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Glucose Control and Mortality in Critically Ill Patients

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Context Hyperglycemia is common in critically ill patients, even in those without diabetes mellitus. Aggressive glycemic control may reduce mortality in this population. However, the relationship between mortality, the control of hyperglycemia, and the administration of exogenous insulin is unclear.

Objective To determine whether blood glucose level or quantity of insulin administered is associated with reduced mortality in critically ill patients.

Design, Setting, and Patients Single-center, prospective, observational study of 531 patients (median age, 64 years) newly admitted over the first 6 months of 2002 to an adult intensive care unit (ICU) in a UK national referral center for cardiorespiratory surgery and medicine.

Main Outcome Measures The primary end point was intensive care unit (ICU) mortality. Secondary end points were hospital mortality, ICU and hospital length of stay, and predicted threshold glucose level associated with risk of death. .

Results Of 531 patients admitted to the ICU, 523 underwent analysis of their glycemic control. Twenty-four–hour control of blood glucose levels was variable. Rates of ICU and hospital mortality were 5.2% and 5.7%, respectively; median lengths of stay were 1.8 (interquartile range, 0.9-3.7) days and 6 (interquartile range, 4.5-8.3) days, respectively. Multivariable logistic regression demonstrated that increased administration of insulin was positively and significantly associated with ICU mortality (odds ratio, 1.02 [95% confidence interval, 1.01-1.04] at a prevailing glucose level of 111-144 mg/dL [6.1-8.0 mmol/L] for a 1-IU/d increase), suggesting that mortality benefits are attributable to glycemic control rather than increased administration of insulin. Also, the regression models suggest that a mortality benefit accrues below a predicted threshold glucose level of 144 to 200 mg/dL (8.0-11.1 mmol/L), with a speculative upper limit of 145 mg/dL (8.0 mmol/L) for the target blood glucose level.

Conclusions Increased insulin administration is positively associated with death in the ICU regardless of the prevailing blood glucose level. Thus, control of glucose levels rather than of absolute levels of exogenous insulin appear to account for the mortality benefit associated with intensive insulin therapy demonstrated by others.

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MODERN CRITICAL CARE IS predicated upon the principle of restoring aberrant respiratory, cardiovascular, and other parameters to physiologic levels, while therapeutic interventions are applied to correct underlying pathological conditions. Thus, many attempts have been made in critically ill populations to manipulate indices, particularly relating to oxygen delivery and uptake, to normal or even supranormal levels in the belief that such maneuvers would confer a survival benefit. However, the use of aggressive volume resuscitation and pressors to achieve supranormal targets was shown to be detrimental in established sepsis.[1] By contrast, limiting tidal volumes to below normal levels appears to be beneficial in patients with the acute respiratory distress syndrome who are receiving mechanical ventilation.[2] This suggests that physiological targets should be just sufficient to preserve organ homeostasis, while minimizing any detrimental effects of the intervention itself. Moreover, it is likely that therapeutic targets will differ according to the parameter selected for investigation and manipulation.

Recently, a prospective randomized study targeting blood glucose to lower levels (80-110 mg/dL [4.4-6.1 mmol/L] vs 180-200 mg/dL [10.0-11.1 mmol/L]) using intensive insulin therapy demonstrated a significant reduction in intensive care unit (ICU) and hospital mortalities,[3] although the mechanisms of this benefit were unclear. First, the mortality reduction may have been attributable either to the avoidance of hyperglycemia, the administration of exogenous insulin, or the combination of glucose and insulin.[4-6] Second, the most appropriate target level for blood glucose was not identified, in that approximately 35.6% of the intervention group dis-

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played levels above the target range at 6 AM. Moreover, it is likely that at certain times even patients managed conventionally in this study achieved the target glycemic levels achieved by the intensively managed group, even without insulin. Both of these phenomena may have diluted the observed benefit attributable to the intervention.

We therefore explored prospectively the relationships between glucose control, insulin administration, and outcome in critically ill patients, using a computerized clinical information system that stores high-quality, high-resolution data. Our primary outcome of interest was ICU mortality. We sought to determine whether control of glucose metabolism or the degree of insulin administration was the most important variable in influencing outcome. We also explored whether there was evidence for a threshold glucose level above which there was an increased risk of death.

METHODS

Patients

Data were collected prospectively for all patients admitted to the adult ICU of the Royal Brompton Hospital, London, England, during the first 6 months of 2002. The unit supports the work of a national referral center for cardiorespiratory surgery and medicine, and admits only patients older than 16 years. The methods of data collection and analysis were approved by the research ethics committee of the hospital.

Data Collection

Per our standard procedure, all clinical observations and laboratory measurements for every patient admitted to the operating rooms and critical care facilities within our hospital were recorded in a computerized clinical information system (CareVue, Phillips Medical Systems, Andover, Mass). Physiological monitors communicate electronically with CareVue, while laboratory results and rates of intravenous infusions were entered manually by nursing staff. Archived CareVue data were deposited into a data warehouse, the clinical data archive, and were accessed using the information support mart. The information support mart acts as an interface, organizing the data stored within the clinical data archive into a series of tables that can be interrogated using Microsoft Access 2000 (Microsoft Corp, Redmond, Wash).

Data retrieval was performed for all measurements of blood glucose levels, the rates of insulin infusions (if any), and the specific time at which all observations were made. Body mass index (BMI) was calculated as patient weight in kilograms divided by the square of height in meters. Standard BMI cutoffs were used to define patients who were underweight (<18.5), overweight (>25), or obese (>30). Hospital length of stay and mortality were determined from a computerized hospital-wide patient administrative system.

Blood Glucose Control

Blood glucose measurements were determined on heparinized arterial blood samples using the MediSense Precision G point-of-care testing system (Abbott Laboratories, Reading, England). Monitors underwent high and low quality control at least weekly; none failed during the study period. It is our practice to maintain levels of blood glucose between 90 and 145 mg/dL (5.0 and 8.0 mmol/L) using infusions of soluble human insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark). Infusion rates are set at the discretion of the attending/senior nurse unconstrained by a fixed regimen, with the goal of achieving rapid and tight control of blood glucose levels. Typically, infusion rates are increased proportionally to the rate of increase of blood glucose level; therefore, rates of up to 50 IU/h were administered during the study period.

Caloric intake was similar for all patients. Per our standard procedure, all compatible drugs were diluted with 5% dextrose solution. Enteral feeding was instituted on admission except in those patients in whom extubation was planned within 12 hours. Prokinetic drugs and jejunal feeding tubes were used sequentially and rapidly if gastric aspirates are large. Parenteral nutrition was used infrequently. Total caloric input is based on UK national guidelines.[7]

Six bands of glycemic control were prospectively defined: hypoglycemic (blood glucose level <80 mg/dL [4.4 mmol/L]), stringent (80-110 mg/dL [4.4-6.1 mmol/L], normal (111-144 mg/dL [6.1-8.0 mmol/L], intermediate (145-180 mg/dL [8.0-10.0 mmol/L], liberal (181-200 mg/dL [10.0-11.1 mmol/L]), and hyperglycemic (≥201 mg/dL [11.1 mmol/L]). Each band defined a range of blood glucose values. The stringent and liberal bands corresponded to ranges used by others previously,[3] while the intermediate range was split into 2 bands. During a single admission, patients will have glucose levels that fall in several bands. For each patient, the possibility of bias occurring if the number of values in each glycemic band was recorded was recognized. When parameters deviated significantly from normal values, observations may have been made more frequently as appropriate clinical interventions were applied. The timing of the observations was therefore used to weight the variables appropriately. Time-weighting was undertaken by calculating the number of minutes spent within each band, assuming a linear trend between individual measurements, and expressing the result as a proportion of the whole admission. Thus for each patient the proportion of the admission that he or she spent within each of the 6 bands was computed.

Severity of Illness

Severity of illness was assessed using the Acute Physiology And Chronic Health Evaluation 2 (APACHE II) scoring system. Although APACHE II is a common system used to describe the severity of illness in cohorts of critically ill patients,[8] it is not necessarily valid following cardiac surgery, especially since scoring variables may have been manipulated intraoperatively. Therefore, organ dysfunction also was evaluated using the Sequential Organ Failure Assessment (SOFA) score.[9] Scoring of the

APACHE II and SOFA instruments was performed on the worst parameters recorded in the 24 hours following admission to the ICU; these data were retrieved from the CareVue system. According to standard practice, missing parameters were scored as normal.

Data Analysis

Patient parameters were assembled through the relational database Microsoft Access 2000. Data were modeled mathematically using STATA version 7 (Stata Corp, College Station, Tex). Multivariable logistic regression was performed using ICU outcome as the response variable and insulin dose and time in glucose band as the main exposure variables. A separate model was generated for each of the 6 glucose bands. Time in each band was represented in the model by means of a variable containing 3 categories based on tertiles: thus, for each glucose band the percentage of time spent in that band was categorized into 3 groups so that each subgroup contained the same number of people. Insulin doses for each patient were calculated from the area under the time–insulin dose curve relative to the length of admission. Any possible confounding variables (APACHE II score, SOFA score, age, sex, BMI, reason for admission, and length of stay) were initially included in the models alone and as an interaction with time in glucose band. The models were then refined by backward exclusion of nonconfounding variables (age, sex, and BMI). All interactive terms were nonsignificant and thus not included in the final models. Appropriate functional forms of the continuous variables were assessed by initially testing for a linear association with outcome; length of stay was recoded into 3 equal categories. Finally, modeling was repeated using only data from patients without diabetes.

Comparisons between groups were performed using S-Plus version 6 Professional Release 2 (Insightful Corp, Seattle, Wash). Differences between variables were assessed using a Wilcoxon rank-sum test for nonparametric data. Contingency tables were analyzed using a Fisher exact test. Statistical significance was defined at the 95% level.

RESULTS

Patient Characteristics

A flow diagram of the study protocol is presented in FIGURE 1. During the 6-month study period, 531 patients (545 admissions) were admitted to the ICU. Since second admissions are not independent of the first, analysis was restricted to the first admission for the 14 patients admitted twice. A further 8 were not analyzed: 2 because active therapy was withdrawn within 24 hours of admission, and 6 because no blood glucose level was recorded during brief admissions following minor procedures such as electrical cardioversion, gastrostomy insertion, or tensilon testing. The remaining 523 patients underwent analysis of their glycemic control.

The clinical characteristics of all 523 patients are shown in TABLE 1. The patient population was predominantly male, older than 60 years, and over-

Figure 1. Flow of Patients Through the Trial

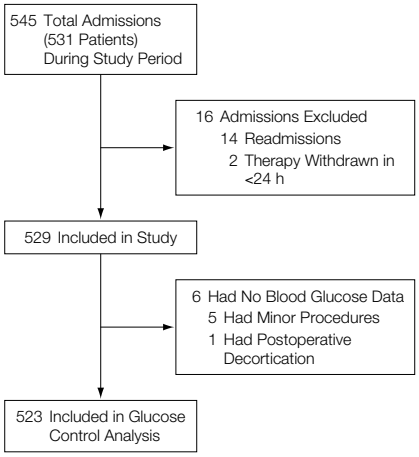


Table 1. Demographic Characteristics of Study Patients

Characteristic	All Patients (N = 523)	Patients Without Diabetes (n = 437)	Patients With Diabetes (n = 86)	*P* Value*
Patient Characteristics				
Men, No. (%)	381 (72.8)	320 (73.2)	61 (70.9)	.69
Age, median (IQR), y	64 (54-71)	64 (54-71)	65 (58-71)	.21
BMI, median (IQR)†	26.6 (23.6-29.6)	25.9 (23.1-29.0)	29.2 (27.2-33.9)	<.001
Underweight, No. (%)	17 (3.3)	17 (3.9)	0	
Overweight, but not obese, No. (%)	213 (40.7)	172 (39.4)	41 (47.7)	
Obese, No. (%)	118 (22.6)	85 (19.5)	33 (38.4)	
Diabetes mellitus				
All, No. (%)			86/523 (16.4)	
Type 1			2	
Type 2, not insulin-treated			60	
Type 2, insulin-treated			24	
Admission Characteristics				
Reason for admission, No. (%)				
Cardiac surgery				
Coronary artery surgery	251 (48.0)	189 (43.2)	62 (72.1)	
Valve surgery	160 (30.6)	146 (33.4)	14 (16.3)	
Other cardiac surgery	34 (6.5)	33 (7.6)	1 (1.2)	
Thoracic surgery	17 (3.3)	17 (3.9)	0	
Medical admission	61 (11.7)	52 (11.9)	9 (11.2)	
Day-1 APACHE II score, median (IQR)‡	16 (13-20)	17 (13-20)	16 (13-20)	.84
Day-1 SOFA score, median IQR‡	5 (3-6)	5 (3-6)	5 (3-6)	.53

Abbreviations: APACHE II, Acute Physiology And Chronic Health Evaluation 2; BMI, body mass index; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.
*Based on 2-sided Fisher exact tests (categorical variables) or 2-sided Wilcoxon rank-sum tests (continuous variables), comparing patients with and without diabetes.
†Calculated as weight in kilograms divided by the square of height in meters.
‡APACHE II scores range from 0-71; SOFA scores, from 0-24.

weight or obese. Only 17 patients were considered to be underweight. Eighty-six patients (16.4%) had diabetes, 26 of whom (30.2%) required long-term preoperative insulin therapy. The patients with diabetes had significantly higher BMIs than the rest of the population ($P<.001$).

Admission Characteristics

Admission data are presented in Table 1. Most admissions followed cardiac surgery (85.1%). The data sets for APACHE II and SOFA scores were 98.29% and 99.49% complete, resulting in median (interquartile range [IQR]) scores of 16 (13-20) and 5 (3-6), respectively. Median (IQR) scores for patients with diabetes were not significantly different from those for patients without diabetes (APACHE II: 16 vs 17 [13-30 for both]; $P=.84$; SOFA: 5 [3-6] for both; $P=.53$). Rates of ICU and hospital mortality were 5.2% and 5.7%, respectively; median lengths of stay were 1.8 (IQR, 0.9-3.7) days and 6 (IQR, 4.5-8.3) days, respectively (TABLE 2). Values for cardiac surgery mortality reflect the large proportion of repeat surgery performed at our institution. Scores on the APACHE II and the SOFA instruments were significantly higher in those patients who did not survive, irrespective of whether this was considered at discharge from ICU or hospital ($P<.001$ for all, data not shown). In the study group, patients with diabetes had neither significantly different mortality nor length of stay, irrespective of whether these outcomes were assessed at discharge from ICU or our hospital. Neither underweight nor overweight, as defined by BMI, was associated with increased mortality or prolonged length of stay (data not shown).

Table 2. Clinical Outcome Measures for All Admissions

Admission Characteristic	Deaths, No. (%)		Length of Stay, Median (IQR)	
	ICU	Hospital	ICU	Hospital*
All patients	27 (5.2)	30 (5.7)	1.8 (0.9-3.7)	6.0 (5.0-8.0)
Reason for admission				
Cardiac surgery				
Coronary artery surgery	6 (2.4)	7 (2.8)	1.0 (0.8-1.9)	5.0 (4.0-6.0)
Valve surgery	4 (2.5)	5 (3.1)	1.8 (0.9-3.6)	7.0 (5.0-10.0)
Other cardiac surgery	2 (5.9)	2 (5.9)	2.2 (1.1-15.9)	7.0 (5.0-9.0)
Thoracic surgery	0	0	1.0 (0.8-1.9)	8.0 (5.0-10.0)
Medical admission	15 (24.6)	16 (26.2)	7.7 (3.7-16.2)	5.0 (0.0-11.0)
Diabetes				
Not diabetic	21 (4.8)	23 (5.3)	1.8 (0.9-3.6)	6.0 (5.0-8.0)
Type 1			3.0 (1.9-4.0)	6.5 (3.3-9.8)
Type 2, not insulin-treated	4 (6.7)	4 (6.7)	1.5 (0.8-4.0)	5.5 (4.8-8.0)
Type 2, insulin-treated	2 (8.3)	3 (12.5)	1.8 (0.9-3.8)	5.0 (4.8-8.3)

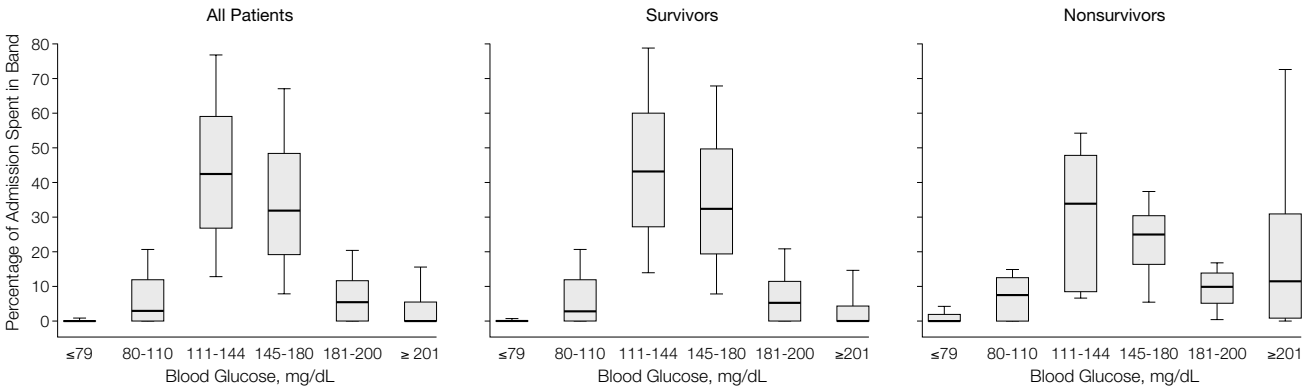
Abbreviations: ICU, intensive care unit; IQR, interquartile range.
*Hospital length of stay presented for time after discharge from ICU.

Blood Glucose Values and Administered Insulin

A total of 20353 blood glucose measurements was recorded for the patients studied, equating to 1 measurement approximately every 2.96 patient-hours. The proportions of time spent within each band are presented for all patients in FIGURE 2. Most patients spent time in multiple bands and therefore were included in several bars. Blood glucose results were split according to whether patients survived their ICU stay (Figure 2). The amount of exogenous insulin administered is shown in TABLE 3.

The relationship between ICU outcome and the quality of blood glucose control and insulin administration was modeled using multivariable logistic regression. The odds ratios (ORs) of death and *P* values for the whole patient population are presented in TABLE 4. Odds ratios of death are expressed relative to the tertile that spent the most time in a specific glucose band.

Figure 2. Blood Glucose Results for All Patients in Study, Survivors, and Nonsurvivors



Percentages of admissions spent in bands were calculated as proportions of the whole admission. Thick lines indicate medians; shaded areas, interquartile ranges; error bars, 90th centiles. To convert blood glucose values expressed in mg/dL to mmol/L, multiply by 0.0555.

Table 3. Relationship Between Outcome and Administration of Exogenous Insulin in Study Group

Characteristic	ICU			Hospital		
	Deaths (n = 27)	Survivors (n = 496)	*P* Value*	Deaths (n = 30)	Survivors (n = 493)	*P* Value*
Infusions, No. (%)	23 (85.2)	274 (55.2)	<.001	25 (83.3)	272 (55.2)	<.001
Daily dose of insulin, median (IQR)†						
IU	39.9 (15.6-89.9)	4.02 (0.0-29.6)	<.001	35.7 (12.4-84.1)	4.0 (0.0-30.1)	<.001
IU/d	0.593 (0.191-1.246)	0.066 (0.000-0.426)	<.001	0.549 (0.155-1.168)	0.064 (0.000-0.425)	<.001

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
*Based on 2-sided Fisher exact tests (categorical variables) or 2-sided Wilcoxon rank-sum tests (continuous variables).
†Doses per day calculated using the duration of the admission as the denominator.

At a prevailing glucose level of 111-144 mg/dL (6.1-8.0 mmol/L), increased administration of insulin was positively and significantly associated with ICU mortality (OR, 1.02; 95% confidence interval, 1.01-1.04). Indeed, in all glucose bands, increased insulin administration was associated with a significantly increased risk of death (ie, OR>1.0), indicating that glucose control rather than administration of exogenous insulin was the dominant factor in improving mortality. This finding also is supported by the predictions (although statistically nonsignificant) for ORs of death according to time spent in a band. Thus, in higher glucose bands, a shorter duration of exposure was associated with predicted ORs of death of less than 1.0, whereas in lower glucose bands the same phenomenon was associated with predicted ORs of death of greater than 1.0.

When the modeling was repeated excluding patients with diabetes the results were the same (data not shown), emphasizing the importance of glycemic control even in patients without diabetes.

COMMENT

The results of this study complement and extend those of previous publications.[3,10] The unblinded design of the large randomized trial of intensive insulin therapy[3] may have resulted in the treatment group receiving better critical care overall. This may be particularly relevant for the benefits observed in those patients admitted for more than 5 days, such as the lower incidences of sepsis and renal dysfunction.

Table 4. Relationship Between ICU Mortality and Quality of Blood Glucose Control and Insulin Administration*

Model/Exposure Variable	ICU Mortality, OR (95% CI)†	*P* Value‡
Hypoglycemic (blood glucose ≤79 mg/dL)		
Time spent in glucose band, tertile		
Least	2.3 (0.31-17.13)	.41
Intermediate	0.9 (0.14-6.36)	.96
Greatest	Reference	
Insulin dose administered§	1.02 (0.99-1.04)	.06
Stringent (blood glucose 80-110 mg/dL)		
Time spent in glucose band, tertile		
Least	3.9 (0.46-33.6)	.20
Intermediate	4.2 (0.76-23.77)	.07
Greatest	Reference	
Insulin dose administered§	1.02 (1.01-1.04)	<.001
Normal (blood glucose 111-144 mg/dL)		
Time spent in glucose band, tertile		
Least	1.0 (0.17-5.85)	.99
Intermediate	2.4 (0.49-11.5)	.27
Greatest	Reference	
Insulin dose administered§	1.02 (1.01-1.04)	<.001
Intermediate (blood glucose 145-180 mg/dL)		
Time spent in glucose band, tertile		
Least	1.4 (0.13-14.57)	.79
Intermediate	3.7 (0.39-34.33)	.20
Greatest	Reference	
Insulin dose administered§	1.02 (1.01-1.03)	<.001
Liberal (blood glucose 181-200 mg/dL)		
Time spent in glucose band, tertile		
Least	0.3 (0.07-1.71)	.18
Intermediate	0.4 (0.1-1.65)	.21
Greatest	Reference	
Insulin dose administered§	1.02 (1.01-1.03)	<.001
Hyperglycemic (blood glucose ≥201 mg/dL)		
Time spent in glucose band, tertile		
Least	0.4 (0.08-2.46)	.34
Intermediate	0.5 (0.1-2.34)	.37
Greatest	Reference	
Insulin dose administered§	1.02 (1.003-1.03)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
SI conversion factors: To convert glucose values to mmol/L, multiply mg/dL values by 0.0555.
*Table presents the results of all 6 models examined, 1 for each glucose band. Statistically significant ORs of greater than 1 indicate parameters that are predictive of death. Regarding time spent in a glucose band, the OR of death reflects the comparison with patients who spent the greater proportions of their admission in that band.
†From Wald test.
‡From likelihood ratio test.
§For a 1-IU/d increase.

We have demonstrated that glucose levels are inherently difficult to control. Thus, patients spent considerable periods of time with glucose levels outside the target range. At least in part, this likely reflects the plethora of variables that have an impact on levels of blood glucose,[6] including feeding regimen, catecholamine administration, stress response, insulin administration, inherent biovariability, and possibly apathy about a variable that may be considered by clinical staff to be of relatively minor importance. Since we wished to investigate the consequences of glucose control per se rather than its etiology, these variables were not included in the mathematical models. Moreover, we used indices of the 24-hour glucose control actually achieved, rather than measurements at a single reference time in our analyses, to incorporate the variability of the parameter into our models. We believe that this is an important characteristic of our study.

Our data suggest that hyperglycemia is the relevant variable determining outcome rather than absolute hypoinsulinemia, since increased insulin administration was associated with an increased risk of death, irrespective of prevailing glucose level. This is in agreement with the findings of other investigators,[3,10] as well as with other observational data indicating that level of plasma glucose at admission represents an independent risk factor for long-term prognosis after myocardial infarction,[11] in women following coronary artery bypass graft surgery (even in those without diabetes),[12,13] and in patients without diabetes but with traumatic brain injuries.[14,15] While there is still no proven mechanism to explain the detrimental effects of hyperglycemia, in vitro data demonstrate that the responsiveness of leukocytes stimulated with inflammatory mediators is inversely correlated with indices of in vivo glycemic control.[16] Other as-yet unproven explanations include exacerbation of polyneuropathy in critical illness, thereby prolonging mechanical ventilation, and undefined alterations in use of cellular energy substrates.

The detrimental effects of excessive exogenous insulin are interesting since the OR of death after increased administration of insulin was the same (1.02) for all glycemic bands. It is thus highly unlikely that there is a predictive mathematical interaction between insulin and glucose in our models. Since this interaction would be a marker of insulin resistance, this phenomenon is not additionally predictive of death in our model when all confounding variables are considered. Furthermore, the detrimental effects of excessive exogenous insulin parallel data from trials of growth hormone, another anabolic hormone, in critically ill patients.[17]

Hyperglycemia is common in critically ill patients, even those without diabetes mellitus.[6] However, if both hyperglycemia and increased administration of insulin are associated with increased risk of death, can manipulation of blood glucose to lower levels with infusions of soluble insulin reduce mortality? Published evidence suggests that such a strategy is effective in certain groups of critically ill patients,[3] as well as in those who have experienced acute myocardial infarction. The randomized, multicenter Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study[18] demonstrated a 30% reduction in 1-year mortality in patients with diabetes receiving an infusion of glucose-insulin-potassium acutely following myocardial infarction to maintain levels of blood glucose to below 210 mg/dL [11.7 mmol/L]. Similar benefits appear to be accrued in patients without diabetes even with concomitant thrombolysis.[19] Furthermore, a pilot study of glucose-insulin-potassium infusion in patients following ischemic brain injury has demonstrated its safety and strongly suggests a mortality benefit.[20] The main multicenter randomized trial testing this strategy (ie, the United Kingdom Glucose Insulin in Stroke Trial [GIST-UK]) is recruiting patients currently. The role of concomitant substrate administration in these studies is not defined. Finally, specific to the post–cardiac surgery population, intravenous infusions of insulin in patients with diabetes are associated with a lower incidence of sternal wound breakdown,[21] a complication that occurred in only 1 patient included in the current study.

The apparent contradiction between the adverse effects of hyperglycemia and increased administration of insulin provokes debate about the most appropriate target for glucose control. Our data suggest a threshold glucose level. Although the predicted ORs for time of exposure to specific bands were not statistically significant for the models presented, there is a transition from predictions of less than 1.0 in the top 2 glycemic bands to greater than 1.0 in the 4 lower glycemic bands. This suggests that patients who spent the least time within the top 2 bands (≥181 mg/dL [10.0 mmol/L]) were less likely to die than those who spent the most time there. This implies the presence of a threshold in the region of 180 mg/dL, but since the data were grouped into bands it is possible that the threshold is below 180 mg/dL (ie, somewhere within the band 145-180 mg/dL [8.0–10.0 mmol/L]). Thus, as long as more patients were advantaged than were disadvantaged in this lower band, the overall effect would still indicate no increased risk of death. Consequently, the most conservative estimate for the threshold lies at the lower point of this band, that is, 145 mg/dL. A similar argument applies to the band above (181-200 mg/dL [10.0-11.1 mmol/L]), which would indicate the most liberal estimate for the threshold to be 210 mg/dL. We therefore suggest that the most appropriate upper limit for glucose control is defined by the lower boundary of our threshold prediction (145 mg/dL [8.0 mmol/L]). This more relaxed target for glucose control will carry less risk of hypoglycemia, a complication with few subjective warning signs in sedated patients.

Our predicted ORs for time in glycemic band lacked statistical significance due to the strong influence of increased insulin dose on mortality coupled with the inevitably powerful relationship between high glucose lev-

els and increased administration of insulin. Indeed, when insulin was excluded from the models, ORs of less than 1.0 were statistically significant in the top 2 glycemic bands (data not shown). However, despite this limitation we believe the data demonstrate a coherent and consistent pattern.

Our data therefore imply that the control group (180-200 mg/dL [10.0-11.1 mmol/L]) in the recent study of intensive insulin therapy in critically ill patients[3] may have been disadvantaged, as opposed to there being a specific advantage conferred upon those whose blood glucose levels have been managed to 80 to 110 mg/dL [4.4-6.1 mmol/L]. This represents a subtle change in emphasis concerning that study's important results, but may be of critical importance in any confirmatory trials that may be undertaken.[22]

The limitations of our study should be noted. First, it represents an analysis of data that are automatically acquired, and is therefore liable to the inaccuracies inherent in this approach. Second, we cannot be certain that bias did not occur as blood glucose results deviated from the required range and more observations were made (see "Methods" section). Nevertheless, we attempted to obviate this possibility by time-weighting our observations. Finally, in common with previously published work,[3] our results apply to a relatively restricted ICU population, the majority of whom had undergone cardiothoracic surgery. Nevertheless, such patients represent the largest single-speciality consumer of critical-care resources in the United Kingdom.[23]

In conclusion, control of glucose levels, rather than absolute levels of exogenous insulin, account for the mortality benefit associated with intensive insulin therapy demonstrated by others.[3] On the basis of our observational data, we speculate that a target blood glucose level of less than 145 mg/dL (8.0 mmol/L) may be adequate. This target would be likely associated with less risk of inadvertent hypoglycemia than other suggested targets. We also have demonstrated the inherent variability in control of glucose levels. We suggest that studies investigating supportive strategies in critically ill patients, which target physiological parameters to specific ranges, consider the variability of the parameter in question and assess the actual time spent within the specific target range rather than using a single observation in time as a surrogate for this variable.

Author Contributions: Dr Finney, as principal investigator of this study, had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design; drafting of the manuscript: Finney, Evans.
Acquisition of data: Finney, Elia.
Analysis and interpretation of data; statistical expertise: Finney, Zekveld.
Critical revision of the manuscript for important intellectual content: Zekveld, Elia.
Administrative, technical, or material support: Elia.
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