

## EFFECT OF HYPERGLYCEMIA AND CONTINUOUS INTRAVENOUS INSULIN INFUSIONS ON OUTCOMES OF CARDIAC SURGICAL PROCEDURES: THE PORTLAND DIABETIC PROJECT

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### ABSTRACT

**Objective:** To describe the main findings of the Portland Diabetic Project, which elucidates the adverse relationship between hyperglycemia and outcomes of cardiac surgical procedures in patients with diabetes and delineates the protective effects of intravenous insulin therapy in reducing those adverse outcomes.

**Results:** In this ongoing 17-year prospective, nonrandomized, interventional study of 4,864 patients with diabetes who underwent an open-heart surgical procedure, we investigated the effects of hyperglycemia, and its subsequent reduction by continuous intravenous insulin (CII) therapy, on in-hospital outcomes. Increasing blood glucose levels were found to be directly associated with increasing rates of death, deep sternal wound infections (DSWI), length of hospital stay (LOS), and hospital cost. In separate multivariate analyses, increasing hyperglycemia was found to be independently predictive of increasing mortality ( $P < 0.0001$ ), DSWI ( $P = 0.017$ ), and LOS ( $P < 0.002$ ). Conversely, CII therapy, designed to achieve predetermined target blood glucose levels, independently reduced the risks of death and DSWI by 57% and 66%, respectively ( $P < 0.0001$  for both). Target blood glucose levels of less than 150 mg/dL and a 3-day postoperative duration of CII therapy are both important variables that determine the effect of the CII therapy on improved outcomes. Coronary artery bypass grafting-related mortality (2.5%) and DSWI rates (0.8%) in patients with diabetes were normalized to those of the nondiabetic population by the use of the Portland CII Protocol.

**Conclusion:** Perioperative hyperglycemia in patients undergoing a cardiac surgical procedure affects biochemical and physiologic functions, which, in turn, adversely alter mortality, LOS, and infection rates. The Portland CII

Protocol is a cost-efficient method that effectively eliminates hyperglycemia and reduces postoperative morbidity and mortality in patients with diabetes undergoing an open-heart operation. CII protocols should be the standard care for glycometabolic control in all patients undergoing cardiac surgical procedures. (*Endocr Pract.* 2004; 10[Suppl 2]:21-33)

### Abbreviations:

**AHA** = American Heart Association; **3-BG** = 3-day average postoperative blood glucose; **CABG** = coronary artery bypass grafting; **CII** = continuous intravenous insulin; **DSWI** = deep sternal wound infection; **ICU** = intensive-care unit; **LOS** = length of hospital stay; **OR** = odds ratio; **RR** = relative risk; **SQI** = subcutaneous insulin

### INTRODUCTION

The Portland Diabetic Project is a prospective, nonrandomized, interventional research study of the effects of hyperglycemia and its pharmacologic reduction on the adverse outcomes of cardiac surgical procedures in patients with diabetes. The general hypothesis of this ongoing 17-year project is that the normalization of perioperative hyperglycemia in patients with diabetes undergoing open-heart surgical procedures will eliminate any incremental morbidity and mortality risks previously ascribed to the preoperative risk factor "diabetes."

For effective testing of this hypothesis, an automated continuous intravenous insulin (CII) protocol was designed to maintain the blood glucose levels of patients within a predetermined target range. Over time, this has become known as the "Portland Protocol." Our logic-based temporal study design has always first sought to demonstrate a significant independent association between hyperglycemia and each outcome endpoint studied. Second, we serially investigated whether a CII protocol significantly reduced the incidence of that hyperglycemia-related outcome. Finally, we have reviewed the basic science literature in an attempt to explain to practicing clinicians the potential underlying biochemical or physiologic mechanisms responsible for

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the altered outcome. This report will summarize and update our published findings to date.

## DEMOGRAPHICS AND METHODS

Between January 1987 and September 2003, a total of 21,614 patients underwent open-heart surgical procedures at St. Vincent Medical Center in Portland, Oregon. All patients with diabetes who had any open-heart surgical procedure (N = 4,864; 23% of the aforementioned overall group of patients) were included in this study. To date, this subgroup includes 4,021 coronary artery bypass grafting (CABG) procedures, 365 isolated valve procedures, 419 combined valve and CABG operations, and 59 other operations. Preadmission methods of glycemic control included subcutaneous administration of insulin in 33%, orally administered hypoglycemic agents alone in 51%, and diet alone in 11%. Five percent of the patients in this study had undiagnosed diabetes at the time of admission for the open-heart operation. The mean age of the patients was 65 ± 10 years, and 62% of the patients were men.

All patients in the Portland Diabetic Project have undergone prospective measurement of blood glucose levels (by finger-stick method or arterial line drop sample) every 30 minutes to 2 hours throughout the perioperative period. Average daily glucose levels, along with known preoperative risk factors for morbidity or mortality, were routinely entered into our database for later analysis.

### Definitions

Definitions from the database of the Society of Thoracic Surgeons were used for all variables common with that database. Other variables unique to this study were defined as indicated in the following material.

### Diabetes

All patients admitted to the hospital with a comorbid diagnosis of diabetes mellitus qualified for entry into this study. Patients not previously diagnosed as having diabetes but who had persistently high postoperative blood glucose levels (>200 mg/dL) and a dismissal requirement for pharmacologic glycemic control were also included. These patients were identified as having newly diagnosed diabetes during their admission for CABG. Patients who had transient perioperative (stress-related) hyperglycemia but who did not leave the hospital with a requirement for pharmacologic reduction of blood glucose levels were not included in this study.

### 3-Day Average Postoperative Blood Glucose

The composite average of the daily mean blood glucose levels from the day of the surgical intervention as well as the first and second postoperative days was labeled as the 3-day average postoperative blood glucose (3-BG). This variable was used as the primary indicator of the pharmacologic effectiveness of hyperglycemic treatment in this study.

### Deep Sternal Wound Infection

A deep sternal wound infection (DSWI) was any chest wound infection involving the sternum or mediastinal tissues, including mediastinitis, within 12 months after the date of the cardiac surgical procedure.

### Mortality or Death

Mortality was considered any in-hospital death occurring at any time during admission for CABG after the start of that surgical procedure.

### Cardiac-Related Mortality

All deaths in which arrhythmia or pump failure was identified as the seminal cause of death were classified as cardiac-related mortality.

### Study Groups

All study patients with diabetes who underwent an open-heart operation were divided into two sequential groups, based on the type of perioperative glycemic control they received.

### Subcutaneous Insulin Group

Patients operated on between January 1987 and September 1991 (N = 968) received subcutaneous insulin (SQI) injections every 4 hours in a directed aggressive attempt to maintain their blood glucose levels below 200 mg/dL. Sliding-scale dosage of insulin was titrated to each patient's glycemic response over the previous 4 hours. These every-4-hour sliding-scale SQI injections were continued throughout the patients' hospital course, even after they resumed their preoperative glucose control regimen.

### Continuous Intravenous Insulin Group

All patients with diabetes who underwent CABG between October 1991 and December 2001 (N = 3,896) received a CII infusion titrated by protocol (the Portland Protocol) during the perioperative period. The latest version of the Portland Protocol (Appendix 1) was implemented in gradual steps designed to maintain patient safety, prevent hypoglycemia, and ensure nursing comfort and compliance, while rapidly and effectively bringing blood glucose values into the "target range." This protocol prescribes insulin initiation, infusion, and titration rates and glucose testing frequency requirements for safe maintenance of a patient's blood glucose concentration between desired target levels. Between 1991 and 1998, the target blood glucose range was 150 to 200 mg/dL; in 1999, it was decreased to 125 to 175 mg/dL; and in 2001, the target glucose range was again lowered to 100 to 150 mg/dL. From 1992 to 1994, the Portland Protocol was used postoperatively only in the intensive-care unit (ICU) and was stopped when the patient was transferred to the telemetry unit. In January 1995, use of the protocol was expanded, with initiation in the operating room (before sternotomy, after induction of anesthesia, with continuation during cardiopulmonary bypass) and uniform continuation until 7

AM of the third postoperative day, even for patients who had been transferred out of the ICU (Table 1).

Serum potassium levels were maintained between 4.0 and 5.5 mEq/L through the administration of exogenous potassium. In the ICU, this was accomplished through the intravenous administration of potassium by standardized protocol. Oral potassium supplementation was given to maintain these levels once patients were tolerating enteral nutrition and their CII and glucose levels had stabilized.

**Data Analysis**

Infection, length of hospital stay (LOS), and in-hospital mortality were the primary endpoints of the various phases of this study to date. Patient groups were analyzed on an intent-to-treat basis. Univariate analyses between groups were done with use of *t* tests and chi-square analyses. Bonferroni's correction was applied to adjust for multiple comparisons between groups. Stepwise logistic regression was used to produce risk models for infection and hospital death, whereas Cox regression was used for LOS. Model discrimination was measured by use of *c*-statistics (area under the receiver operating characteristic curve), and the Hosmer-Lemeshow goodness-of-fit test was used to measure calibration. All statistical analyses were performed with use of SPSS software, version 10.0 (SPSS Inc, Chicago, IL).

**FINDINGS**

**Is hyperglycemia associated with an increased incidence of DSWI (including mediastinitis)?**

*Original Data and Conclusions*

Among 1,500 patients studied between 1987 and 1994 (1), hyperglycemia during the first 48 hours after the cardiac surgical procedure was found to be univariately

( $P < 0.001$ ), and independently ( $P = 0.017$ ), associated with a significant increase in the incidence of DSWI. Specifically, patients with mean 48-hour blood glucose levels above 200 mg/dL had a 2.2 times higher risk of DSWI than those with glucose levels of less than 200 mg/dL. In addition, those patients who had DSWI were shown to have had significantly higher perioperative blood glucose levels (before the onset of infection) than those who did not have DSWI (207 mg/dL versus 187 mg/dL;  $P < 0.01$ ).

Importantly, detailed examination of our data indicated that not only were blood glucose levels on the day of the cardiac surgical procedure and the first postoperative day (the components of the mean 48-hour blood glucose value) independently predictive of DSWI but also mean glucose levels on the second postoperative day were likewise predictive of an increased risk of DSWI ( $P < 0.01$ ). Blood glucose levels on the third and fourth postoperative days, however, were not independently, or univariately, associated with an increased risk of DSWI. For this reason, all subsequent analyses (beginning in 1995) have used our current definition of "3-BG," as indicated in "Demographics and Methods."

We concluded that hyperglycemia in patients with diabetes—not the diagnosis of diabetes itself—was the causal factor for infection and that this association persists for at least the day of the surgical intervention and the first and second postoperative days.

*2003 Update*

Current data, through September 2003, continue to support our original findings, first presented in 1995. An increasing 3-BG has a direct relationship with the incidence of DSWI (Fig. 1). We have now identified an apparent inflection point at 175 mg/dL, at which the incidence of DSWI begins to increase significantly. This finding cor-

**Table 1**  
**Phased Implementation of the**  
**Portland Continuous Intravenous Insulin Protocol\***

Dates	BG control	Hospital location	Target BG (mg/dL)	3-BG <200 mg/dL (%)
1987-1991	SQI	ICU/floor	<200	47
1992-1994	CII	ICU only	150-200	75
1995-1998	CII	OR/ICU/floor	150-200	78
1999-2000	CII	OR/ICU/floor	125-175	94
2001-2003	CII	OR/ICU/floor	100-150	99.7

\*BG = blood glucose; 3-BG = 3-day average postoperative blood glucose; CII = continuous intravenous insulin; ICU = intensive-care unit; OR = operating room; SQI = subcutaneous insulin.

relates well with the proposed biochemical mechanism for increased infection-associated hyperglycemia discussed in the subsequent material.

**Does CII infusion, designed to reduce the incidence of significant hyperglycemia, reduce the incidence of DSWI?**

**Original Data and Conclusions**

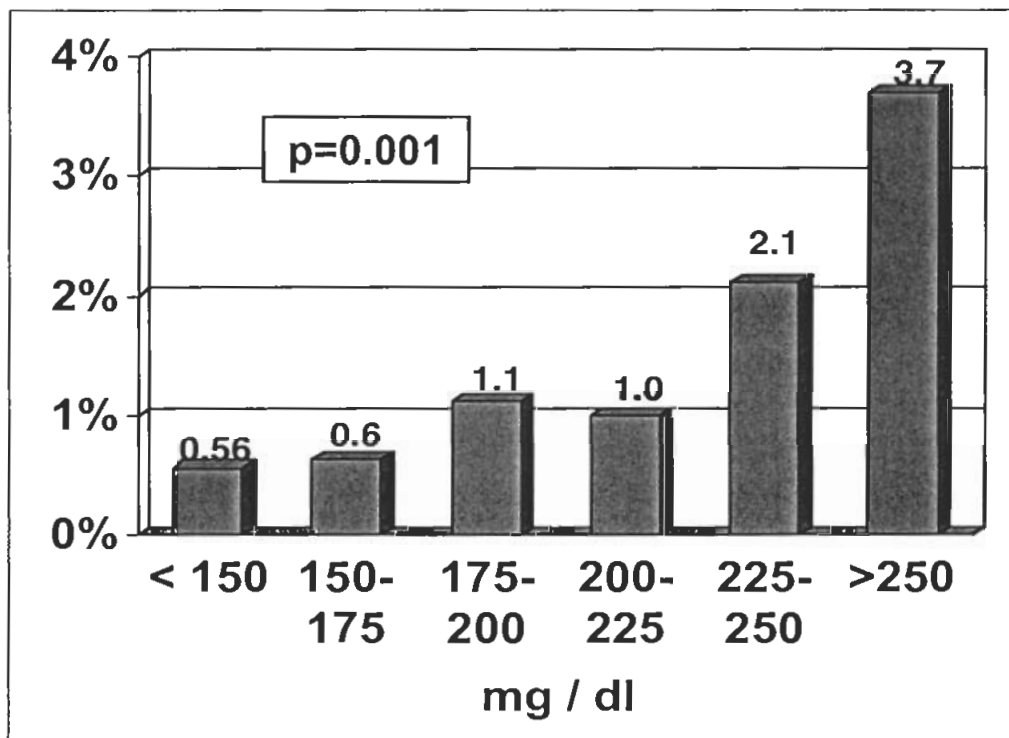
This second hypothesis was investigated in 2,467 patients enrolled in our study between 1987 and 1997 (2). By this time, 968 patients had been enrolled in the SQI group, and 1,499 patients were enrolled in the CII group at a blood glucose target of 150 to 200 mg/dL. The resultant incidence of DSWI in the CII group was only 0.8%, whereas that in the SQI group was 2.0% ( $P < 0.01$ ). This significant reduction in DSWI with CII therapy occurred despite a significantly negative bias against the CII group in terms of the prevalence of other risk factors for infection in that group. These factors included a more obese population and higher rates of chronic obstructive pulmonary disease, corticosteroid use, emergent surgical procedures, and multiple internal thoracic artery grafting. Of note, the 2.0% DSWI rate in the SQI control group was, at that time, the lowest published incidence of DSWI in a population of patients with diabetes undergoing an open-heart surgical procedure and being given SQI therapy.

Multivariate analysis revealed that the Portland CII Protocol significantly and independently reduced the risk of DSWI by 66% (relative risk [RR], 0.34;  $P < 0.005$ ; c-sta-

tistic, 0.762). At this point, obesity was the only other independent predictor of DSWI, increasing the risk by 6% for each unit increase in body mass index ( $P = 0.03$ ). The introduction and modification of the Portland CII Protocol had a dramatic effect on the annual incidence of DSWI at our medical center (Fig. 2). Since 1994, no significant differences in the rates of DSWI have been found between patients with and those without diabetes who have undergone open-heart surgical procedures at our institution.

Of note, the rates of DSWI in patients with diabetes were normalized to those of the nondiabetic population only after the duration of use of the protocol was expanded to include initiation in the operating room and continuation on the non-ICU telemetry floors until 7 AM of the third postoperative day (Fig. 2 and Table 1). This protocol expansion occurred because of the significant data found during the first phase of our study correlating infection rates with hyperglycemia even on the second postoperative day. In patients in whom the protocol was used only in the ICU (for less than the currently recommended 3 days), the incidence of DSWI was 1.3%—a significant reduction from that with use of SQI therapy but not normalized to that of the nondiabetic population.

We again concluded that hyperglycemia through the first 3 days after an open-heart surgical procedure was the causal factor for infection and that the incidence of DSWI in patients with diabetes could be normalized to that of the nondiabetic population through the Portland CII Protocol, which substantially and safely eliminates hyperglycemia. The biochemical mechanisms responsible for the increase



**Fig. 1.** Rates of deep sternal wound infection in 4,864 patients with diabetes who underwent an open-heart surgical procedure, stratified by 3-day average postoperative blood glucose sextile. Note apparent inflection point at 175 to 200 mg/dL.

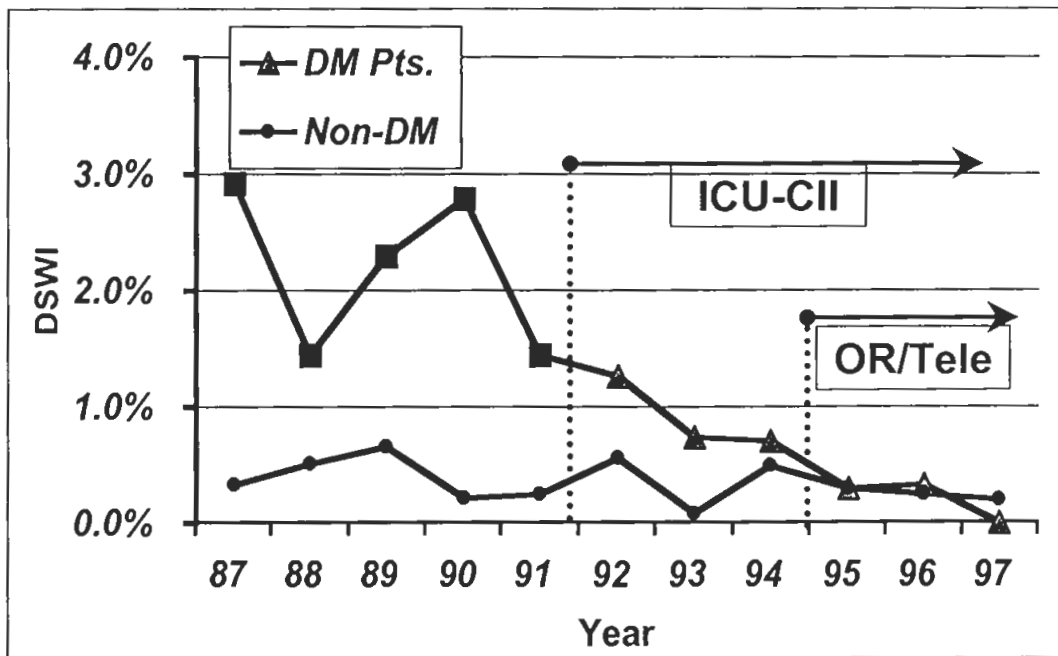


Fig. 2. Incidence of deep sternal wound infection (DSWI) in patients with and without diabetes mellitus (DM) who underwent an open-heart surgical procedure at St. Vincent Medical Center (Portland, Oregon) between 1987 and 1997. Data points to the left of the longer vertical dotted line indicate patients treated with subcutaneous insulin injections; initiation of the Portland Continuous Intravenous Insulin Protocol in the intensive-care unit (ICU-CII) in 1992 and expansion of that protocol to the operating room and non-ICU telemetry floors (OR/Tele) in 1995 are marked (vertical dotted lines).

in infection rates are related to the direct effects of hyperglycemia on proteins critical to adequate immune function. These mechanisms are explained in more detail elsewhere in this issue.

### 2003 Update

In 4,864 patients to date, the Portland CII Protocol continues to provide a protective effect against DSWI. Thus far, the overall incidence of DSWI in all our patients receiving CII therapy is 0.7%. The current annual incidence ranges from 0.3 to 0.7%. CII therapy continues to be a powerful independently protective factor against DSWI (RR, 0.39;  $P < 0.01$ ).

### Does the Portland Protocol safely and effectively reduce the incidence of hyperglycemia?

As noted in detail in "Demographics and Methods," the Portland CII Protocol was implemented in gradual steps designed to maintain patient safety, prevent hypoglycemia, and ensure nursing comfort and compliance, while rapidly and effectively bringing blood glucose levels into the target range.

Because of the automated and aggressive nature of the Portland CII Protocol, it was not feasible for us to conduct this study in synchronously randomized fashion. Administrative, institutional review board, and nursing acceptance of the use of CII titration in patients with what was considered euglycemia, or mild hyperglycemia in 1992 through 1996, was initially difficult programmatically. Nursing and administrative concerns about iatrogeni-

cally induced hypoglycemia in this "high-visibility" patient population had to first be assuaged. This goal was gradually accomplished first in the ICU and then on the telemetry floor through rigorous and repeated in-service training conferences. When the protocol was finally functioning smoothly in the desired units, target blood glucose levels were then gradually lowered. Thus, strides toward the goal of universal euglycemia in this patient population through 3 postoperative days have been implemented through four successive iterations of the CII protocol (Table 1). Each successive iteration of the protocol was modified from lessons learned during use of the previous protocol to achieve the target range more rapidly, to avoid hypoglycemia more completely, and to maintain 3-BG at near-euglycemic levels more safely on the non-critical-care floor, where the nurse-to-patient ratios are 1:6. The addition of ultra-short-acting insulin analogues to the protocol in 1998 was instrumental in achieving these goals in nonfasting, non-critical-care patients.

The effectiveness of the various iterations of our CII protocol is shown in Figure 3. Although the protocols are specific and strict, the use of a wide target range provides some leeway for the nurses who administer the protocol. Thus, nurses, sometimes-unaware of the advantages of strict glucose control, have tended to maintain patients at the upper limits of the target blood glucose range and hence often allow patients to have blood glucose levels above that target for short periods. This psychologic impediment to complete glucose control can be overcome only by relentless and repeated education of the nursing

staff to the dramatic outcome advantages afforded by “tight” control of blood glucose.

Nonetheless, evaluation of our various protocols reveals successive improvements in 3-BG control (Table 1 and Fig. 3). As shown in Figure 4, strict control of 3-BG took years to implement and achieve fully. Detailed examination of this figure reveals that only five patients have had 3-BG above 200 mg/dL since our current protocol was implemented in 2001. When the current protocol is strictly followed, 94% of the patients will have blood glucose levels in the target range within 3 hours and will be safely maintained at that level. Thus far, the incidence of chemical hypoglycemia (blood glucose levels less than 60 mg/dL) in patients in whom the protocol was strictly followed has been 0.5%. The incidence of symptomatic hypoglycemia has been 0.04% (2 of 4,864 patients)—and in both those patients, the protocol was not followed by the nurses involved. The Portland CII Protocol was, and will continue to be, a nonsurgical nursing-controlled intervention that improves cardiac surgical outcomes.

### Is hyperglycemia associated with an increased risk of perioperative death?

#### Original Data and Conclusions

At the annual meeting of the American Heart Association (AHA) in 1999, we presented the mortality results of the first 2,110 CABG patients with diabetes who were enrolled in this project (3). That study analyzed the association between hyperglycemia and in-hospital mortality. Among patients who had 3-BG in excess of 200 mg/dL, the mortality was 5.0%. In comparison, patients with 3-BG of less than 200 mg/dL had a 1.8% mortality

( $P < 0.001$ ). Again, a direct correlation existed between the 3-BG levels and mortality ( $P < 0.0001$ ).

Multivariate analysis, with use of preoperative risk variables in combination with 3-BG values, revealed that increasing hyperglycemia was independently predictive of an increasing mortality (RR, 1.02 per mg/dL;  $P < 0.0001$ ; c-statistic, 0.835). Because we realized that the postoperative use of epinephrine infusions in critically ill CABG patients would independently increase blood glucose levels—possibly causing hyperglycemia to act as a surrogate variable for epinephrine use—the multivariate analysis was recalculated by using the postoperative variables epinephrine use and prolonged inotropic support. Both of these new variables were significant contributors to the model; nonetheless, hyperglycemia remained a significant predictor of death (RR, 1.01 per mg/dL;  $P < 0.005$ ; c-statistic, 0.891), independent of the use of epinephrine or inotropic support.

We concluded, as reported at the AHA meeting, that intraoperative hyperglycemia and postoperative hyperglycemia adversely affect postoperative mortality in CABG patients with diabetes and that CABG mortality in patients with diabetes might be reduced to that in the nondiabetic population with a CII protocol that would substantially and safely eliminate hyperglycemia.

#### 2003 Update

The direct relationship between hyperglycemia and mortality has been sustained through 3,959 patients with diabetes who underwent CABG between 1987 and 2003 (Fig. 5). The mortality for patients with 3-BG levels of more than 200 mg/dL is now 6.0%, and that for patients with 3-BG levels of less than 200 mg/dL is now 1.6%

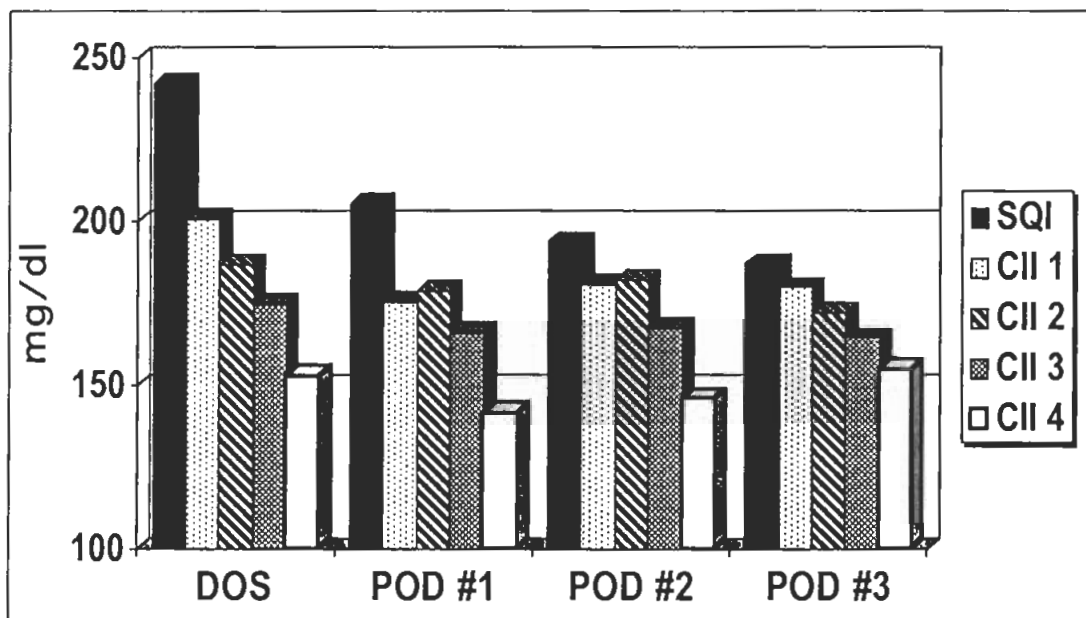


Fig. 3. Daily mean blood glucose levels with use of successive iterations of the Portland Continuous Intravenous Insulin (CII) Protocol listed in Table 1. Note trend toward universal euglycemia with increasingly aggressive CII protocols over time. DOS = day of surgical procedure; POD = postoperative day; SQI = subcutaneous insulin.

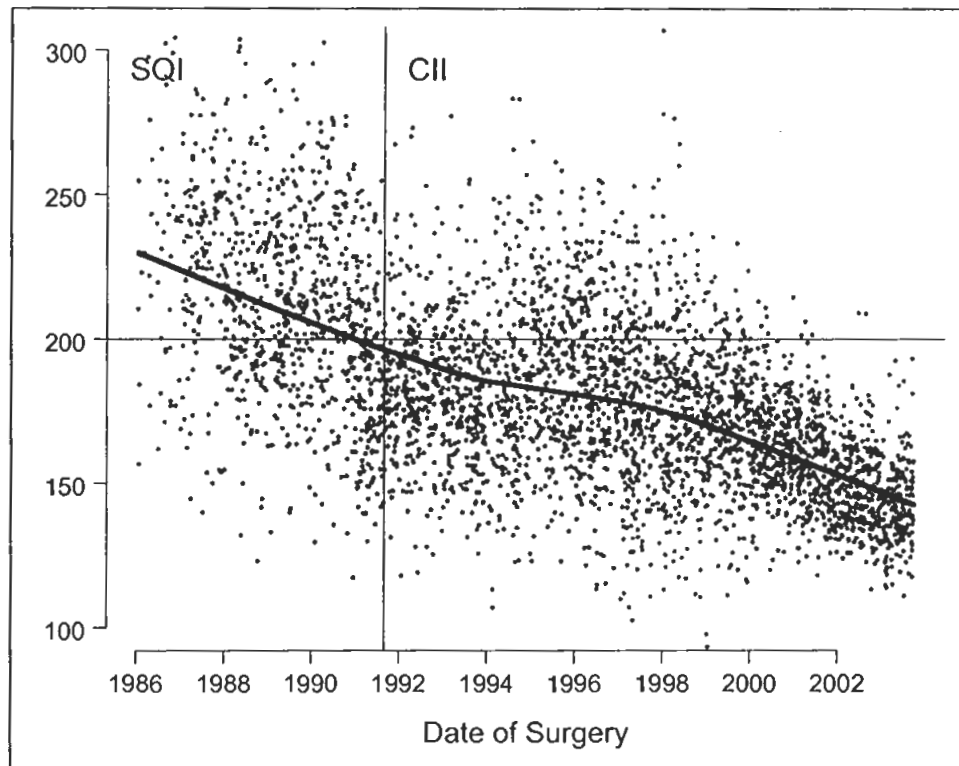


Fig. 4. Scattergram of the 3-day average postoperative blood glucose levels of all 4,864 patients with diabetes who underwent an open-heart operation, plotted by date of surgical procedure. A smoothed local regression (Loess) curve is superimposed. Vertical line = initiation of the Portland Continuous Intravenous Insulin (CII) Protocol. Note gradual reduction of blood glucose levels over time and virtual elimination of values exceeding 200 mg/dL. SQI = subcutaneous insulin.

( $P < 0.001$ ). The 3-BG level remains a significant independent predictor of death (RR, 1.02;  $P < 0.001$ ; c-statistic, 0.9). Thus, the risk of post-CABG mortality is doubled for each 50 mg/dL increase in 3-BG.

#### Does hyperglycemia adversely affect LOS?

##### Original Data and Conclusions

In the same 2,110 CABG patients with diabetes from the previous cohort, we examined the effects of hyperglycemia on LOS (4). These data revealed that hyperglycemia is directly associated with increased LOS ( $P < 0.001$ ). Cox regression analysis showed that 3-BG was independently predictive of a longer LOS (regression coefficient, 0.2 day/10 mg/dL;  $P < 0.002$ ). Thus, this analysis predicts 1 increased LOS day for each 50 mg/dL increase in 3-BG—the outcome that was found and continues to be seen. We concluded that hyperglycemia adversely affects LOS in CABG patients with diabetes.

##### 2003 Update

Glucose levels continue to be independently predictive of, and directly correlated with, LOS at a rate of 1 extra hospital day for every 50 mg/dL increase in 3-BG (Fig. 6).

#### Does the Portland CII Protocol reduce perioperative mortality?

##### Original Data and Conclusions

At the annual meeting of the American Association for Thoracic Surgery in 2002, we presented our data comparing CABG mortality in patients with diabetes who had received SQI versus CII treatment of hyperglycemia (5). By the end of 2001, 942 CABG patients with diabetes had received SQI therapy, and 2,612 patients had been treated with one of the four iterations of the Portland CII Protocol. The overall mortality was 3.2%: 5.3% in the SQI group and 2.5% in the CII group ( $P < 0.0001$ ). Of the deaths, 71% were cardiac-related mortality (see earlier "Definitions"). Multivariate analysis, with use of preoperative risk factors, revealed that CII therapy was protective against death (odds ratio [OR], 0.43;  $P = 0.001$ ; c-statistic, 0.874), reducing that adverse outcome by 57%. As mentioned previously, postoperative epinephrine use and DSWI have both been associated with an increase in glucose levels and mortality. When these variables were added to the model, they actually increased the independent protective significance of CII therapy (OR, 0.36;  $P < 0.001$ ; c-statistic, 0.9). External risk adjustment, with use of the Society of Thoracic Surgeons CABG risk algorithm, revealed a 50%

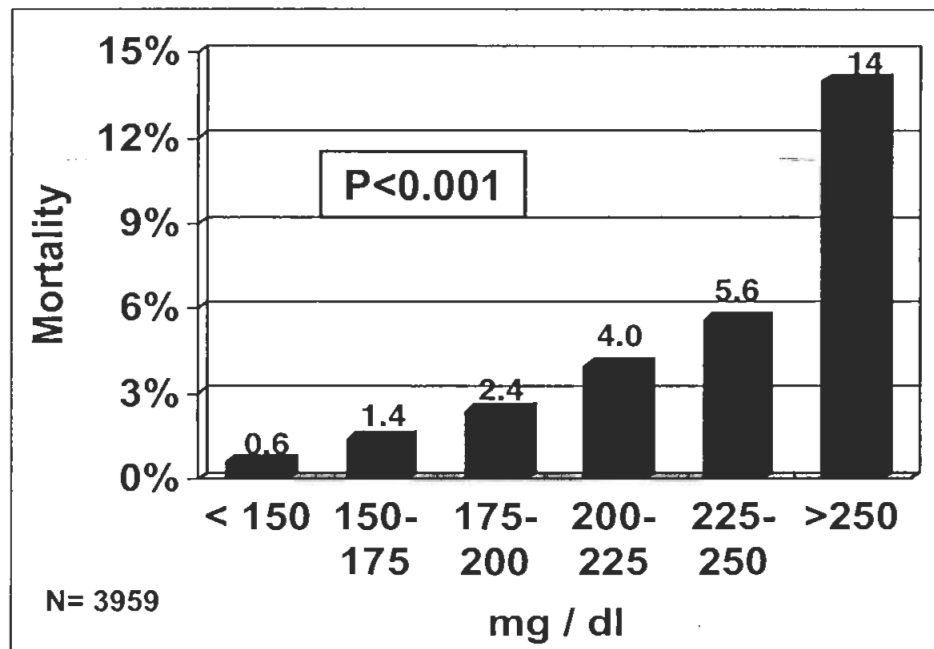


Fig. 5. Mortality among 3,959 patients with diabetes who underwent coronary artery bypass grafting between 1987 and 2003, stratified by 3-day average postoperative blood glucose sextile.

reduction in risk-adjusted mortality attributable solely to the use of CII treatment through the first 3 postoperative days (OR, 0.5;  $P = 0.005$ ; c-statistic, 0.839).

Once again, our data revealed that, in addition to 3-BG, the individual daily mean glucose levels from the day of the surgical procedure (OR, 1.006 per mg/dL;  $P < 0.003$ ) and from the first (OR, 1.013 per mg/dL;  $P < 0.001$ ) and second postoperative days (OR, 1.018 per mg/dL;  $P < 0.015$ ) were each significant independent predictors of death when entered into the model in lieu of the composite 3-BG. Blood glucose levels on the third postoperative day did not have a significant independent effect on mortality ( $P = 0.1$ ). This finding further implies that the protective effects of CII therapy are available at least until the third postoperative day, and it corroborates our continuing assertion that both the target range of the CII therapy (<150 mg/dL) and the duration of that therapy (at least 3 days) affect the outcomes of cardiac surgical procedures.

This reduction in overall mortality with use of CII therapy was found to be completely attributable to a reduction in cardiac-related deaths, which significantly rose with increasing glucose levels (Fig. 7) while noncardiac mortality did not. The cardiac-related mortality in the SQI group was 4.4%, and that in the CII group was 1.6% ( $P < 0.0001$ ). These findings corroborate our mechanistic postulate (see subsequent paragraph) of the beneficial glycometabolic effects of intravenous insulin therapy on the biochemistry of the myocardial cell to alter it favorably and improve its metabolism.

Hence, we concluded that the Portland CII Protocol independently reduced absolute CABG mortality by 57% and reduced risk-adjusted mortality by 50%. It did so by

lowering the risk of cardiac-related death. As such, CII therapy adds an independently protective effect on mortality to the constellation of risk factors already in the Society of Thoracic Surgeons risk model. Therefore, diabetes, per se, is not the true risk factor for death after CABG; rather, it is the underlying glycometabolic state of the myocardium that influences mortality. The protective effect of CII treatment may be derived from improved glycometabolic control, which down-regulates the paradoxical overutilization of free fatty acids and enhances the effective utilization of oxidative glycolysis. We further concluded that insulin infusions, such as the 3-day Portland CII Protocol, should become the standard of care for glycometabolic control in all patients with diabetes who undergo CABG.

#### 2003 Update

The 2003 updated annual incidence of death after CABG at our institution is shown in Figure 8. With use of the Portland CII Protocol, CABG mortality in patients with diabetes has been normalized to that of the nondiabetic population, and for the past few years, CABG mortality in patients with diabetes has actually been lower than that in the nondiabetic population. Multivariate analysis now reveals that CII therapy independently reduces mortality by 60% (OR, 0.4;  $P < 0.001$ ; c-statistic, 0.868).

#### What are the socioeconomic benefits of the Portland CII Protocol—that is, is it cost-effective?

In 1998, we conservatively examined the additional hospital costs and LOS attributable to DSWI (2). For that analysis, we assessed these variables in only those patients who had DSWI during the same admission as their heart



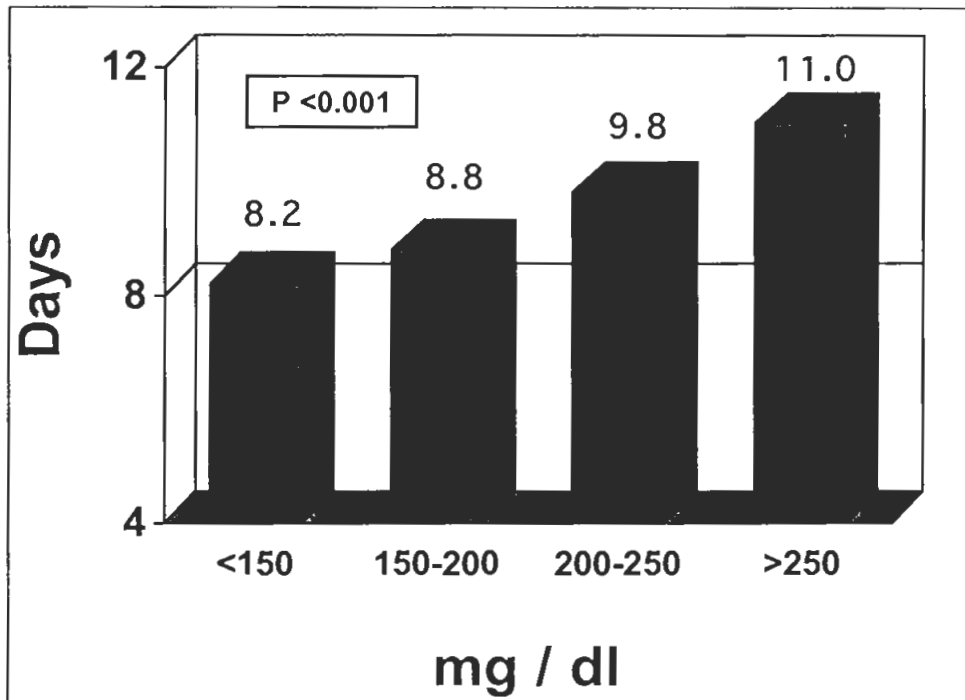


Fig. 6. Length of hospital stay for 3,959 patients with diabetes who underwent coronary artery bypass grafting between 1987 and 2003, stratified by blood glucose quartile.

operation, inasmuch as they would have lower costs and shorter LOS than patients readmitted for DSWI. In comparison with the non-DSWI population, these patients with DSWI incurred additional costs of \$26,400 through a mean of 16 extra hospital days ( $P < 0.001$  for both). In addition, the death rate in patients with diabetes who had DSWI was 20%. Thus, at that time, we were able to provide a conservative estimate of the annualized socioeconomic savings—attributable to prevention of DSWI alone—attainable in the United States if the Portland CII Protocol were universally adopted.

The 1998 AHA heart and stroke statistical update (6) reported that there were 742,000 cases of open-heart surgical procedures in the United States in 1995. If we assume a conservatively low 20% incidence of diabetes in this population and also further assume that all centers would have only a 2% incidence of DSWI with use of SQI therapy (as previously mentioned, 2% was the lowest incidence published to date, and all other studies demonstrated rates of 3.5% or higher), in that one year alone we would have predicted that 2,968 cases of DSWI would have occurred at a cost of 564 lives, 47,488 extra hospital days, and approximately \$78.4 million. The current study demonstrated an independent 66% reduction in the incidence of DSWI with use of CII therapy. Therefore, in that one year alone, universal use of the Portland CII Protocol would have saved the following: 1,959 cases of DSWI, 31,344 extra hospital days, approximately \$52 million, and 372 lives by the prevention of DSWI alone.

We have further examined the direct and indirect costs of both our SQI and CII protocols to determine the increase in hospital costs attributable to the Portland CII

Protocol. Direct costs for SQI therapy included the insulin, test strips, and syringes. Direct costs for CII therapy included the insulin, test strips, and intravenous bag, tubing, and pump. Indirect costs for both SQI and CII treatments included nursing and pharmacy time (including benefits at \$55 and \$65 per hour, respectively) involved in administration of the two protocols.

Accordingly, the total (direct + indirect) costs of 3 days of SQI therapy were very inexpensive—approximately \$32 per patient. The total (direct + indirect) costs of the Portland CII Protocol for the hospital were \$138 per patient. Nevertheless, to account for these costs without accounting for the savings they produce would be poor logic.

#### Conservative Cost Analysis

The Portland CII Protocol reduced the incidence of DSWI in our population (from 2.0% with SQI therapy to 0.8% with CII therapy) by 1.2%. This 1.2% reduction equates to 1 case of DSWI eliminated for every 83 patients in whom the CII protocol is applied. The conservative cost estimate of a single DSWI (see previous material) is \$26,400. Thus, the CII-related savings attributable to prevented DSWI are \$318 per patient (\$26,400 per 83 patients). Furthermore, if the 3-BG level were reduced by a conservative 50 mg/dL through the use of CII therapy, we would have to include the additional savings of a single hospital day. Because costs vary throughout the United States, we will assume a very low average cost of \$500 per day to care for a cardiac surgical patient with diabetes. Thus, the conservative cost savings due to reduced LOS

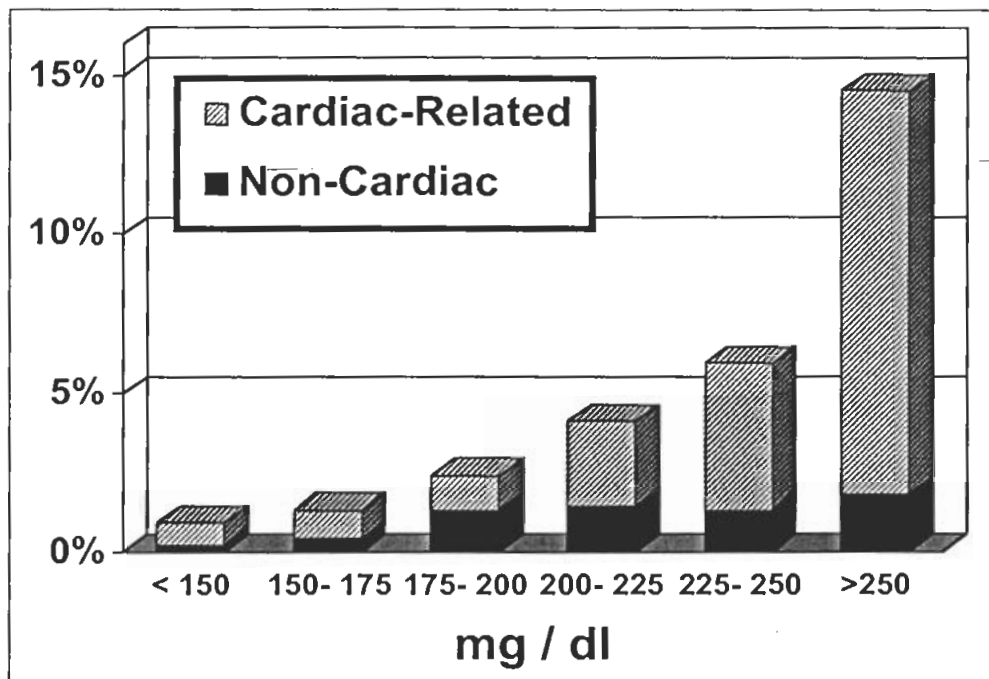


Fig. 7. Cardiac-related and noncardiac mortality in 3,554 patients with diabetes who underwent coronary artery bypass grafting (5), stratified by glucose sextile. Overall mortality in each sextile is represented by the total height of the bar. Note that increase in overall mortality is overwhelmingly accounted for by an increase in cardiac-related mortality. (Noncardiac mortality did not increase with blood glucose levels above 175 mg/dL.)

and DSWI total \$818 (\$318 + \$500) per patient. Having determined that the increased hospital costs attributable to the Portland CII Protocol are \$138 per patient, we can readily calculate that the Portland Protocol conservatively saves the hospital and insurers at least \$680 per patient.

#### Actual Cost Analysis

The foregoing analysis is conservative for several reasons. (1) The 2% incidence of DSWI with SQI therapy in this study is the lowest DSWI rate ever published in the diabetic population; the accepted rate from several other studies is 3.5% or higher (7). (2) The overall rate of DSWI in the CII population of 0.8% in this study was averaged over 6 years—during the time when the protocol was enhanced, improved, and modified; the actual current annual rate of DSWI at our institution ranges from 0.3 to 0.5% (Fig. 2). (3) The actual costs of a single readmission for DSWI in the population of patients with diabetes are published at \$81,000 (7). (4) The actual averaged costs of a single hospital day for patients undergoing an open-heart surgical procedure have been reported to be as high as \$1,150. (5) The average blood glucose level in patients with diabetes who underwent a cardiac operation and were given SQI therapy in 2003 was 267 mg/dL (8); our current protocol attains 3-BG levels of 132 mg/dL—a 135 mg/dL reduction (not a 50 mg/dL reduction).

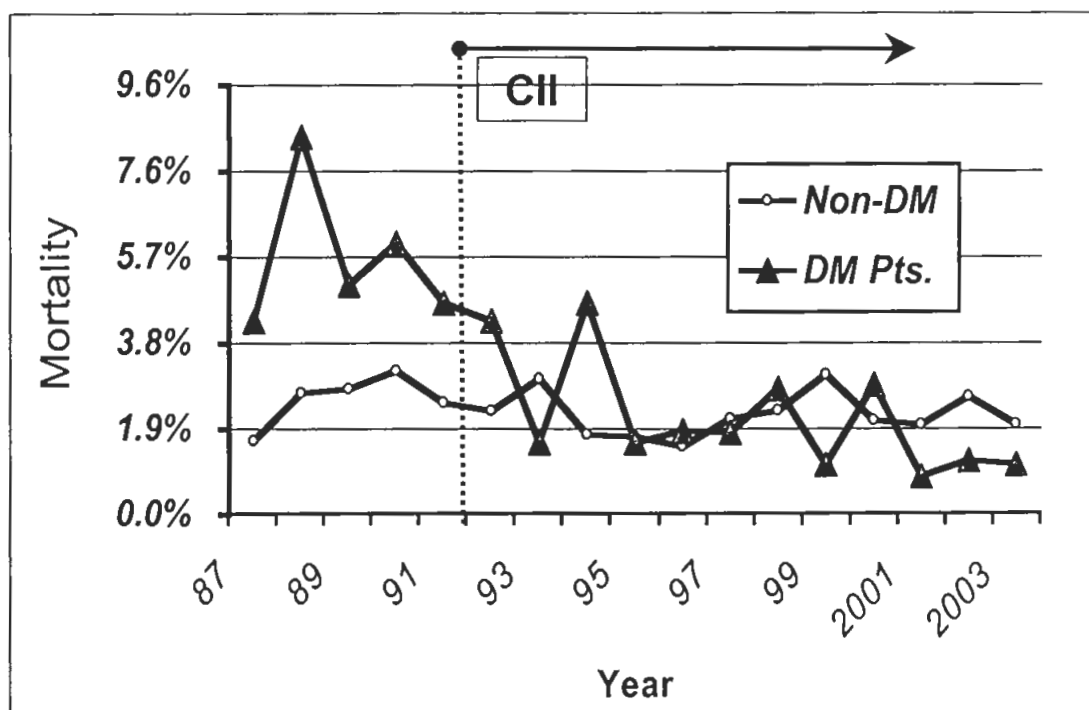
Therefore, if we redo the cost-benefit analysis with use of the actual data from the previous paragraph, we see that DSWI cases are reduced 3.2% (from 3.5% to 0.3%),

equating to 1 case of DSWI eliminated for every 31 patients treated with the CII protocol. The actual cost savings per patient from prevented DSWI is \$2,613 (\$81,000 per 31 patients). A 135 mg/dL reduction in 3-BG level suggests a 2.7-day decrease in LOS (135 mg/dL divided by 50 mg/dL per hospital day). The actual savings from the decreased LOS is therefore \$3,105 per patient (2.7 days  $\times$  \$1,150/day). Thus, the total cost savings attributable to reduced LOS and DSWI are \$5,718 (\$2,613 + \$3,105), for a net savings of \$5,580 (\$5,718 - \$138) per patient treated with the Portland Protocol.

The 57% CII-related reduction in mortality further suggests that, in the United States alone, 1 life would be saved for every 38 patients so treated. Therefore, for every life saved with the Portland CII Protocol, hospitals and insurers save \$212,040 (38  $\times$  \$5,580) in health-care costs. If universally applied to just the annual population of 102,950 patients with diabetes undergoing CABG in the United States, the Portland CII Protocol would thus save 1,959 DSWI, 2,676 lives, and 278,000 hospital days. Moreover, the health-care system would save between \$70 million (conservative) and \$574 million (actual) per year.

#### SUMMARY

The Portland Diabetic Project has shown that perioperative hyperglycemia on the day of open-heart operation and through the first 2 postoperative days significantly and adversely affects wound infection rates, LOS, and in-hos-



**Fig. 8.** Annualized mortality in all patients—those with and those without diabetes mellitus (*DM*)—who underwent coronary artery bypass grafting between 1987 and 2003 at St. Vincent Medical Center (Portland, Oregon). Mortality in the nondiabetic group has not changed over time; however, mortality in the 3,959 patients with diabetes has been dramatically lowered. Currently (1995 to 2003), no statistically significant difference exists between these two groups. Vertical dotted line = initiation of Portland Continuous Intravenous Insulin (*CII*) Protocol.

pital mortality. Furthermore, glycometabolic control with use of the Portland CII Protocol on the day of the surgical procedure and through the first 2 postoperative days effectively and safely reduced 3-BG to near-euglycemic levels. Concomitantly, dramatic and statistically significant reductions occurred in DSWI (reduced 66%), LOS (1 hospital day saved per 50 mg/dL reduction in 3-BG), and CABG mortality in patients with diabetes (reduced by 57%).

## CONCLUSION

We conclude that diabetes mellitus is *not* the actual risk factor for the increased infection, LOS, and mortality after open-heart surgical procedures in patients with diabetes. Rather, it is the presence of perioperative hyperglycemia that affects biochemical and physiologic functions, which, in turn, adversely alter mortality, LOS, and infection rates. The Portland CII Protocol is a cost-efficient method that safely and effectively eliminates hyperglycemia and enhances myocardial glycometabolic function. Accordingly, it reduces postoperative morbidity and mortality and thereby eliminates the increase in risk-adjusted outcomes previously ascribed to diabetes. Insulin infusions should become the standard care for glycometabolic control in all patients undergoing open-heart surgical procedures.

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**APPENDIX 1**  
**Portland Continuous Intravenous Insulin Protocol (Version 2001):**  
**Target Blood Glucose Level, 100 to 150 mg/dL**

1. Start "Portland Protocol" during surgical procedure and continue through 7 AM of the third postoperative day (POD). Patients who are not taking enteral nutrition on POD 3 should remain on this protocol until taking at least 50% of a full liquid or soft American Diabetes Association (ADA) diet.
2. For patients with no previous diagnosis of diabetes mellitus (DM) who present with hyperglycemia: start PDX protocol if blood glucose (BG) level >200 mg/dL. Consult endocrinologist on POD 2 for DM workup and follow-up orders.
3. Start insulin infusion through pump "piggybacked" to maintenance intravenous line, as follows:

Blood glucose (mg/dL)	Intravenous insulin bolus (U)	Initial insulin rate (U/h) (circle one)	
		Type 2 DM preoperatively	Type 1 DM preoperatively
80-119	0	0.5	1.0
120-179	0	1.0	2.0
180-239	0	2.0	3.5
240-299	4	3.5	5.0
300-359	8	5.0	6.5
≥360	12	6.5	8.0

4. Test BG level by finger-stick method or arterial line drop sample. The frequency of BG testing should be as follows:
  - a. If BG ≥200 mg/dL, check BG every 30 minutes.
  - b. If BG <200 mg/dL, check BG every hour.
  - c. When titrating vasopressors (such as epinephrine), check BG every 30 minutes.
  - d. If BG is 100 to 150 mg/dL with <15 mg/dL change *and* insulin rate has remained unchanged for 4 hours ("stable infusion rate"), then may test BG every 2 hours.
  - e. May stop every-2-hour testing on POD 3 (see items 5 and 8 below).
  - f. At night on telemetry unit:
    - If BG is 150 to 200 mg/dL, test every 2 hours.
    - If BG <150 mg/dL and stable insulin infusion rate exists, test every 4 hours.

5. Insulin titration guidelines:

Blood glucose (mg/dL)	Action
<50	Stop insulin; give 25 mL of 50% dextrose; recheck BG in 30 minutes When BG >75 mg/dL, restart with rate 50% of previous rate
50-75	Stop insulin; if previous BG >100 mg/dL, then give 25 mL of 50% dextrose; recheck BG in 30 minutes When BG >75 mg/dL, restart with rate 50% of previous rate
76-100	If <10 mg/dL lower than last test, decrease rate by 0.5 U/h If >10 mg/dL lower than last test, decrease rate by 50% If ≥ last test result, maintain same rate
101-150	Use same rate
151-200	If 20 mg/dL lower than last test, use same rate Otherwise, increase rate by 0.5 U/h
>200	If ≥30 mg/dL lower than last test, use same rate If <30 mg/dL lower than last test (OR if higher than last test), increase rate by 1 U/h <b>AND</b> —if >240 mg/dL, give intravenous bolus of regular insulin per “Intravenous insulin bolus” dosage scale (see item 3 above) <b>Recheck BG in 30 minutes</b>

If BG >200 mg/dL and has not decreased after 3 consecutive increases in insulin: give intravenous bolus per item 3 and double the insulin rate

If BG >300 mg/dL for 4 consecutive readings: call physician for additional intravenous bolus orders

6. Begin use of 1,800-calorie ADA diabetic diet with any oral intake.
7. Postmeal subcutaneous insulin lispro (Humalog) supplement in addition to insulin infusion when oral intake advances beyond clear liquids:
  - a. If patient eats 50% or less of servings on breakfast, lunch, or supper tray, then give 3 U of insulin lispro subcutaneously immediately after that meal.
  - b. If patient eats more than 50% of serving on breakfast, lunch, or supper tray, then give 6 U of insulin lispro subcutaneously immediately after that meal.
8. On POD 3: Restart preadmission glycemic control medication, unless patient is not tolerating enteral nutrition—then maintain insulin drip per protocol.