

Rationale for Glycemic Control in Cardiac Surgical Patients: The Portland Diabetic Project

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Since 1987, the Portland Diabetic Project has enrolled >5000 patients with diabetes mellitus (DM)—including patients with noninsulin-dependent DM and patients with insulin-dependent DM—in a prospective nonrandomized study of the effects of perioperative insulin administration on morbidity and mortality after open-heart surgical procedures. In the early stages of the study, patients received SC insulin. In 1991, we instituted a continuous intravenous insulin (CII) protocol, which has been refined several times since its introduction. Our principal measure of glycemic control is the mean blood glucose value obtained by measuring glucose every 0.5 to 2 hours during the initial 3-day postoperative period (3-BG). There is a strong relationship between postoperative mortality and 3-BG value, even after adjusting for other clinical variables that influence mortality. The postoperative mortality rate was significantly lower among patients who received CII rather than SC insulin after coronary artery bypass grafting (CABG) or cardiac surgery of any type. We have also found that 3-BG is strongly associated with the risk of postoperative deep sternal wound infection (DSWI), and that treatment with CII significantly reduces the risk of infection. Our CII glucose protocol is slightly more expensive to administer than conventional SC insulin. However, when cost savings associated with a reduced rate of serious infection and reduced length of hospital stay are considered, CII results in total savings of >\$4500 per patient. Widespread use of our CII protocol to manage perioperative hyperglycemia in patients with diabetes who undergo open-heart surgical procedures would result in substantial reductions in morbidity, mortality, and overall costs to the health care system.

THE PORTLAND DIABETIC PROJECT

The Portland Diabetic Project is a prospective nonrandomized study of the effects of hyperglycemia and the use of IV insulin on morbidity and mortality in patients undergoing open-heart surgical procedures.¹ Between 1987 and 2004, this project enrolled 5099 patients from a total patient population of 21,278 patients (age 65 [10] years; 65% male and 35% female) with noninsulin-dependent or insulin-dependent DM: 4200 patients undergoing CABG, 359 isolated valve procedures, 459 combined valve and CABG operations, and 59 other operations.² Individuals with DM accounted for 24% of all patients who underwent cardiac surgery at Providence St. Vincent Medical Center in Portland, Oregon, during this period.² Before hospitalization, blood glucose level was controlled primarily by oral agents for 51% of patients, by SC insulin for 33%, and by diet for 11%; 5% of the patients were unaware that they had DM at the time of initial hospitalization and were not receiving therapy.² Periodic reports of our experience with a protocol of CII infusion over the course of up to 3 days have been published, including a recent overview of 4864 patients with diabetes who were enrolled in the study between 1987 and 2003.¹

Our CII glucose protocol has evolved gradually over time. Initially, between 1987 and 1991, no perioperative

patients were permitted to receive IV insulin, and a total of 986 patients underwent perioperative blood glucose control with SC insulin administered every 4 hours. Between 1992 and 1994, CII was permitted only in the intensive care unit (ICU), with a target blood glucose value of 150 to 200 mg/dL. From 1995 to 1998, the use of IV insulin was expanded to include the operating room (OR) and telemetry unit, with the same target blood glucose value. Blood glucose targets have been gradually lowered since 1998, and our current blood glucose targets are 70 to 110 mg/dL for patients in the OR or ICU, and 80 to 120 mg/dL for patients in telemetry. Overall, 4041 patients received IV insulin using the Portland CII Protocol from 1987 to 2004.²

For all patients, blood glucose level was measured from an arterial line drop, a venous line drop, or a capillary finger stick, in that order of preference, every 30 minutes to 2 hours. Blood draws were performed on the day of surgery and through postoperative day 4. Between 24 and 72 glucose measurements were obtained on the day of surgery and the first 2 postoperative days, which were averaged to provide a 3-BG that was used as an assessment of the patient's glycemic control. As shown in **Figure 1**, 3-BG values have declined gradually since we began to use operative insulin, and we now have virtually eliminated postoperative patients with 3-BG values >200 mg/dL.

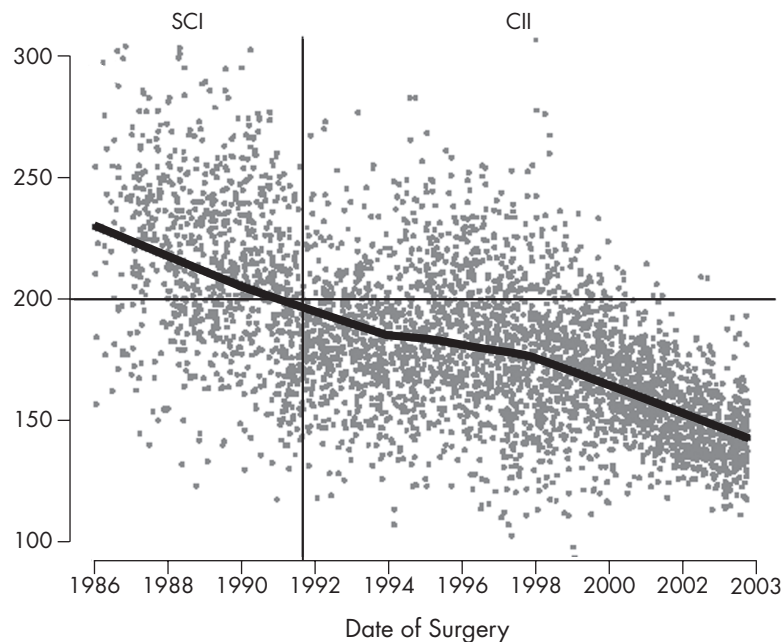


Figure 1. Scattergram of the 3-day mean postoperative blood glucose levels of 4864 patients with diabetes who underwent open-heart surgery at Providence St. Vincent Medical Center in Portland, Oregon, between January 1987 and September 2003, plotted by date of surgical procedure. A smoothed local regression curve is superimposed. Vertical line = initiation of the Portland Continuous Intravenous Insulin (CII) Protocol; SCI = subcutaneous insulin. Reprinted with permission from American Association of Clinical Endocrinology as featured in Furnary AP et al. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: The Portland Diabetes Project. *Endocr Pract.* 2004;10(Suppl 2):21–33.

HYPERGLYCEMIA, INSULIN, AND MORTALITY

Alterations of myocardial energy metabolism in DM predispose the heart to ischemic injury when myocardial oxygenation is reduced.³ In the normal myocardium, insulin causes the binding of blood glucose to the cellular membrane, where it is phosphorylated and transferred to the cytosol. Within the cytosol, glucose undergoes anaerobic glycolysis to produce pyruvate, which passively diffuses across the mitochondrial membrane. Pyruvate is converted by the mitochondrial enzyme pyruvate dehydrogenase to yield acetyl coenzyme A (acetyl CoA). Acetyl CoA is used in mitochondrial energy metabolism via the Krebs cycle to produce adenosine triphosphate (ATP), which provides energy for myocardial contraction. ATP is also produced by a second pathway, which requires the active transport of free fatty acids (FFAs) from the cytosol to the mitochondria. FFAs are then processed by β -oxidation to produce acetyl CoA molecules, which are used in mitochondrial energy metabolism. In DM, lack of insulin results in reduced glucose binding to the cell membrane, decreased transfer of glucose to the cytosol, and increased concentration of glucose in plasma. Owing to the decreased availability of glucose, the cell does not produce sufficient ATP by the pyruvate dehydrogenase pathway. In addition, glycolysis and the enzymatic activity

of pyruvate dehydrogenase are also reduced in DM. As a result, there is a shift in cellular ATP production toward the FFA pathway. Although this pathway is able to provide acetyl CoA to support cellular energy metabolism, it requires active transport of FFA molecules into the mitochondria, and therefore requires more ATP and oxygen.

In patients with diabetes who experience myocardial ischemia, oxygen deprivation reduces the ability of cardiomyocytes to use FFAs as a source of mitochondrial energy metabolism, resulting in the accumulation of acetyl CoA within the mitochondria. β -Oxidation becomes less efficient and begins to generate toxic by-products with long carbon chains.⁴ This accumulation of β -oxidized FFA intermediates promotes cardiac arrhythmias, endothelial dysfunction, capillary leakage, and edema. Insulin treatment in patients with diabetes is thought to promote movement of glucose back into cells, thereby restoring aerobic glycolysis, improving mitochondrial energy metabolism, and reducing the effects of ischemia on endothelial cell function and edema.⁴

Although it has long been known that DM increases the likelihood of poor outcomes in patients with coronary artery disease, it was not clear that this was a direct consequence of hyperglycemia. For example, in the Society of Thoracic Surgeons (STS) database of cardiac surgery patients,⁵ the

incidence of mortality following CABG is 4.5% among patients with DM and 2.7% among those without DM. We have found a strong relationship between post-CABG mortality and plasma glucose concentration in the Portland Diabetic Project (Figure 2). In multivariate analysis, 3-BG values were highly predictive of mortality after adjustment for other clinical variables, such as cardiogenic shock, renal failure, patient age, ejection fraction, history of atrial fibrillation, and the use of epinephrine. Blood glucose concentrations on the day of surgery and on the next 2 days were also independently associated with increased mortality. On the third postoperative day, blood glucose concentration was not a significant independent predictor of increased mortality, nor was the preoperative blood glucose value or the glycosylated hemoglobin value. In addition, postoperative mortality was significantly reduced by the adoption of perioperative CII in patients with diabetes who underwent CABG surgery, from 5.3% with SC insulin to 2.5% with CII ($P < 0.001$).⁴ In multivariate analysis, mortality among patients undergoing CABG was found to be significantly reduced by treatment with CII (odds ratio = 0.4; $P = 0.001$) after adjustment for other clinical variables.⁴ Cardiac-related mortality—due to arrhythmias or pump failure—was also significantly reduced for all patients undergoing CABG, from 4.4% with SC insulin to 1.6% with CII ($P < 0.001$).

When we began to examine the use of perioperative insulin administration for patients undergoing cardiac surgery in the late 1980s, the incidence of CABG-related mortality was much higher among patients with DM than among patients without DM. Since we began to use IV insulin, we

have observed a steady decrease in the mortality rate among patients with diabetes. In recent years, the incidence of mortality following CABG has been similar for patients with and without DM (Figure 3).

HYPERGLYCEMIA AND INFECTION

In addition to its effects on cellular energy metabolism, hyperglycemia impairs immune function by several different mechanisms, including the stimulation of inflammatory cytokines and cell adhesion molecules, and the inhibition of leukocyte function.⁶ As a result, patients with diabetes are at increased risk of infection, including DSWI following cardiac surgery. In a recently published meta-analysis, the incidence of DSWI after cardiac surgery was 5.6% among patients with DM prior to the use of IV insulin. In contrast, patients without DM had a DSWI rate of only 0.8%.⁵

In our Portland patient cohort, we found that the rate of DSWI was clearly associated with blood glucose, increasing from 0.6% at 3-BG values of <175 mg/dL, increasing to 1.0%, 2.1%, and 3.7% at 3-BG concentrations of 175 mg/dL, 225 mg/dL, and 250 mg/dL, respectively.¹ In multivariate analysis, a 3-BG value >175 mg/dL was a significant independent risk factor for DSWI (odds ratio = 3.4; $P = 0.007$). The risk of DSWI was also related to blood glucose values on each of the postoperative days 1 through 3. Conversely, lowering the glucose concentration with insulin reduces infection risk. In our patient cohort, the incidence of DSWI was 2.0% with SC insulin and 0.7% with CII ($P = 0.001$).¹ When controlling for other factors, the CII infusion protocol was associated with a relative risk reduction of 66% ($P = 0.005$).

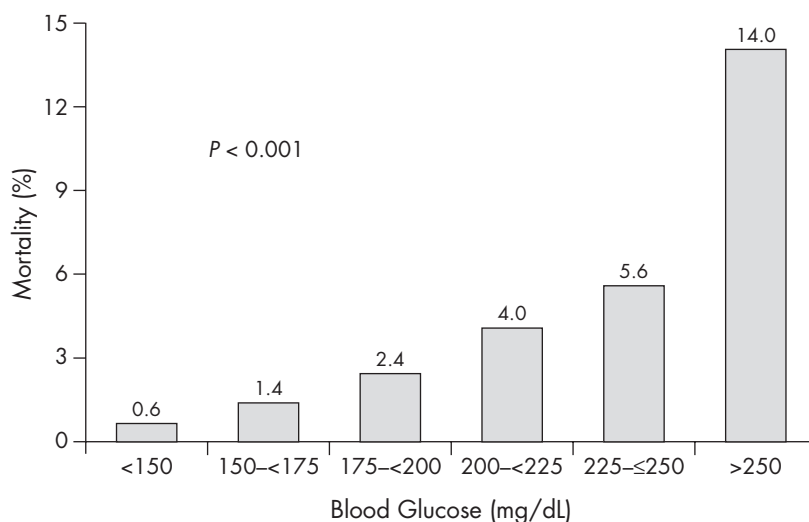


Figure 2. Mortality among 3959 patients with diabetes who underwent coronary artery bypass grafting at Providence St. Vincent Medical Center in Portland, Oregon, between 1987 and 2003, stratified by 3-day mean postoperative blood glucose sextile. Reprinted with permission from American Association of Clinical Endocrinology as featured in Furnary AP et al. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: The Portland Diabetic Project. *Endocr Pract.* 2004;10(Suppl 2):21–33.

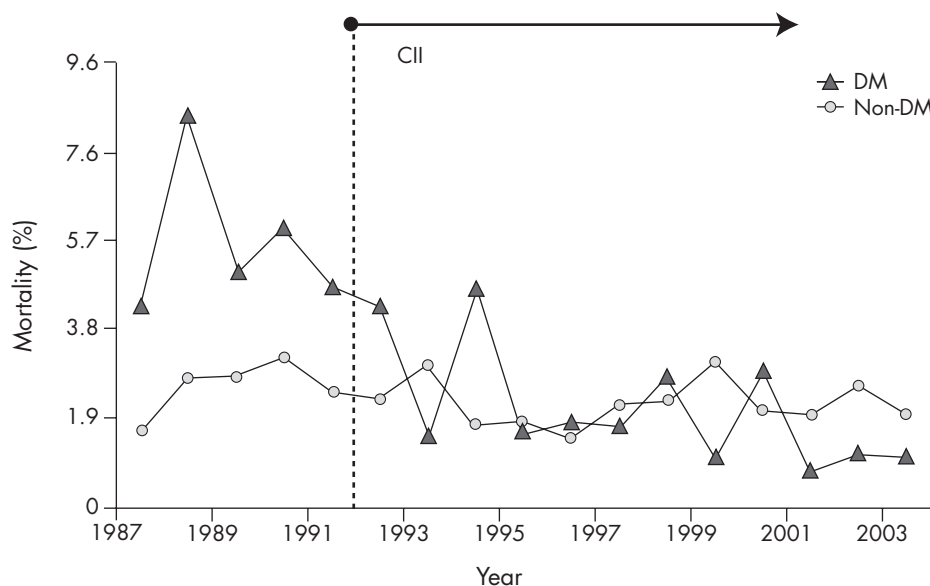


Figure 3. Annualized mortality in patients with and without diabetes mellitus (DM) who underwent coronary artery bypass grafting at Providence St. Vincent Medical Center, Portland, Oregon, between 1987 and 2003. Vertical broken line = initiation of the Portland Continuous Intravenous Insulin (CII) Protocol. Reprinted with permission from American Association of Clinical Endocrinology as featured in Furnary AP et al. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: The Portland Diabetes Project. *Endocr Pract.* 2004;10(Suppl 2):21–33.

We also examined the incidence of DSWI between 1987 and 1997 for patients with and without DM. Before the introduction of CII, the incidence of DSWI was much higher among patients with DM (Figure 4). After the introduction of CII in the ICU in 1991, the rate of DSWI began to decline. The rate declined further after 1994, when CII was extended to use in the OR and telemetry. This suggests that the total duration of insulin treatment, and not only the plasma glucose concentration, is important in reducing the risk of infection. For insulin therapy to reduce the risk of hyperglycemic complications in patients with heart disease, continuing insulin therapy for at least 48 hours postoperatively may be required.

SOCIOECONOMIC OUTCOMES WITH THE PORTLAND PROTOCOL

Patients with DM have a longer mean duration of hospital stay than patients without DM after cardiac surgery. In the STS database, the mean length of stay after cardiac surgery was 7.5 days for patients with DM and 6.6 days for those without DM.⁵ In the Portland Diabetic Project, we found that length of stay was strongly and independently associated with increasing 3-BG values. Each decrease of 77 mg/dL in 3-BG was associated with a savings of 1 day in length of stay; this translates to an expected savings of ~278,000 hospital-stay days each year.

We also examined the cost-effectiveness of CII in patients undergoing cardiac surgery. We compared the direct cost of IV insulin (eg, insulin, IV bags, tubing, pumps) with the costs

of SC insulin (insulin, SC syringes, and strips), and we also included indirect costs such as nursing and pharmacy time. The total direct and indirect costs per patient were \$32 for 3 days of SC insulin therapy and \$170 for CII therapy, for a difference of \$138 per patient.¹ This increase in cost was more than offset by savings that resulted from reduced risk of serious infection. It has been reported that DSWI is associated with mean charges of \$81,000 per diabetic patient.⁷ In our patient series, the incidence of DSWI was 0.3%, compared with the best previously published rate of DSWI in the SC-treated population of 3.5%. This results in savings of 1 case of DSWI per 31 patients treated, for a mean per-patient savings of \$2631 in costs associated with DSWI.

The CII regimen also reduces costs associated with hospital length of stay. Our current CII protocol produces a mean 3-BG value of 128 mg/dL (2004 3-BG average) in patients undergoing cardiac surgery, compared with published estimates of 267 mg/dL in patients who receive SC insulin.⁸ This represents a mean reduction in 3-BG value of 139 mg/dL. As noted previously, a reduction in 3-BG of 77 mg/dL was associated with a savings of 1 day in length of stay. Thus, the reduction in 3-BG value with the CII protocol would be expected to result in the mean savings of 1.8 days of hospitalization per patient. At a mean charge of \$1150 per day after patients have undergone CABG (excluding OR charges), this amounts to mean savings of \$2081 per patient. When the costs and savings of the CII protocol are combined, the net savings per patient is >\$4500. The implementation of this protocol in the 103,000 patients

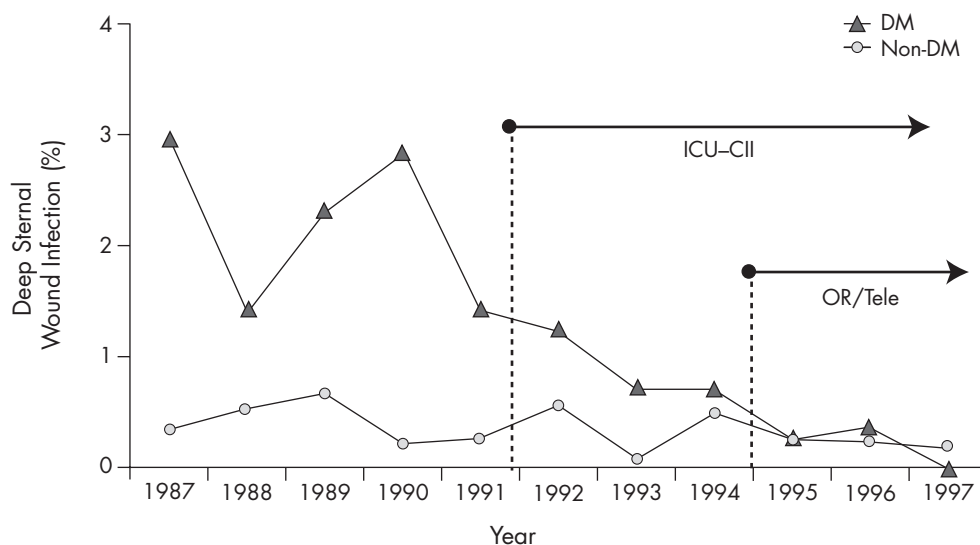


Figure 4. Incidence of deep sternal wound infection in patients with and without diabetes mellitus (DM) who underwent open-heart surgery at Providence St. Vincent Medical Center, Portland, Oregon, between 1987 and 1997. Data points to the left of the longer vertical broken line indicate patients treated with SC insulin injections. Initiation of the Portland Continuous Intravenous Insulin Protocol in the intensive care unit/critical care unit (ICU-CII) in 1992 and expansion of that protocol to the operating room and telemetry unit (OR/Tele) in 1995 are marked by the vertical broken lines. Reprinted with permission from American Association of Clinical Endocrinology as featured in Furnary AP et al. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac procedures: The Portland Diabetes Project. *Endocr Pract.* 2004;10(Suppl 2):21–33.

with diabetes who undergo CABG each year in the United States would result in nationwide health care savings of ~\$470 million.

Our protocol would also result in a considerable reduction in mortality if adopted on a nationwide basis. According to the American Heart Association,⁹ 690,000 cardiothoracic surgical procedures, of which 467,000 are CABG procedures, are performed each year. Our data and the STS patient database suggest that ~24% of the individuals undergoing these procedures have DM, for a total of ~165,000 patients. If the reductions in mortality observed in our patient series were extrapolated to the nationwide population of patients with diabetes undergoing cardiothoracic surgery, CII therapy would be expected to reduce the number of CABG-related deaths by 2700 and the number of deaths from complications of DSWI by 765, for a total mortality decrease of 3565 patients per year. The CII protocol would

also be expected to reduce the number of DSWI infections in the United States by 3825 incidences.

CONCLUSIONS

In patients with DM, perioperative hyperglycemia affects biological and physiological functions that increase mortality, postoperative infection, and length of hospital stay. The Portland CII Protocol is a cost-efficient method that effectively eliminates hyperglycemia, thereby reducing postoperative mortality and morbidity in patients with diabetes who require cardiac surgery. The incidence of DSWI in patients with DM is reduced to a level that is similar to the risk in patients without DM. The nationwide adoption of the Portland CII Protocol would result in annual expected savings of 3825 sternal infections, 3545 lives, and 278,000 hospital-stay days, and would save the US health care system an estimated \$470 million per year.

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