Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes (RABBIT 2 Trial)

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OBJECTIVE — We sought to study the optimal management of hyperglycemia in non–intensive care unit patients with type 2 diabetes, as few studies thus far have focused on the subject.

RESEARCH DESIGN AND METHODS — We conducted a prospective, multicenter, randomized trial to compare the efficacy and safety of a basal-bolus insulin regimen with that of sliding-scale regular insulin (SSI) in patients with type 2 diabetes. A total of 130 insulin-naive patients were randomized to receive glargine and glulisine ($n = 65$) or a standard SSI protocol ($n = 65$). Glargine was given once daily and glulisine before meals at a starting dose of 0.4 units · kg^{-1} · day^{-1} for blood glucose 140–200 mg/dl or 0.5 units · kg^{-1} · day^{-1} for blood glucose 201–400 mg/dl. SSI was given four times per day for blood glucose >140 mg/dl.

RESULTS — The mean admission blood glucose was 229 ± 6 mg/dl and A1C 8.8 ± 2%. A blood glucose target of <140 mg/dl was achieved in 66% of patients in the glargine and glulisine group and in 38% of those in the SSI group. The mean daily blood glucose between groups ranged from 23 to 58 mg/dl, with an overall blood glucose difference of 27 mg/dl ($P < 0.01$). Despite increasing insulin doses, 14% of patients treated with SSI remained with blood glucose >240 mg/dl. There were no differences in the rate of hypoglycemia or length of hospital stay.

CONCLUSIONS — Treatment with insulin glargine and glulisine resulted in significant improvement in glycemic control compared with that achieved with the use of SSI alone. Our study indicates that a basal-bolus insulin regimen is preferred over SSI in the management of non–critically ill, hospitalized patients with type 2 diabetes.

Hyperglycemia in hospitalized patients is a common, serious, and costly health care problem with profound medical consequences. Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiologic or benign condition but is a marker of poor clinical outcome and mortality (1–3). Extensive evidence from observational studies, including our own, indicates that in hospitalized patients with critical illness, hyperglycemia is associated with an increased risk of complications and mortality (3–9). Prospective randomized trials in critically ill patients have shown that intensive glucose control reduces the risk of multiorgan failure, systemic infections, and short- and long-term mortality. Effective management of hyperglycemia is also associated with a decreased length of intensive care unit and hospital stay (4,6,8–10) and decreased total hospitalization cost (11). The importance of glycemic control on outcome is not limited to patients in critical care areas but also applies to patients admitted to general surgical and medical wards. In such patients, the presence of hyperglycemia has been associated with prolonged hospital stay, infection, disability after hospital discharge, and death (1,5,12). In general surgery patients, the relative risk for serious postoperative infections (sepsis, pneumonia, and wound infection) increased 5.7-fold when any postoperative day 1 blood glucose was >220 mg/dl (12). More recently, studies in patients with community-acquired pneumonia reported that hyperglycemia was associated with increased risk of in-hospital complications and mortality (13,14).

Insulin, given either intravenously as a continuous infusion or subcutaneously, is the most effective agent for immediate control of hyperglycemia in the hospital. In the critical care setting, a variety of continuous insulin infusion protocols have been shown to be effective in achieving glycemic control, with a low rate of hypoglycemic events, and in improving hospital outcomes (6,10,15). In general medicine and surgery services, however, hyperglycemia is frequently overlooked and inadequately addressed. Several reports from academic institutions have shown that most patients are treated with SSI and that basal insulin is prescribed in less than one-half of patients (16,17). Few clinical trials have focused on the optimal management of inpatient hyperglycemia in the noncritical setting. Accordingly, we conducted this prospective, randomized study to compare the efficacy and safety of a basal-bolus insulin regimen with that of SSI in patients with type 2 diabetes admitted to general medicine wards.
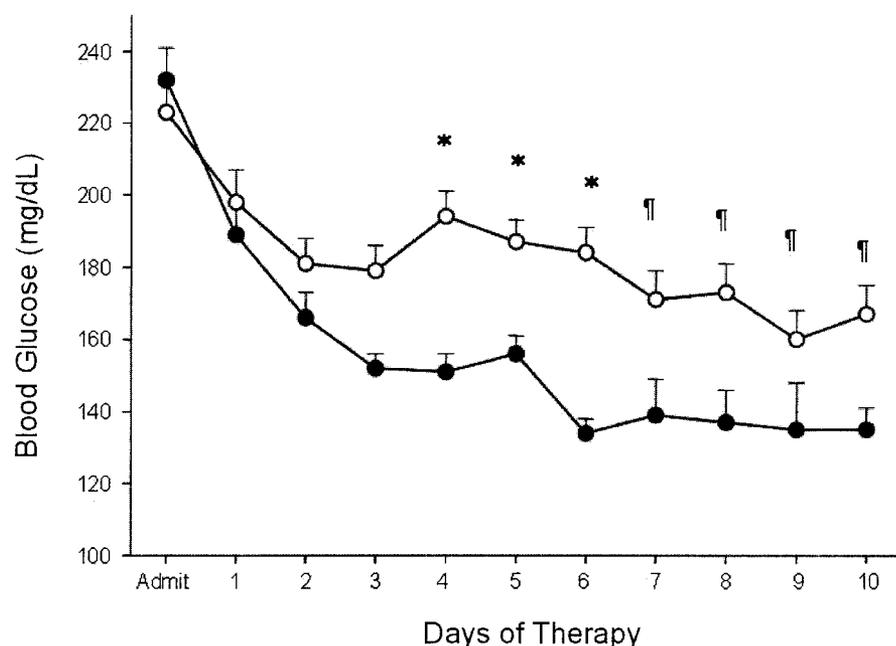
Figure 1—*Changes in blood glucose concentrations in patients treated with glargine plus glulisine (●) and with SSI (○). *P < 0.01; ¶P < 0.05.*

RESEARCH DESIGN AND METHODS

In this multicenter, prospective, open-label, randomized study, we enrolled 130 nonsurgical, insulin-naive patients with a known history of diabetes for >3 months, aged 18–80 years, and admitted to medical general services with a blood glucose level between 140 and 400 mg/dl. Further inclusion criteria included diabetes treatment with either diet alone or any combination of oral antidiabetic agents and the absence of diabetic ketoacidosis (18). Exclusion criteria included subjects without a known history of diabetes, intensive care unit patients, the use of corticosteroid therapy, subjects expected to undergo surgery during the hospitalization course, patients with clinically relevant hepatic disease, serum creatinine ≥3.0 mg/dl, pregnancy, and any mental condition rendering the subject unable to understand the scope and possible consequences of the study.

This study was conducted at Grady Memorial Hospital in Atlanta, Georgia, and at the Jackson Memorial Hospital in Miami, Florida. The institutional review boards at Emory University and the University of Miami approved the study protocol. All patients were managed by members of the internal medicine residency program, who received a copy of the assigned treatment protocol. The primary care team decided the treatment for the medical problem(s) for which patients were admitted. No follow-up visit after discharge was included in this study. A teaching endocrinologist rounded daily with the house officers.

Patients were randomly assigned to receive either SSI or a basal-bolus regimen with insulins glargine and glulisine (Lantus and Apidra, respectively; Sanofi-Aventis, Bridgewater, NJ). Oral antidiabetic drugs were discontinued on admission. Patients treated with glargine and glulisine were started at a total daily dose of 0.4 units/kg for blood glucose concentration between 140 and 200 mg/dl or 0.5 units/kg for those between 201 and 400 mg/dl (Table 1). One-half of the total daily dose was given as glargine once daily, and the other half was given as glulisine before meals. Insulin glulisine was given in three equally divided doses before each meal. To prevent hypoglycemia, if a patient was not able to eat, the dose of insulin glargine was given but the premeal insulin glulisine held until meals were resumed. The daily dose of insulin glargine was increased by 20% if the fasting and premeal blood glucose measurements were >140 mg/dl. The dose of insulin glargine was reduced by 20% after an episode of hypoglycemia (<70 mg/dl). Supplemental insulin with insulin glulisine was given in addition to the scheduled premeal insulin for blood glucose >140

mg/dl per the sliding-scale protocol (Table 1).

Patients randomized to SSI received regular insulin four times daily for glucose levels >140 mg/dl (Table 1). Patients able to eat received regular insulin before each meal and at bedtime according to the "usual" column of the sliding-scale protocol. Patients not able to eat received regular insulin every 6 h, following the "insulin sensitive" column. If fasting and premeal plasma glucose levels remained persistently >140 mg/dl in the absence of hypoglycemia, the insulin dosing was progressively increased from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin resistant" column. If the mean daily blood glucose level was >240 mg/dl, or if three consecutive values were >240 mg/dl on the maximal sliding-scale dose, patients were switched to a basal-bolus regimen starting at a total daily dose of 0.5 units/kg. If a patient on SSI developed hypoglycemia, the insulin scale was decreased from the "insulin resistant" to the "usual" column or from the "usual" to the "insulin sensitive" column.

Blood glucose was measured before each meal and at bedtime (or every 6 h if a patient was not eating) using a glucose meter. In addition, glucose was measured at any time if a patient experienced symptoms of hypoglycemia. A1C level was measured on the first day of hospitalization. The results of blood glucose measurements are presented as fasting glucose, random glucose (nonfasting glucose measured at any time during the day), and mean blood glucose during the hospital stay (all glucose values during the hospital stay).

The goal of insulin therapy was to maintain fasting and premeal blood glucose levels <140 mg/dl while avoiding hypoglycemia. The primary end point was to determine differences in glycemic control between treatment groups as measured by the mean daily blood glucose concentration. Secondary outcomes include differences between treatment groups in number of hypoglycemic events, number of episodes of severe hyperglycemia, length of hospital stay, and mortality rate.

Statistical analysis was performed using the SPSS software package. Change in blood glucose during the study period was analyzed by repeated-measures ANOVA. A P value of <0.05 was considered significant.

Table 1—*Insulin treatment protocols*

A. Basal-bolus regimen with insulin glargine and glulisine
- Discontinue oral antidiabetic drugs on admission.
- Start total daily insulin dose:
  0.4 units $\cdot$ kg body wt^{-1} $\cdot$ day^{-1} when the admission blood glucose concentration is 140-200 mg/dl
  0.5 units $\cdot$ kg body wt^{-1} $\cdot$ day^{-1} when the admission blood glucose concentration is between 201-400 mg/dl
- Give one-half of total daily dose as insulin glargine and one-half as insulin glulisine.
- Give insulin glargine once daily at the same time of the day.
- Give insulin glulisine in three equally divided doses before each meal. Hold insulin glulisine if patient is not able to eat.

Supplemental insulin
  Give supplemental insulin glulisine following the "sliding-scale" protocol for blood glucose >140 mg/dl.
- If a patient is able and expected to eat all or most of his/her meals, give supplemental glulisine insulin before each meal and at bedtime following the "usual" column.
- If a patient is not able to eat, give supplemental glulisine insulin every 6 h (6–12–6–12), following the "insulin-sensitive" column.

Insulin adjustment
- If the fasting or mean blood glucose during the day is >140 mg/dl in the absence of hypoglycemia, increase insulin glargine dose by 20% every day.
- If patient develops hypoglycemia (<70 mg/dl), decrease glargine daily dose by 20%.

Blood glucose monitoring
  Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).

B. Sliding scale regimen with regular insulin
- Discontinue oral antidiabetic drugs on admission.
- If patient is able and expected to eat all or most of his/her meals, give regular insulin before each meal and at bedtime, following the "usual" column.
- If patient is not able to eat, give regular insulin every 6 h (6–12–6–12), following the "insulin sensitive" column.

Insulin adjustment
- If fasting and premeal plasma glucose are persistently >140 mg/dl in the absence of hypoglycemia, increase insulin scale from the "insulin sensitive" to the "usual" column or from the "usual" to the "insulin-resistant" column.
- If a patient develops hypoglycemia (blood glucose <70 mg/dl), decrease regular insulin from "insulin-resistant" to "usual" column or from the "usual" to "insulin-sensitive" column.

Blood glucose monitoring
  Measure blood glucose before each meal and at bedtime (or every 6 h if n.p.o.).

C. Supplemental insulin scale

	□ Insulin sensitive	□ Usual	□ Insulin resistant
Blood glucose (mg/dl)			
>141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
>400	14	16	18

Check appropriate column and cross out other columns. The numbers in each column indicate the number of units of glulisine or regular insulin per dose. Supplemental dose is to be added to the scheduled dose of glulisine or regular insulin.

RESULTS — A total of 130 insulin-naive patients with type 2 diabetes admitted to general medicine services were recruited. Of these, 65 patients were randomized to receive insulin glargine and glulisine and 65 to receive SSI. The clinical characteristics of study patients are shown in Table 2. There were no significant differences in the mean age, racial distribution, BMI, admission blood glucose, or A1C between treatment groups. The most common admitting illnesses included a variety of cardiovascular (40%), infectious (20%), pulmonary (18%), re-nal (4%), and gastrointestinal (12%) disorders. The mean hospital length of stay was 5.3 ± 6 days in patients treated with basal-bolus and 5.1 ± 4 days in the SSI-treated group (P = NS). Only one death was reported in a patient in the basal-bolus treatment group who was admitted with shortness of breath and later developed respiratory failure secondary to a pulmonary embolism.

Patients treated with insulin glargine and glulisine had greater improvement in glycemic control than those treated with SSI (P < 0.01) (Fig. 1). The mean admis-sion blood glucose for study patients was 227 ± 65 mg/dl and the mean A1C 8.8 ± 2%. The mean admission glucose values in the glargine and glulisine and SSI treatment groups were 229 ± 71 and 225 ± 60 mg/dl, respectively (P = NS). Compared with the basal-bolus regimen treatment, treatment with SSI was associated with higher mean fasting glucose (165 ± 41 vs. 147 ± 36 mg/dl, P < 0.01), mean random glucose (189 ± 42 vs. 164 ± 35 mg/dl, P < 0.001), and mean glucose during the hospital stay (193 ± 54 vs. 166 ± 32 mg/dl, P < 0.001). The mean

Table 2—Baseline clinical characteristics*

	Basal bolus	SSI
n	65	65
Age (years)	56 ± 13	56 ± 11
Race (white/black/Hispanic)	4/43/18	3/48/14
Sex (male/female)	42/23	21/44
BMI (kg/m^2)	32 ± 8	32 ± 9
Length of hospital stay (days)	5.2 ± 6	5.1 ± 4
White blood cell ×10^6	9.6 ± 4	8.7 ± 4
Hemoglobin (g)	13 ± 2	12.6 ± 2
Creatinine (mg/dl)	1.0 ± 0.5	1.1 ± 0.5
A1C (%)	8.9 ± 2	8.7 ± 2.5
Admission blood glucose (mg/dl)	229 ± 71	225 ± 60
Mean blood glucose during hospital stay (mg/dl)	166 ± 32	193 ± 54*
Mean fasting blood glucose (mg/dl)	147 ± 36	165 ± 41†
Mean random blood glucose (mg/dl)	164 ± 35	188 ± 45*

Data are means ± SD unless otherwise indicated. *$P < 0.001$. †$P < 0.01$.

glucose concentration during the last day of hospitalization was significantly higher in patients treated with SSI compared with that in patients treated with the basal-bolus regimen (187 vs. 140 mg/dl, $P < 0.001$). The overall inpatient blood glucose difference between treatment groups was 27 mg/dl ($P < 0.01$), with a mean daily blood glucose difference ranging from 23 to 58 mg/dl during days 2–6 of therapy ($P < 0.01$). The percentage of patients within the mean glucose target (<140 mg/dl) was 66% in patients treated with glargine and glulisine versus 38% in those treated with SSI.

Nine (14%) patients treated with SSI remained with blood glucose >240 mg/dl despite increasing the SSI dose to the maximal or insulin-resistant scale (Fig. 2). Compared with the remaining patients treated with SSI, these patients (aged 57 ± 10 years, BMI 29 ± 7 kg/m^2) had a higher but not significant difference in mean admission glucose (252 ± 73 vs. 220 ± 57 mg/dl, respectively, $P = 0.1$). Glycemic control rapidly improved in all of the SSI failure subjects after they were switched to the basal-bolus insulin regimen.

The mean insulin daily dose was significantly higher in the basal-bolus regimen compared with that in the SSI treatment group ($P < 0.001$). The mean daily dose of insulin glargine was 22 ± 2 units, and the daily dose of insulin glulisine was 20 ± 1 units. A total of 26 patients had the lantus dose adjusted, and 44 patients required supplemental glulisine insulin during the hospital stay. Patients treated with SSI received a mean daily dose of 12.5 ± 2 units regular insu-

lin/day, with approximately one-half of patients receiving <10 units/day.

Hypoglycemia (defined as blood glucose <60 mg/dl) occurred in two patients in each treatment group. Of the 1,005 glucose readings in the insulin glargine and glulisine treatment group, there were only four (0.4%) glucose values <60 mg/dl and no glucose values <40 mg/dl. Of the 1,021 glucose readings in the SSI group, there were only only two (0.2%) glucose values <60 mg/dl and no glucose values <40 mg/dl. Hypoglycemia was

corrected with oral dextrose, and none of these episodes was associated with adverse outcomes.

CONCLUSIONS — This is the first prospective randomized clinical trial aimed to compare the efficacy and safety of a basal-bolus insulin regimen with that of SSI in non–critically ill patients with type 2 diabetes. We observed that treatment with insulin glargine and glulisine results in a significant improvement in glycemic control compared with that re-
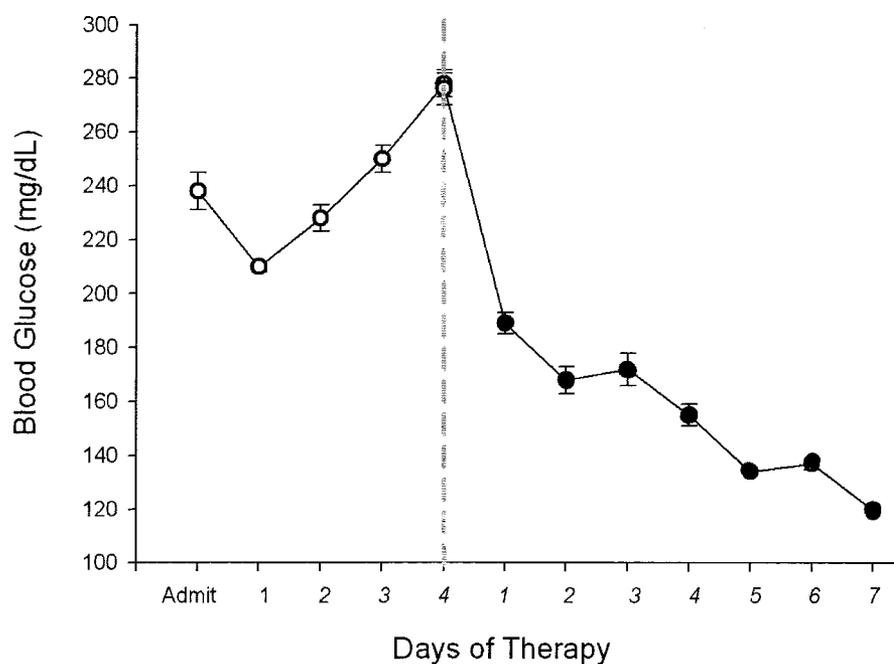
Figure 2—*Mean blood glucose concentration in subjects who remained with severe hyperglycemia despite increasing doses of regular insulin per the sliding-scale protocol (○). Glycemic control rapidly improved after switching to the basal-bolus insulin regimen (●). P < 0.05.*

sulting from the sole use of SSI. The mean daily glucose difference between groups ranged from 23 to 58 mg/dl during days 2–6 of therapy. A blood glucose target of <140 mg/dl was achieved in two-thirds of patients treated with insulin glargine and glulisine, whereas only one-third of those treated with SSI achieved target glycemia. Despite increasing insulin doses, 14% of patients treated with SSI had persistently elevated glucose levels >240 mg/dl. In such patients, glycemic control rapidly improved after switching to the basal-bolus insulin regimen. Based on these results, we conclude that a basal-bolus insulin regimen is preferred over SSI alone in the management of non–critically ill patients with type 2 diabetes.

Differences in glycemic control between treatment groups can be explained by the fact that an SSI regimen treats hyperglycemia after it has already occurred instead of preventing the occurrence of hyperglycemia (2,5,19). In addition, we found significant differences in daily insulin dose between patients treated with the basal-bolus regimen compared with that in the SSI treatment group. Patients randomized to receive insulin glargine and glulisine received an approximately three times higher total insulin dose (~40 units/day) than those treated with SSI (~15 units/day). Despite the higher insulin dose and improved glycemic control, the use of the basal-bolus insulin regimen was safe and was associated with a low rate of hypoglycemic events. The overall rate of hypoglycemia (<60 mg/dl) occurred in 3% of patients in each treatment group, and no cases of hypoglycemia were associated with clinical adverse outcome. There were no episodes of severe hypoglycemia (glucose <40 mg/dl) in either treatment group. Minimizing the rate of severe hypoglycemia events is of major importance in hospitalized patients because they have been shown to be an independent risk factor for poor clinical outcomes (12).

Despite increasing evidence in support of intensive glycemic control in critically ill patients, glucose control continues to be deficient and is frequently overlooked in general medicine and surgery services (1,2,5). Many factors could explain the lack of glycemic control in the hospital. First, the overwhelming majority of hospitalizations in patients with hyperglycemia occur for a variety of comorbid conditions (1,2,20), with <10% of hospital discharges in the U.S. listing diabetes as the primary diagnosis

(5). Second, physicians often perceive hyperglycemia as a consequence of stress and acute illness and often delay treatment until blood glucose levels exceed 200 mg/dl (2,21). Third, fear of hypoglycemia constitutes a major barrier to efforts to improve glycemic control, especially in patients with poor caloric intake (5,22). Finally, physicians frequently hold their patient's previous outpatient antidiabetes regimen and initiate sliding-scale coverage with regular insulin, a practice associated with limited therapeutic success and suboptimal glycemic control (16,17, 23,24).

The use of SSI was first introduced by Elliot P. Joslin shortly after the discovery of insulin (25). He recommended giving regular insulin per sliding scale according to the amount of glycosuria. Following the introduction of capillary blood glucose monitoring in the 1970s, urinary algorithms were abandoned, and different algorithms became available using blood glucose targets (26,27). Although these algorithms were not intended to be used as the sole method of insulin administration, they were rapidly modified and adopted by practitioners and resulted in the sliding-scale algorithms currently available. Potential advantages of SSI are convenience, simplicity, and promptness of treatment. It is possible that in some patients with good glycemic control treated with diet alone or with oral antidiabetic agents before admission or in subjects with mild hyperglycemia kept n.p.o., the use of SSI may be sufficient for glycemic control over the short term. The use of SSI, however, as a single insulin regimen in hospitalized subjects has never been associated with improved clinical outcome (23,28–30). Yet this remains the most popular default regimen in the majority of institutions across the country.

We acknowledge the following limitations in this study. We excluded patients without a known history of diabetes before admission. Patients meeting these criteria make up a substantial percentage of hospitalized patients. We recently reported that hyperglycemia was present in 38% of patients admitted to the hospital and that one-third of these patients had no history of diabetes before the admission (1). We also excluded patients treated with insulin and corticosteroids because they were considered at higher risk of severe hyperglycemia if treated with SSI. Another limitation is that the study was not powered to demonstrate

differences in mortality or clinical outcome between treatment groups. A large prospective randomized clinical trial of strict glycemic control is certainly needed to address these important issues. Such studies should include additional treatment regimes including the use of basal insulin alone (glargine, detemir, or NPH insulin) and fixed, regular doses of regular insulin.

In summary, our basal-bolus insulin algorithm using insulin glargine once daily and insulin glulisine before meals represents a simple and more effective regimen than SSI for glucose control in non–critically ill patients with type 2 diabetes. Despite the simplicity of SSI, this regimen fails to provide adequate glycemic control and should not be used in the management of hospitalized subjects with diabetes. Implementing standardized subcutaneous insulin order sets promoting the use of scheduled insulin therapy and discouraging the sole use of SSI are key interventions that might reduce complications associated with severe hyperglycemia and hypoglycemia in hospitalized patients.

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