Prediction and Prevention of Treatment-Related Inpatient Hypoglycemia

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Abstract

Background:

Prolonged severe hypoglycemia (SH) in hospitalized patients is associated with increased morbidity and mortality. This study was undertaken to identify risk factors for SH, to apply that knowledge to the development of a prediction algorithm, and to institute a prevention program at a tertiary medical center.

Methods:

We analyzed SH events for 172 patients and developed computer algorithms to predict SH that were tested on a population of 3028 inpatients who were found to have blood glucose (BG) <90 mg/dl during their hospital stay. Variables with significant bivariate associations were entered into partition analyses to identify interactions. Logistic regression was performed by calculating parameters related to the odds of hypoglycemia below each cut point. Sensitivity and specificity were determined at various cut points. The cut points resulting in 50% sensitivity for each hypoglycemia level were determined. These algorithms were tested against the initial 172 adjudicated patients.

Results:

Variables related to the BG <40 mg/dl cut off point were basal and adjustment scale insulin doses, weight, and creatinine clearance, while variables related to the 60 mg/dl and 70 mg/dl cut points were basal, prandial, and adjustment scale insulin doses, weight, creatinine clearance, and sulfonylurea use. The 50% sensitivity cut point developed using the <70 mg/dl algorithm correctly identified 71% of the adjudicated cases, while the <60 mg/dl and <40 mg/dl algorithms identified 70% and 55% respectively.

Conclusions:

A validated prediction algorithm for SH can aid in the identification of patients at risk for SH and may be useful in the development of prevention strategies.

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Introduction

Treatment-related hypoglycemia is a potentially dangerous and common complication of insulin therapy in the hospital. Hypoglycemia has been associated with mortality in multiple intensive care unit studies, but this association is not as clear on the medical wards.[1–4] Hypoglycemia in the outpatient setting is a recognized risk factor for mortality and morbidity including cardiovascular, cerebrovascular, and patient fall events.[5,6] The prevalence of hypoglycemia (<70 mg/dl) was reported to be 5.7% of all point-of-care blood glucose (BG) tests in a 2009 survey of 575 hospitals.[7] The commonly used definition for severe hypoglycemia (SH) (a low BG level that requires the assistance of another person for recovery) does not apply in the hospital setting, so a defined BG level, <40 mg/dl, has been adopted as the level likely to cause harm in the hospital setting.[6] It has been recognized that early therapeutic changes after treatment for mild hypoglycemia can prevent more SH episodes[8] and that clinicians do not consistently adjust their patients' antidiabetic regimens appropriately following treatment of hypoglycemia, placing the patient at additional risk.[3] Treatment-related hypoglycemia is an iatrogenic event that should be prevented; however, the tools available are inadequate.

Inpatient hypoglycemia may be due to excessive insulin dose, inappropriate timing of insulin or antidiabetes therapy, unaddressed antecedent hypoglycemia or changes in the nutritional regimen, creatinine clearance, or steroid dose.[9] Failure of effective communication between physicians and nurses is an underlying problem.[9] The diverse nature of potential errors in the treatment of inpatients with hyperglycemia supports the need for a decision-making model that can be used to predict and prevent hypoglycemia. Development of practices to prevent hypoglycemia is the challenge addressed by this study.

We carefully analyzed the clinical and dosing factors associated with SH (BG <40 mg/dl) and less severe hypoglycemia (LSH BG <60 mg/dl and <70 mg/dl) at Barnes-Jewish Hospital during a 6-month interval. The data was then used to develop a predictive model that could interface with the Internet protocol electronic health record (EHR) to provide alerts.

Methods

Study 1 was conducted at Barnes-Jewish Hospital, a 1259-bed tertiary care center in St. Louis, MO, from June 1 to November 30, 2009, to assess risk factors predisposing to inpatient hypoglycemia and to identify proximate causes of hypoglycemia. The EHR was programmed to identify patients with BG <40 mg/dl within 12–36 h of the event. A clinical pharmacist completed a "patient hypoglycemic event review form" for all events associated with the administration of an antihyperglycemic oral agent or insulin. Data recorded on the form included: patient demographics, serum creatinine, hemoglobin A1c (A1C) (if available), BG levels, dietary intake, use of corticosteroid medications, and dose and administration times of all antihyperglycemic medications. The proximate cause of the hypoglycemia was identified using multiple factors that were not mutually exclusive. The category of excess insulin was used if the dose was the singular proximate cause of the hypoglycemic event as verified by the absence of subsequent hypoglycemia after the insulin dose was modified. The category of inadequate monitoring was used to describe patients who demonstrated hypoglycemia (BG <70 mg/dl) without subsequent diabetic medication dose reduction and subsequently progressed to experience SH. The other categories included administration errors, hypoglycemia occurring in the setting of the treatment of hyperkalemia, and computer order entry errors. Hypoglycemic event data were entered into the hospital's computerized safety event system. A study physician evaluated the completed forms and provided patient management recommendations and comments. The study physician then emailed the document to the patient's hospital physician(s) for educational purposes. Patients' physicians were asked to complete an evaluation form to assess the value of this educational tool in their care of diabetes patients.

Severe hypoglycemia event tracking at our institution utilizes a "hypoglycemic harm score," which is generated and reviewed on a monthly basis. The numerator for the harm score is the total number of BG values <40 mg/dl occurring in the setting of active orders for diabetes therapy. Hypoglycemia events are tracked if they involve a BG level between 15 and 39 mg/dl in a patient with an order for a hypoglycemic agent that is active within 24 h of the event. Erroneous levels are identified and removed from the audit if a subsequent BG >39 mg/dl is generated within 10 min of the suspect level. The use of this rule eliminates about 10% of the total events, a rate that has been stable over time. The denominator for the harm score is defined as "at risk patient days" and involves patients with an order for a hypoglycemic agent whose hospital stays minimally include a midnight within the stay.

Study 2 used a population of inpatients found to have any BG <90 mg/dl (n = 9995 patients) during their hospital stay, corresponding to the same time period as study 1. After limiting study patients to those that had received insulin while in the hospital, 3028 patients were assessed at three levels of hypoglycemia: <70 mg/dl (n = 1525), <60 mg/dl (n = 955), and <40 mg/dl (n = 232). The risk factors identified in the study 1 analysis were used. Chi-square analyses and t-tests were run to identify bivariate associations. Significant variables were entered into a partition analysis to identify interactions. Logistic regression was performed to verify the significance of associations and interactions and to calculate parameters related to the odds of hypoglycemia below each cut point. This resulted in three separate models. Receiver operating characteristic curve analysis was used to determine sensitivity and specificity at various cut points. The cut points that resulted in 50% sensitivity for each hypoglycemia level were determined. PASW® Statistics 18, release version 18.0.0 (IBM, Armonk, NY) and the R-part package in the R software program[10,11] were used to run these analyses.

Results

Study 1 showed 244 hypoglycemic events (BG <40 mg/dl) reported during the 6-month period. Forty-five events involved erroneous BG readings, and 27 reports involved patients without orders for insulin or oral antihyperglycemic therapy. The remaining 172 events (70% of reports) were investigated and are included in this study. Twenty patients had a second hypoglycemic event, 6 patients had a third event, and 3 patients had more than 3 events. Hypoglycemia occurred between 12:00 a.m. and 6:59 a.m. in 48% of patients, between 7:00 a.m. and 3:59 p.m. in 30% of patients, and between 4:00 p.m. and 11:59 p.m. in 22% of patients. In 20% of the events (34 patients), the patient's physician was contacted by the study pharmacist, and a drug therapy modification was implemented during that hospital stay. Otherwise, contact occurred via email after discharge. Physicians found this educational feedback process useful to their medical practice: 33% very useful; 60% useful; 0% marginally useful; 6% not useful. Physicians rated the future impact of the intervention on their care of diabetes patients: 36% significant impact; 50% important impact; 7% slight impact; 7% no impact. Patient variables and proximate causes associated with the hypoglycemic events are presented in **Figures 1 and 2**. As a consequence of these efforts, the hypoglycemia harm score was 5.01 events in 2008, compared with 3.90 in 2010.

Study 2 developed models that predicted levels of hypoglycemia and used the adjudicated population to define sensitivity and specificity for prediction. The results of the bivariate tests are shown in **Table 1**. Blood glucose levels were related to receiving both prandial and adjustment scale insulin (chi-square $p < .05$, linear association $p < .01$), basal dose (chi-square $p < .001$, linear association $p < .001$), weight (chi-square $p < .001$, linear association $p < .001$), and creatinine clearance (chi-square $p < .001$, linear association $p < .001$). Significant linear associations were found for the combination of sulfonylurea and adjustment scale insulin ($p < .05$) and an interaction of sulfonylurea use by dose of basal insulin ($p < .05$).

The logistic regressions indicated that variables related to BG <40 mg/dl were basal and adjustment scale insulin dose, weight, and creatinine clearance, while variables related to 60 mg/dl and 70 mg/dl cut points were basal, prandial, and adjustment scale insulin dose,
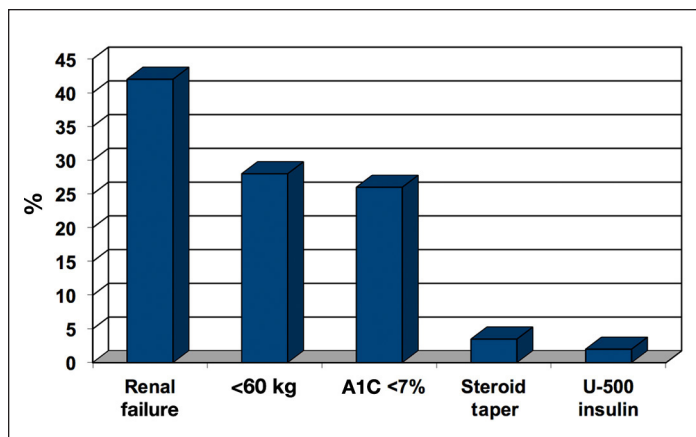

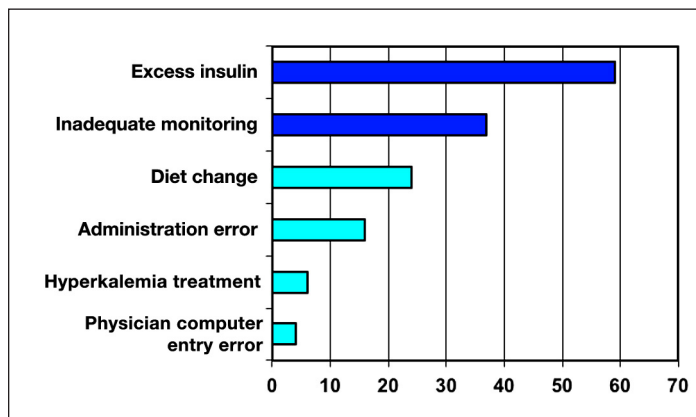**Figure 1.** Percentage of patient variables associated with hypoglycemic events.

Figure 2. Incidence percentage of proximate causes of hypoglycemia.

Table 1. Bivariate Associations with Glucose Level (mg/dl)							
Variable and level		BG ≥60 and <90	BG ≥40 and <60	BG <40	Total BG <90	Chi-square p-value	Linear association p-value
Prandial insulin	Yes	238 (11.5%)	96 (13.3%)	33 (14.2%)	367 (12.1%)	0.263	0.107
	No	1835 (88.5%)	627 (86.7%)	199 (85.8%)	2661 (87.9%)		
Adjustment scale insulin	Yes	1614 (77.9%)	553 (76.5%)	194 (83.6%)	2361 (78.0%)	0.072	0.278
	No	459 (22.1%)	170 (23.5%)	38 (16.4%)	667 (22.0%)		
Sulfonylurea	Yes	162 (7.8%)	70 (9.7%)	13 (5.6%)	245 (8.1%)	0.100	0.996
	No	1911 (92.2%)	653 (90.3%)	219 (94.4%)	2783 (91.9%)		
Prandial and adjustment scale	Yes	43 (49.4%)	34 (61.8%)	19 (82.6%)	96 (58.2%)	0.013	0.004
	No	44 (50.6%)	21 (38.2%)	4 (17.4%)	69 (41.8%)		
Sulfonylurea and adjustment scale	Yes	24 (75.0%)	17 (94.4%)	6 (100.0%)	47 (83.9%)	0.105	0.043
	No	8 (25.0%)	1 (5.6%)	0 (0.0%)	9 (16.1%)		
Sulfonylurea and basal dose	Yes	32 (19.8%)	18 (25.7%)	6 (46.2%)	56 (22.9%)	0.074	0.037
	No	130 (80.2%)	52 (74.3%)	7 (53.8%)	189 (77.1%)		
Three level basal dose	≥.25	256 (12.3%)	175 (24.2%)	63 (27.2%)	494 (16.3%)	<.001	<.001
	>0 and <.25	282 (13.6%)	166 (23.0%)	61 (26.3%)	509 (16.8%)		
	No basal dose	1535 (74.0%)	382 (52.8%)	108 (46.6%)	2025 (66.9%)		
Four level weight	≥80	1142 (57.2%)	345 (50.1%)	90 (40.5%)	1577 (54.2%)	<.001	<.001
	≥70 and <80	337 (16.9%)	111 (16.1%)	45 (20.3%)	493 (17.0%)		
	≥60 and <70	263 (13.2%)	105 (15.3%)	44 (19.8%)	412 (14.2%)		
	<60	255 (12.8%)	127 (18.5%)	43 (19.4%)	425 (14.6%)		
Three level creatinine clearance	≥48	1264 (65.7%)	343 (50.7%)	101 (45.9%)	1708 (60.5%)	<.001	<.001
	≥38 and <48	187 (9.7%)	82 (12.1%)	17 (7.7%)	286 (10.1%)		
	<38	474 (24.6%)	252 (37.2%)	102 (46.4%)	828 (29.3%)		

weight, creatinine clearance, and sulfonylurea use (**Table 2**). The area under the curve (AUC) value for the <60 mg/dl equation was 0.692 and the Nagelkerke R^2 was 0.134 (**Table 3**). The 50% sensitivity cut point correctly identified 70% of the adjudicated patients. The same analysis for <40 mg/dl gave an AUC value of 0.697, and the Nagelkerke R^2 was 0.095. The 50% sensitivity cut point correctly identified 55% of the adjudicated cases. For <70 mg/dl, an AUC value of 0.679 and a Nagelkerke R^2 of 0.129 were found. The 50% sensitivity cut point correctly identified 71% of the adjudicated cases. Eliminating events where a value below 60 mg/dl occurred as an initial value, we were able to predict 60.3% of events <60 mg/dl with our equation. This reflected 324 patients, of whom 78 (24.1%) had BG <40 mg/dl and met the criteria for SH. A <60 mg/dl alert was triggered in 28.1% of patients, where a value <60 mg/dl did not occur while in the hospital. The equation used for the alert was:

$$(\text{value} <60) = -0.055 + 1.062 \times (\text{basal} <0.25 \text{ U/kg})$$
$$+ 1.234 \times (\text{basal} \geq 0.25 \text{ U/kg}) - 0.294 \times (\text{weight } 60\text{–}69 \text{ kg})$$
$$- 0.540 \times (\text{weight } 70\text{–}79 \text{ kg}) - 0.786 \times (\text{weight} \geq 80 \text{ kg})$$
$$-0.389 \times (\text{creatinine clearance } 38\text{–}47)$$
$$- 0.680 \times (\text{creatinine clearance} \geq 48) - 0.239 \times (\text{sliding yes})$$
$$- 0.556 \times (\text{meal yes}) + 0.951 \times (\text{sliding and meal})$$
$$+ 0.336 \times (\text{sulfonylurea yes})$$

$$\text{Risk Score} = 100 \times [\exp (\text{value} <60)/(1 + \exp (\text{value} <60)].$$

Discussion

Treatment of hyperglycemia in hospitalized patients carries a significant risk for iatrogenic hypoglycemia. The risk for harm is less clear because the events are often transient and rapidly treated in the inpatient setting.[1,3,12–14] Outpatient studies have more complete data on the prevalence of severe events requiring intervention. The Diabetes Control and Complications Trial reported

Table 2.
Model Parameters

Risk score	Constant	Basal <.25 units/kg	Basal ≥.25 units/kg	Weight 60–69 kg[a]	Weight 70–79 kg	Weight ≥80 kg	Creatinine clearance 38–47[b]	Creatinine clearance ≥48	Adjustment dose yes	Meal dose yes	Adjustment and meal	Sulfonylurea yes
Glucose <40	–2.490	1.090	1.693	-0.375	0.065	-0.375	-0.907	-0.792	0.402	—	—	—
With weight 60–69	—	0.791	0.042	—	—	—	—	—	—	—	—	—
With weight 70–79	—	–0.139	–1.166	—	—	—	—	—	—	—	—	—
With weight ≥80	—	–0.551	–1.020	—	—	—	—	—	—	—	—	—
Glucose <60[c]	-0.055	1.062	1.234	–0.294	–0.540	–0.786	–0.389	–0.680	–0.239	–0.556	0.951	0.336
Glucose <70	0.577	0.908	1.254	–0.153	–0.360	–0.690	–0.402	–0.626	–0.101	–0.062	0.702	0.296

[a] Referent category weight <60 kg
[b] Referent category creatinine clearance <38
[c] Used for alert score

Table 3.
Testing

Testing Against Each Cut Point

Glucose cut	Nagelkerke R^2	AUC rounded	Sensitivity at cut point	Specificity at cut point	Predictive value of a positive test	Predictive value of a negative test	False positive number (% of those at glucose level or above)	False negative number (% of those below glucose level)
40	0.10	0.70	0.50	0.79	0.17	0.95	541 (21%)	107 (50%)
60	0.13	0.69	0.54	0.74	0.49	0.78	492 (26%)	400 (46%)
70	0.13	0.68	0.51	0.76	0.69	0.60	325 (24%)	692 (49%)

Testing Against Severe Hypoglycemia (BG <40 mg/dl)

BG cut point mg/dl	Sensitivity at cut point	Specificity at cut point	Predictive value of a positive test	Predictive value of a negative test	False positives	False negatives	Number (%) of those in 6-month study identified	Number (%) of those in 6-month study not identified
40	0.50	0.79	0.17	0.95	541 (21%)	107 (50%)	63 (54.8)	52 (45.2)
60	0.58	0.67	0.13	0.95	837 (33%)	90 (42%)	81 (70.4)	34 (29.6)
70	0.61	0.65	0.13	0.95	903 (36%)	84 (39%)	82 (71.3)	33 (28.7)

61 episodes per 100 patient years of SH in the intensive treatment arm,[15] and the 2007 U.K.2 Hypoglycemia Study Group in patients with either type 1 or type 2 diabetes reported 110 episodes per 100 patient years.[16] Overall, the risk of hypoglycemia is less prevalent in type 2 diabetes patients, but with advanced disease, the rate approaches that seen in type 1 diabetes. The U.K.2 reported 1020 episodes of mild hypoglycemia and 70 episodes of SH per 100 patient years in type 2 diabetes patients treated with insulin for >5 years. Based on this data, patients admitted to the hospital on antihyperglycemic therapy are clearly at risk for further events.

Development of hypoglycemia has been linked to mortality and morbidity, although direct causality has been questioned through two arguments. The first relates

to the timing of the events in relationship to the morbid outcome, and the second is the suggestion that SH simply identifies persons with greater underlying illness severity. The timing argument is clearly flawed because an event can create a cascade that predisposes to a fatal outcome such as an arrhythmia.[12,17–19] Additionally, sampling of the blood glucose may miss the hypoglycemia event entirely. Continuous glucose monitoring system data clearly show that hypoglycemic events are being under-reported by self-monitoring of blood glucose and may be clinically silent.[1,20,21] Data linking SH to brain death and arrhythmia has been reported in humans and in animal models. The level of hypoglycemia needed to cause cell death is not entirely clear, but once the process has been programmed, treatment with glucose may have detrimental effects on survival.[22,23] These findings support the notion that prediction and prevention of hypoglycemia should be the top priority and that an intervention before cell death is needed to avoid morbidity and mortality.

Hospitalized patients with diabetes have an increased incidence of medical errors, incurring >0.53 errors per patient days and >1.72 errors per patient period.[9] The office of the inspector general has listed SH as a "diabetes never event."[24] Given the prevalence of diabetes in the general population and in the hospital setting, it is not surprising that "diabetes never events" are the most common among serious medical errors. Interestingly, setting higher glucose targets does not necessarily prevent hypoglycemia.[20] Clearly there is a need for clinicians to improve their understanding of risk factors for inpatient SH and for health system initiatives to facilitate an improved flow of actionable information to the patient care providers.

Implementation of the initial hypoglycemic surveillance and education program at Barnes-Jewish Hospital has produced increased awareness of the risks of hypo-glycemia among the hospital's administrative, nursing, pharmacy, and medical staffs. The data outlined in the original 172-patient data set confirms the findings of other investigators in demonstrating that nocturnal hypo-glycemia is a common problem. We have demonstrated that risk factors for hypoglycemia include acute kidney injury or end-stage renal disease, low body weight (weight <60 kg), A1C <7%, and corticosteroid tapering therapy. The proximate causes of hypoglycemia in our study population included excessive insulin doses, inadequate monitoring of blood glucose trends, changes in nutritional status without a change in the antidiabetic therapy, nursing administration errors, and insufficient glucose with insulin for acute treatment of hyperkalemia. Consequently, interventions were developed that included:

a recommended change in the treatment for acute hyperkalemia,[25] creation of a nursing educational tool that focuses on using critical thinking skills in the assessment of patients receiving insulin, implementation of a case-based insulin dosing curriculum for all medical staff, and a redesign of the hospital's supplementary insulin dosing protocols for bedtime administration. These changes have decreased the rate of SH <40 mg/dl from a rate of 5.01 events per 1000 at-risk patient days in 2008 to 3.90 per 1000 at-risk patient days in 2010 at Barnes-Jewish Hospital. This improvement confirms that changes in systems and policies can have an impact. However, further improvement will require a more creative approach.

The presence of antecedent mild hypoglycemia is commonly reported.[8,26] We saw antecedent hypoglycemia in >60% of the 172 severe events, suggesting that identification of at-risk individuals and prevention is possible. The difference in the reported rates for antecedent hypoglycemia in the literature is related to the target that is used in the analysis and the threshold for the mild event as well as the definition of the hypoglycemic target. The target chosen at our institution for the analysis was a BG ≤90 mg/dl, based on the 2006 American College of Endocrinology Guidelines, which contrasts with a target BG <100 mg/dl in the American Diabetes Association consensus guideline and the Society of Hospital Medicine guidelines.[27,28] Despite this change, the use of the 90 mg/dl cut point benefits our analysis because it allows the partition analysis to be more specific to the development of true or risk-related hypoglycemia and should limit the false positive rates in the predictive equation.

We analyzed our data at three cut points to create the predictive equations for <70 mg/dl, <60 mg/dl, and <40 mg/dl. These levels were somewhat arbitrary but have scientific backing. The accepted level for the definition of hypoglycemia in outpatients is 70 mg/dl, which corresponds to the level at which counterregulatory hormones are released.[29,30] The basis for 60 mg/dl as a population grouping was it is clearly in the low range but is still above the 50 mg/dl level where cognitive impairment occurs. A widely accepted definition of SH in the hospital is any glucose <40 mg/dl. This definition is somewhat arbitrary, since the effects of "mild" hypo-glycemia can be severe in individuals who have underlying cardiac or cerebrovascular disease. Variables that defined the populations <70 mg/dl, <60 mg/dl, and <40 mg/dl were similar, but the cut points varied, with many of them showing a trend for linearity. Rubin published an analysis[31] of the total daily dose (TDD) of insulin as it

relates to the odds ratio of hypoglycemia at <70 mg/dl, showing an increasing odds ratio from 1.08 at a TDD of 0.2–0.4 units/kg to 2.95 at a TDD >0.8 units/kg. Our bivariate and the logistic regression analyses informed the variables that were used to develop the model. Variables related to BG <60 mg/dl were basal, prandial, and adjustment scale insulin dose, weight, creatinine clearance, and sulfonylurea use. The <40 mg/dl group had fewer predictive variables but included an interaction of basal dose and weight that was not seen in the other models.

Predictive areas were similar to each other, with the equations designed at 60 mg/dl and 70 mg/dl having the best R^2 values. The 60 mg/dl group was found to be superior compared to the 70 mg/dl group in regard to the predictive value of a negative test without a substantial change in the false positive or false negative rates (26 and 46% vs 24 and 49%). The 60 mg/dl proved to be superior to the 70 mg/dl equation in its ability to predict and identify the SH group with fewer false positives and a smaller number of total alerts (927 vs 987) based on the 6-month analysis. This analysis suggests that the 60 mg/dl equation would represent a reasonable compromise. By eliminating events where an antecedent glucose <60 mg/dl occurred, we were able to predict 60.3% of events <60 mg/dl with our equation. The threshold occurred in 40% before an alert could be activated, suggesting the need to look at prehospital variables in a more standardized way.

The alert development process has had an impact on the incidence of SH at our institution and is a model that can be implemented at other institutions. The failure to predict 40% of the events in the original analysis suggests that a predictive equation is only one tool among many that will need to be developed to protect all inpatients from harm. The work presented here shows that decision analysis can be driven by risk data and that interventions can be designed to reduce the risk of hypoglycemia in hospitalized patients.

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