. Our analyses used state-of-the-art propensity score methods to adjust for case-mix factors that differed substantially across treatment groups, thus improving causal inference and internal validity. With more than 4500 inpatients from both medical and surgical DRGs, our study also addresses limitations of RCTs, including improved external validity and generalization of findings to real-world practice.

Nevertheless, our findings should be interpreted considering some potential limitations. Our study analyzed the initial therapy choice within the first 48 hours of hospital admission; however, patients could have subsequently switched back and forth between therapies several times, reflecting the dynamic nature of real-world hospital glucose management. Our study did not attempt to model this very complicated process. Although we employed propensity score adjustment of many pertinent patient and provider factors that would be used to select the type of insulin therapy on admission, we did not have data available on prior diabetes control. Only 45% of admissions had an A1C value and therefore we were not able to include it in the analysis. Similarly, we did not have preadmission diabetes medications available. Therefore, it is also possible that some residual confounding factors remain that may bias the treatment effect estimates; however, we believe that our adjustment for more than 20 patient and provider factors would minimize such bias. While our BO group was statistically significant, it represented only 7.6% of the overall admissions. A larger RCT would be needed to establish

its effectiveness. Additionally, it must be noted that a BO regimen is not appropriate for all patients. In conditions such as type 1 diabetes or poorly controlled diabetes requiring basal and bolus insulin therapy prior to admission, bolus insulin with carbohydrate intake is more appropriate.

The management of glucose control in hospitalized patients is very complex and influenced by many factors. The recommended basal and bolus insulin regimen may not be the best strategy in all patients and in fact, because of its own complexity, may be harmful if not executed correctly. We advocate a simpler regimen of basal insulin alone as a general strategy in the hospital setting because it requires less coordination of care, while being more effective in reducing hyperglycemia than SS, at least in those patients without high risk for postprandial hyperglycemia. At the very least, more investigation is needed to identify specific inpatient populations that would benefit from different insulin strategies.

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Additional Information

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