Economic Benefits of Intensive Insulin Therapy in Critically Ill Patients

The Targeted Insulin Therapy to Improve Hospital Outcomes (TRIUMPH) Project

ARCHANA R. SADHU, MD[1]
ALFONSO C. ANG, PHD[2]
LESLIE A. INGRAM-DRAKE[3]
DOROTHY S. MARTINEZ, MD[1]
WILLA A. HSUEH, MD[1]
SUSAN L. ETTNER, PHD[2]

OBJECTIVE — The purpose of this study was to analyze the economic outcomes of a clinical program implemented to achieve strict glycemic control with intensive insulin therapy in patients admitted to the intensive care unit (ICU).

RESEARCH DESIGN AND METHODS — A difference-in-differences (quasi-experimental) study design was used to examine the associations of an intensive insulin therapy intervention with changes in hospital length of stay (ICU and total), costs (ICU and total), and mortality. Hospital administrative data were obtained for 6,719 adult patients admitted between 2003 and 2005 to one of five intervention or four comparison ICUs in a large academic medical center. Linear regression models with log transformations and appropriate retransformations were used to estimate length of stay (LOS) and costs; logistic regressions were used to estimate mortality.

RESULTS — After adjustment for observable patient characteristics and secular time trends, the intervention was consistently associated with lower average glucose levels and a trend toward shorter LOS, lower costs, and lower mortality. However, associations with resource use and outcomes were statistically significant in only ICU LOS, with an average reduction of 1.19 days of ICU care per admission. Other associations, although large in magnitude and in the hypothesized directions, were not estimated with sufficient precision to rule out other net effects. The associations with ICU days and costs were larger in magnitude than total days and costs.

CONCLUSIONS — A clinical team focused on hyperglycemia management for ICU patients can be a valuable investment with significant economic benefits for hospitals.

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Increasing evidence supports implementation of intensive insulin therapy (IIT) in critical illness. Close links between hyperglycemia in hospitalized patients and poor clinical outcomes have been demonstrated in a variety of hospital settings, such as during critical illness, after cardiothoracic surgery, organ transplant, stroke, and trauma, and even in general medical wards. Furthermore, interventional studies have demonstrated significant reductions in morbidity and mortality when illness-related hyperglycemia is treated with IIT (1–5). As institutions strive to achieve better glucose control for these patients, they are faced with both clinical and financial obstacles.

Although the evidence for clinical benefits of strict glucose control in hospitalized patients with illness-related hyperglycemia is mounting, the financial benefits are less well documented. Diabetic and nondiabetic patients with hyperglycemia have more complications, resulting in a longer hospital length of stay (LOS) and higher costs (6,7). In a retrospective analysis of cardiothoracic surgery patients with and without diabetes, each 50 mg/dl increase in glucose was associated with 0.76 more postoperative days, $2,824 more inpatient hospital charges, and $1,769 more inpatient hospital costs (6). In stroke patients, hyperglycemia >130 mg/dl on admission was related to a 1-day longer LOS and $1,349 higher inpatient hospital charges (7). These increased costs were partially due to the known complications of hyperglycemia, e.g., nosocomial catheter-related bloodstream infection (8). When one is accounting for morbidities such as the need for mechanical ventilation or dialysis, infections, and other complications, the costs of untreated hyperglycemia could be substantial.

Therefore, intensive treatment of hyperglycemia may reduce morbidity, which can translate to reductions in hospital LOS and costs. In fact, the few studies of IIT treatment that included financial analysis have shown significant cost reductions. A post hoc analysis of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, in which patients with diabetes and myocardial infarction were randomly assigned to intensive versus conventional glycemic control, estimated that IIT saved €16,900 per life-year gained (9). Similarly, a post hoc financial analysis of the 2001 Van den Berghe trial of surgical intensive care unit (ICU) patients demonstrated a cost savings of €2,638 per patient in the IIT group (10). Finally, a before and after design of patients admitted to one mixed medical-surgical ICU estimated that IIT decreased ICU LOS by 0.3 days and resulted in a cost savings of $1,580 per patient for the entire hospitalization (11).

Although suggestive that IIT resulted in hospital cost savings, these studies

From the [1]Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California; the [2]Division of General Internal Medicine and Health Services Research, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California; and the [3]Departments of Human Genetics/Pathology and Laboratory Medicine, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California.
Corresponding author: Archana R. Sadhu, asadhu@mednet.ucla.edu.
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were limited by their inability to distinguish effects of the intervention from secular time trends in hospital LOS, costs, and mortality, hence potentially confounding the estimated intervention effect. Moreover, only the last study was in a U.S. health care system. We sought to address these limitations by using a quasi-experimental study design to report the outcomes of a program dedicated for IIT in ICU patients at an academic U.S. medical center. Measures examined included mean glucose values, ICU LOS, total hospital LOS, ICU costs, total hospitalization costs, and inpatient mortality.

In January 2005, UCLA initiated a new clinical program, TRIUMPH (*Ta*R*-*geted *Ins*U*lin* therapy to i*MP*rove *H*ospital outcomes). The goal was to achieve strict glucose control in accordance with the evidence-based practice supported by American College of Endocrinology guidelines (12). Because UCLA has nine different ICUs, each with specialized patient populations, the program was implemented in several phases. Thus far, five of the nine ICUs have received the TRIUMPH intervention including the medical intensive care, coronary care, and cardiothoracic surgery units. These units were chosen on the basis of previously published benefits in these patient populations (1–6). Medical directors of these units were offered the intervention, and all of them willingly participated. The units that did not receive intervention included liver transplant, neurosurgery, trauma, and other postsurgical units.

A multidisciplinary approach was used to develop new insulin therapy protocols and educate the physicians, nurses, pharmacists, and dietitians. The intravenous insulin therapy protocol was a modified version of the Markovitz protocol (13), and the subcutaneous insulin protocol incorporated basal, nutritional, and corrective insulin (14). In the TRIUMPH units, intravenous insulin infusion was initiated when the measured glucose was >140 mg/dl. Per the 2004 American College of Endocrinology guidelines, the recommended target glucose ranges were 80–110 mg/dl in the ICU setting and 80–110 mg/dl preprandial value with a maximal glucose value of <180 mg/dl in the noncritical care setting (12). For the comparison units, glucose control was left to the discretion of those physicians and incorporated both intravenous insulin infusions and subcutaneous insulin therapy. However, these units did not use the TRIUMPH protocols and had varied glucose thresholds and target ranges.

The core TRIUMPH team consisted of an endocrinologist and a diabetes educator to oversee the management of patients on a daily basis from admission until discharge. Each patient admitted to an intervention ICU had glucose screening at regular intervals. If the glucose level was >140 mg/dl and confirmed on a repeat measurement, the TRIUMPH intravenous insulin protocol was initiated. Subcutaneous insulin was also used when clinically appropriate. In most cases, the TRIUMPH team managed glucose control from admission to discharge.

RESEARCH DESIGN AND METHODS

The study cohort was all patients aged ≥18 years who were admitted to one of five intervention or four comparison ICUs between 2003 and 2005 and who were discharged or died in the hospital by 31 December 2005 (n = 6,719). The main analyses included all patients, but sensitivity analyses (n = 5,787) excluded study patients who died before being discharged from the hospital.

To address potential confounding secular time trends in before and after comparisons, we used a quasi-experimental or "difference-in-differences" (DID) approach as described by Goldman et al. (15,16). We compared the changes between the preintervention (2003–2004) and postintervention (2005) periods among patients discharged from intervention units with comparable changes among patients discharged from comparison units. Comparable changes mean that the trajectories over time (i.e., the slope of the outcome as a function of time) should be similar, even if the starting point (i.e., the intercept) is different. Secular time trends refer to any other changes that are occurring in the health care system (or in this hospital in particular) that would have occurred even in the absence of the intervention. The DID estimate takes the average change over time and subtracts the portion that is likely to be attributable to secular time trends and not to the intervention per se. The validity of the estimated intervention effect relies on the assumption that (adjusting for observable patient characteristics) the underlying time trends in the outcomes would have been similar for the intervention- and comparison-unit patients in the absence of an intervention. However, the intervention effect is the calculated net of the preexisting differences, thus accounting for the possibility that the intervention patients may have started off at lower levels of utilization and costs. Because this study design accounts for secular time trends, it implicitly takes into account factors such as price inflation, changes in hospital-wide financial practices, and ICU procedural changes or other clinical practices not related to glucose management that can affect LOS, hospital costs, and mortality.

Outcome measures

Glucose measurements were obtained from a database consisting of all point of care testing as well as serum glucose measurements from the laboratory. Hospital accounting records were used to obtain information on the total and direct variable costs, total and direct variable ICU costs, total and ICU LOS, and inpatient mortality. Total costs included direct variable, indirect variable, direct fixed, and indirect fixed. Direct costs were those charged specifically to a revenue-producing cost center; these costs were most closely related to providing patient care. Examples of direct departments are nursing units, radiology, clinical laboratories, and pharmacy. Indirect costs represent departments that support patient care rather than provide patient care. Examples of indirect departments are patient escort, nutrition, administration, and financial services. Variable costs change when volume changes, whereas fixed costs do not change, at least for small changes in volume.

Although variable costs are the most relevant in the short run, an argument can be made for examining fixed costs as well. From the point of view of a capacity-constrained medical center, an important benefit of discharging patients earlier is the ability to use the beds for new patients, commonly referred to in hospital economics as "throughput." This benefit is implicitly taken into account when fixed costs are included in the analysis. The fixed costs are proxies for the true "opportunity cost" of the capital (including building space), that is, its value for other uses, such as serving other patients.

Explanatory variables

All regression models included an intercept and the following: patient's sex, race, Latino ethnicity, age and its square, insurance type, indicators for complications before admission, baseline illness severity category (calculated by industry standard

Table 1—*Characteristics of study population by intervention status*

Characteristic	Patients treated in intervention units			Patients treated in comparison units		
	Preintervention period	Postintervention period	*P* value for difference	Preintervention period	Postintervention period	*P* value for difference
n	2,167	1,058		2,406	1,088	
Age (years)	61.2 ± 17.0	61.1 ± 17.6	0.85	54.7 ± 17.3	54.1 ± 17.4	0.29
Female sex	38.4	39.4	0.59	43.8	42.1	0.34
Latino ethnicity	13.7	11.2	0.06	21.1	22.1	0.49
Race						
Caucasian	82.4	79.9	0.08	79.8	79.9	0.94
African American	6.5	7.8	0.16	7.5	7.0	0.60
Asian	7.7	8.3	0.55	8.9	8.4	0.61
Other	3.4	3.7	0.69	3.8	4.1	0.62
Insurance						
Contract/capitated	41.8	43.4	0.39	53.5	51.8	0.35
Medicare	46.2	45.0	0.52	29.3	26.8	0.13
Medi-Cal	7.3	7.7	0.67	8.3	10.6	0.03
Other	4.7	3.9	0.31	8.8	10.7	0.07
Complications at admission	4.7	4.0	0.37	4.1	2.3	0.01
Medical illness severity score	3.17 ± 0.86	3.24 ± 0.84	0.07	3.12 ± 0.98	3.14 ± 0.94	0.63

Data are means ± SD or %.

proprietary software, 3M APR DRG, and based on Medicare All Patient Refined Diagnostic-Related Group system), a linear time trend for the year of admission, an indicator for type of unit (intervention versus comparison), and an interaction between indicators for admission time period (postintervention versus preintervention) and type of unit. Patients were assigned to time periods and units based on their admission date and admission unit.

The linear time trend allows the outcome measures to change over time even in the absence of any intervention, due to secular trends in length of stay and costs. The indicator for type of unit allows the intervention units to start off at higher or lower levels than comparison units. The intervention effect is captured by the interaction between time period and type of intervention. For example, if costs increase over time for both the intervention and comparison units, then the cost increase between the pre- and postintervention periods would have to be smaller for the intervention units than for the control units to conclude that the intervention was associated with a cost reduction. Conversely, if costs decline over time, then the cost decrease would have to be larger for the intervention units.

Statistical analyses

χ^2 and Wilcoxon tests were used to examine differences in the demographic and clinical characteristics of the intervention and comparison patients. Because of the skewed distributions of the cost and LOS measures, these outcomes were log-transformed in linear regressions, and the estimates were retransformed to calculate intervention effects on costs and LOS measured on the original scales. The regression-adjusted differences in cost and LOS associated with the intervention were calculated by predicting the value of a given outcome *Y* under four scenarios (intervention postoutcome, intervention preoutcome, comparison postoutcome, and comparison preoutcome) and taking the DID: $[(Y_{\text{interv, post}} - Y_{\text{interv, pre}}) - (Y_{\text{comp, post}} - Y_{\text{comp, pre}})]$ (15). We used 2003 as the preintervention comparison year, and all other regressors were kept at their reported values. The sample mean of the DID estimate was reported along with the bias-corrected, empirical 95% CI, derived using 1,000 bootstrap replicates with replacement (17). Statistical significance at the 5% level of type I error was determined by examining whether the 95% CI excluded 0.

In early analyses, we examined several alternative regression specifications that allowed more flexibility, e.g., models allowing each unit to have its own intercept. The specifications yielded findings consistent with the final specification, but because of concerns about overfitting and interpretability of the results, the most parsimonious specification was ultimately chosen. We also performed outlier analysis to see whether patients with extremely high resource use were skewing the results. Excluding the outliers did not notably influence our results, although in the end, we used log transformations for skewed outcomes to obtain more efficient estimates. Finally, we estimated random effects models to determine whether the conclusions were sensitive to possible clustering, i.e., within-unit correlation of the error terms. The intraclass correlation was very low, and our conclusions did not change on the basis of these estimates.

RESULTS

Changes over time in the case mix of intervention versus comparison patients

We first examined the changes in observed patient case mix between the pre- and postintervention periods (Table 1). The rate of having any complications at admission declined from 4.1 to 2.3% over time within patients treated in the comparison units ($P = 0.01$). Although the rate also declined among patients treated in intervention units (from 4.7 to 4.0%), the change was smaller and not significant. The only other significant change was a slight increase between the pre- and post-intervention periods in the proportion of comparison-unit patients with Medi-Cal insurance ($P = 0.03$).

Whether the patient had complications at admission was controlled in the regressions so this measure itself should not bias the comparisons. On the other

Table 2—*Association of intervention with changes in costs, LOS, and mortality*

Outcome	Change in outcome (deceased patients included)	Change in outcome (deceased patients excluded)
n	6,719	5,787
Total costs	−$4,746 (−$10,509 to $1,832)	−$2,957 (−$8,347 to $2,692)
Direct variable costs	−$2,210 (−$5,593 to $1,584)	−$1,179 (−$4,409 to $2,056)
Total ICU costs	−$5231 (−$13,775 to $3,591)	−$2948 (−$11,184 to $5,500)
Direct variable ICU costs	−$1143 (−$4,096 to $2,068)	−$426 (−$3,305 to $2,589)
Total days	−0.47 (−1.87 to 1.02)	0.31 (−0.87 to 1.74)
ICU days	−1.19 (−1.93 to −0.43)*	−0.73 (−1.48 to 0.11)
Mortality	−0.011 (−0.05 to 0.03)	—

Data are means (95% empirical, bias-corrected bootstrapped CI) of the DID estimate. Estimates are based on a linear regression with log transformation and appropriate retransformation algorithm (ref. 18). All regressions control for the patient characteristics shown in Table 1, as well as for a squared age term, a linear time trend, an indicator for type of unit (intervention versus comparison), and an interaction between indicators for time period (postintervention versus preintervention) and type of unit. *Significant at $P \leq 0.05$.

hand, the more rapid decline in this rate over time among the comparison patients than among the intervention patients could mean that the comparison patients were becoming relatively healthier over time in ways that were *not* captured by our data. If so, then our study design may yield a conservative estimate of the intervention effects.

Glucose measurements in the intervention and comparison units

The mean glucose value for each patient admitted in each unit was calculated for the years 2004 and 2005. Only one preintervention year, 2004, was used owing to the very large number of measurements. It was assumed that the year 2003 did not differ from 2004 because the clinical practice of glucose control was not different. In addition, any bias would have been in the favor of the comparison units because the practice of strict glucose control was gaining more attention in these years even in the absence of a formal intervention. The reduction in mean glucose between the pre- and postintervention year was 21.5 mg/dl in the intervention units. In the comparison units, the difference in mean glucose was 2.3 mg/dl. Regression models looking at associations of the intervention with changes in blood glucose during the patient stay using the same quasi-experimental study design also showed large intervention effects.

Unadjusted associations of the intervention with outcomes

The DID study design relies on the assumption that the time trends that would have occurred in the absence of any intervention are similar for the intervention and comparison patients. To examine the validity of this assumption, we plotted the unadjusted changes in the outcome measures during the preintervention period (2003–2004) separately for intervention versus comparison patients (Fig. 1*a*–*g* of the online appendix [available at http://dx.doi.org/10.2337/dc07-2456]). Overall, the preintervention time trends looked similar for the intervention and comparison patients. Where they did not, the preintervention trends looked worse for the intervention patients, e.g., LOS and costs increased more rapidly over time and the mortality rate increased instead of declining. Therefore if anything, we expect that the DID estimate would suggest smaller intervention effects than the actual improvements in outcomes associated with the intervention, i.e., a conservative bias.

Regression-adjusted associations of the intervention with the outcomes

After adjusting for observable patient characteristics and confounding time trends using the DID approach, the intervention was consistently associated with lower resource use and better outcomes. However, the associations were statistically significant only in the ICU LOS, with an average reduction of 1.19 days of ICU care per admission (column 2, Table 2). Not surprisingly, the associations of the intervention with direct variable cost were smaller in magnitude than its associations with the total cost measures. Interestingly, the magnitudes of the associations with the intervention were larger for ICU days and costs than for total LOS and costs, suggesting that an increase in non-ICU utilization might have partially offset the decline in ICU use. The one statistically significant association, that of the intervention with ICU days, was quite large in magnitude. To put the magnitude of the reduction in ICU LOS of 1.19 days into context, the baseline mean ICU LOS of the entire intervention units group was 9.53 days (SD = 16.74).

Excluding patients who died before discharge yielded associations that were smaller and not statistically significant (column 3, Table 2). The resource use of the deceased patients was much higher than that of the nondeceased patients. The intervention was associated with an absolute reduction of 1.1% in mortality, compared with a baseline mortality rate of 14%. Even though this association did not reach statistical significance, it explains why the intervention effects on costs are greater when the deceased patients are included.

CONCLUSIONS — Using a DID (or quasi-experimental) study design to account for the potential confounders inherent in pre-post comparisons, we found that a multidisciplinary approach to intensive glucose management of critically ill patients resulted in greater reductions in mean glucose values, whereas comparison patients had essentially no change in mean glucose from the year before to the year after the intervention was introduced. The intervention was also associated with a trend toward lower mortality and lower resource use such as ICU and total inpatient days and all cost measures examined. Statistical significance was confined to the association with ICU days, but the effects on other outcomes were all in the same direction and large in magnitude (e.g., a reduction of $5,231 in total ICU costs). These results suggest that the intervention might have had a broader influence, but that high variability in the

outcome measures reduced our power to measure them with sufficient precision. Although we accounted for obvious costs related to delivering IIT such as increased nursing effort, glucose monitoring supplies, and insulin in the direct cost analysis, our current database did not allow us to identify specific components of clinical care that may be directly related to the observed savings in LOS and costs. This would undoubtedly be a useful area for future research. Effect sizes for the utilization and cost measures were reduced when patients who died (who tended to be more expensive) were excluded from the sample, suggesting that the effect of the intervention on inpatient resource use resulted in part from helping to keep patients alive, at least until discharge. This study is subject to certain limitations. Most notably, the intervention was studied in a single academic medical center, so results may not apply to other settings. Patients whose stays occurred in part before the intervention and in part after the intervention were assigned to the preintervention period. This measurement error may bias our estimates in a conservative direction. In the intervention units, IIT was implemented by the TRIUMPH clinical service under formalized protocols. The comparison units also used insulin therapy at the discretion of the physician, but this was done on an individual basis and without the TRIUMPH protocols. However, this crossover should only lead to a conservative bias of our outcomes.

Our DID study design also relies on the assumption that the secular time trends affecting the intervention and comparison units are similar. If this assumption fails, then our estimates may be misleading. For example, if inflation increased costs in the comparison units to a greater degree than that in the intervention units, then we might overstate the association of the intervention with reductions in costs (although inflation per se would not affect associations with LOS). However, graphs of the preexisting time trends suggest that if anything, the opposite was probably true, i.e., that the intervention units had worse trajectories of change over time, and therefore the improvement in outcomes after the introduction of the intervention represented an even greater achievement. In any event, this DID assumption should be more valid than that of earlier pre-post study designs that did not take secular time trends into account at all.

We calculated a potential ICU cost savings of $5.5 million in the group of patients treated by the TRIUMPH team in the first year after the implementation of the intervention. At $5.0 million, the total cost savings was slightly less than ICU costs, but nevertheless substantial. The costs of setting up the program that were not already included in the analysis were limited to the salaries of a full-time endocrinologist and a diabetes educator. The costs of delivery of care (e.g., insulin, glucose meters and strips, and nursing time) were already included in the cost measures. Thus, the potential savings associated with the intervention appear to far outweigh the costs. As technological advances are made in the areas of automated electronic protocols, continuous glucose sensors, and insulin infusion devices, the costs of implementation may be even less. Furthermore, as physician extenders such as nurse practitioners and physician assistants are used to expand the service to treat larger numbers of ICU patients, the investment in the program will be small in comparison to the potential savings.

Our findings suggest that hospital administrators should seriously consider implementing a dedicated program for intensive glucose management in the ICU. As more knowledge is gained about the benefits of glucose control among non–critically ill patients, these programs might be expanded to this population as well. The per-patient cost savings may not be as impressive in this group, but the larger numbers of patients may allow the intervention to have a significant impact on hospital economics (19,20). Further investigation is needed to determine the level of glucose control that is most beneficial in these patients and how the glucose management program can be tailored to ensure a favorable return on investment.

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References

1. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruynickx F, Schetz M, Vlasselaers D, Ferinande P, Lauwers P, Bouillon R: Intensive insulin therapy in critically ill patients. *N Engl J Med* 345: 1359–1367, 2001
2. Krinsley JS: Effect of intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 79:992–1000, 2004
3. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449–461, 2006
4. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 125:1007–1021, 2003
5. Malmberg K, Ryden L, Efendic S, Werlitz J, Nicol P, Waldenström A, Wedel H, Welin L: Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 26:57–65, 1995
6. Estrada CA, Young JA, Nifong W, Chitwood R: Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg* 75: 1392–1398, 2003
7. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR: Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology* 59:67–71, 2002
8. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, Decruyenaere J, Vogelaers D, Colardyn F, Vendewoude KH: Clinical and economic outcomes in critically ill patients with nosocomial catheter related bloodstream infections. *Clin Infectious Dis* 41: 1591–1598, 2005
9. Almbrand B, Johannesson M, Sjostrand B, Malmberg K, Ryden L: Cost effectiveness of intense insulin treatment after acute myocardial infarction in the DIGAMI study. *Eur Heart J* 21:733–739, 2000
10. Van Den Berghe G, Wouters P, Kesteloot K, Hilleman D: Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. *Crit Care Med* 34:612–616, 2006
11. Krinsley J, Jones R: Cost analysis of intensive glycemic control in critically ill adult patients. *Chest* 129:644–650, 2006
12. Garber AJ, Moghissi ES, Bransome ED Jr, Clark NG, Clement S, Cobin RH, Furnary AP, Hirsch IB, Levy P, Roberts R, Van Den Berghe G, Zamudio V:

American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract* 10: 77–82, 2004
13. Markovitz LJ, Wiechmann RJ, Harris N, Hayden V, Cooper J, Johnson G, Harelstad R, Calkins L, and Braithwaite SS: Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. *Endocr Pract* 8:10–18, 2002
14. Clement S, Braithwaite S, Magee M, Ahnann A, Smith EP, Schafer RG, Hirsch IB: Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 27:553–590, 2004
15. Goldman HH, Frank RG, Burnam MA, Huskamp HA, Ridgely MS, Normand SL, Young AS, Barry CL, Azzone V, Busch AB, Azrin ST, Moran G, Lichtenstein C, Blasinsky M: Behavioral health insurance parity for federal employees. *N Engl J Med* 354:1378–1386, 2006
16. Cook TD, Campbell DT *Quasi-Experimentation: Design and Analysis Issues for Field Settings*. Boston, Houghton Mifflin Company, 1979
17. Mooney CZ, Duval RD. *Bootstrapping: A Nonparametric Approach to Statistical Inference*. Quantitative Applications in the Social Sciences No. 95. Newbury Park, CA, Sage Publications, 1993 18. Duan: 1983
18. Duan N: Smearing estimator: a nonparametric retransformation method. *J Am Stat Assoc* 78:605–610, 1983
19. Olson L, Muchmore J, Lawrence B: The benefits of inpatient diabetes care: improving quality of care and the bottom line. *Endocr Pract* 12 (Suppl. 3):35–42, 2006
20. Newton CA, Young S: Financial implications of glycemic control: results of an inpatient diabetes management program. *Endocr Pract* 12 (Suppl. 3):43–48, 2006