

## CLINICAL EFFECTS OF HYPERGLYCEMIA IN THE CARDIAC SURGERY POPULATION: THE PORTLAND DIABETIC PROJECT

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### ABSTRACT

**Objective:** To determine the outcome effects of hyperglycemia, and its pharmacologic reduction with continuous intravenous insulin infusions (CII) in the cardiac surgery patient population.

**Methods:** The Portland Diabetic Project is a prospective, non-randomized, observational study of 5,510 consecutive diabetic cardiac surgery patients treated between January 1987 and November 2005

**Results:** This study was the first to reveal that hyperglycemia in the first 3 postoperative days is independently predictive of mortality ( $P < 0.0001$ ), deep sternal wound infection ( $P = 0.0001$ ), and increased length of stay ( $P < 0.002$ ) in diabetic cardiac surgery patients. Conversely, CII, designed to achieve predetermined target glucose levels, was shown to independently reduce the risks of death and deep sternal wound infection by 60% and 77%, respectively ( $P < 0.001$  for both). Target glucose levels  $< 150$ mg/dL and a 3-day postoperative duration of CII therapy are both important variables that determine the impact of the CII therapy on improved outcomes.

**Conclusions:** Perioperative hyperglycemia in cardiac surgery patients adversely alters mortality, length of stay, and infection rates. Three days of CII eliminates the incrementally increased risks of these complications previously seen in diabetic patients. (*Endocr Pract.* 2006; 12[Suppl 3]:22-26)

### Abbreviations:

**BG** = blood glucose; **CABG** = coronary artery bypass graft; **CII** = continuous intravenous insulin infusion; **DSWI** = deep sternal wound infections; **ICU** = intensive care unit; **LOS** = length of stay; **OR** = odds ratio; **SQI** = subcutaneous regular insulin injection

### INTRODUCTION

At the time of this writing (in early 2006), the fact that acute hyperglycemia in hospitalized diabetic patients leads to poor in-hospital outcomes has been fairly well established (1-4). Our early work on this subject, which began in 1987, and continues today is known as the Portland Diabetic Project. This ongoing study is a prospective nonrandomized study of the effects of hyperglycemia, and its pharmacologic reduction with intensive intravenous insulin regimens, on outcomes in the diabetic cardiac surgery population. The general hypotheses of our work are twofold: (1) that the increased risks of adverse outcomes seen in diabetic cardiac surgery patients are attributable to perioperative hyperglycemia and (2) that normalization of perioperative hyperglycemia with continuous intravenous insulin infusion (CII) in this patient population would eliminate the incremental risks that previously had been ascribed to the risk factor "diabetes."

We previously published a summary of our project (5), along with the first American College of Endocrinology (ACE) consensus supplement to this journal, in 2004 (6). At that time, our summary data through November of 2003 were used in the presentation at the consensus conference and the report for *Endocrine Practice*. This publication was requested by the ACE as part of the background for the consensus conference. Herein we update our ongoing project with data collected through December 2005.

### METHODS AND DEMOGRAPHICS

All cardiac surgery patients who were operated on at St. Vincent Medical Center between 1987 and 2005, and those who were either admitted or discharged with the diagnosis of "diabetes," were enrolled in the Portland Diabetic Project. Of the 23,619 patients operated on during this period, 5,510 (23% of the overall open heart surgery population at this center) met these inclusion criteria and were entered into the study. The average age was  $65 \pm 10$  years; 70% of the population was male, and 12% of participants were undergoing open heart surgery for at least the second time.

From Providence St. Vincent Medical Center, Portland, Oregon.  
Presented at the American College of Endocrinology and American Diabetes Association Consensus Conference, Washington, DC, January 30-31, 2006.  
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Of the 5,510 open heart operations performed on diabetic patients, there were 4,448 coronary artery bypass graft (CABG) procedures (81%), 566 valve operations in combination with CABG (10%), 465 isolated valve replacements or repairs (8%), and 61 “other” operations (1%). The latter included procedures such as replacement of the ascending aorta, transmyocardial laser revascularization, and repair of various intracardiac defects.

Outpatient glycemic control prior to hospital admission was maintained with subcutaneous injections of insulin in 40% (2,211) of the population, exclusively with oral hypoglycemic agents in 42% (2,308) of the population, and with diet control in 15% (803). The remaining 188 patients (i.e., 3% of the study population) did not enter the hospital with a diagnosis of diabetes, but were found to be diabetic during the course of their hospital stay and were discharged with the diagnosis of, and treatment for, diabetes.

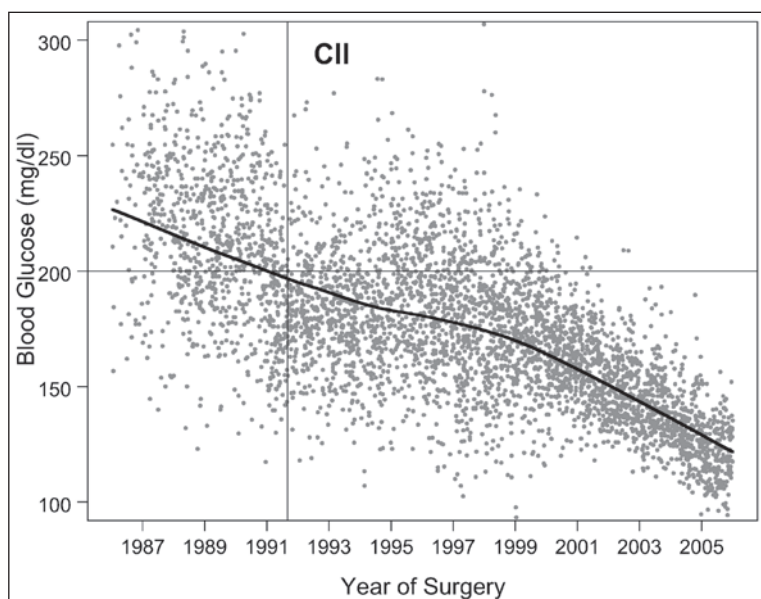
### Glucose Assessment

Assessments of blood glucose (BG) levels were performed as frequently as every 20 minutes (while in the operating room on cardiopulmonary bypass) to every 30 minutes (in the intensive care unit [ICU] and on the floors), and were never more than 2 hours apart. Blood measurement was done with the blood gas analyzer in the operating room and with point-of-care testing equipment in the ICU and on the ward. Blood samples were obtained from the following sources (in order of preference): the efferent

(oxygenated arterial) limb of the cardiopulmonary bypass machine, patient arterial line drop sample, venous line drop sample, and capillary finger stick.

For purposes of data analysis, these glucose data points were then averaged by hospital-stay day. Thus, the average glucose was calculated on the preoperative day, the day of surgery, and the first, second, third, fourth, fifth (and so on) postoperative days. Then, in order to provide a single number that would accurately portray the overall perioperative glycemic state of the patient, we averaged the values for each patient on the day of surgery and the first and second postoperative days. This 3-day average perioperative glucose value (or “3-BG”) comprises no fewer than 24 measurements of glucose, and as many as 72 measurements, during this 3-day period. As such, 3-BG is an extremely accurate representation of the true glycemic state of the patient during the immediate postoperative period.

Perioperative glycemic control was first attempted using subcutaneous regular insulin injections (SQI) every 4 hours in all diabetic cardiac surgery patients between 1987 and 1992. This “SQI group” comprised 968 patients. The remaining 4,542 patients, all operated on after 1992, were treated with one version or another of what has come to be known as “The Portland Protocol”—a CII titrated to keep the patient’s glucose within a prespecified target range. The specified target range was lowered over the study period, to eventually attain total euglycemia in all patients. The progression of this reduction in target has been published previously (5).



**Fig. 1.** Scattergram of the 3-BG measures of all 5,510 patients according to date of operation. Vertical line indicates initiation of the first Portland CII Protocol (target range, 150 to 200 mg/dL) in the ICU in 1992. Expansion to include the non-ICU floors occurred in 1995. Note the increasingly tight 3-BG control in the years since 1999, as the target range was gradually decreased to 70 to 110 (by 2005).

The Portland Protocol of insulin titration has evolved and improved over time; it has been continuously honed to produce rapid achievement of the target range and maintain prevention of hypoglycemia. Current versions of this protocol, at varying target ranges for both ICU and non-ICU wards, are available for download at [www.portlandprotocol.org](http://www.portlandprotocol.org). Also available on this site are updated data slides of topics discussed in this article, as well as answers to frequently asked questions about our protocol and research.

**RESULTS**

**Glycemic Control**

The average 3-BG over time for all 5,510 patients in the study is shown in scattergram form (Fig. 1). As can be seen from this figure, glycemic control improved gradually and steadily over time. Interestingly, it continues to do so as both floor and ICU nurses have become used to the concept of total glycemic control, driving patients into the lower reaches of the specified target ranges. The average 3-BG for all 299 diabetic cardiac surgery patients in calendar year 2005 was 121 mg/dL.

**Mortality**

In the isolated CABG population of patients in this study (n = 4,448), chosen to reflect a homogeneous expected mortality rate, in-hospital mortality was directly influenced by 3-BG (Fig. 2). Multivariable analysis showed that 3-BG affects mortality ( $P < 0.0001$ , odds ratio [OR] =

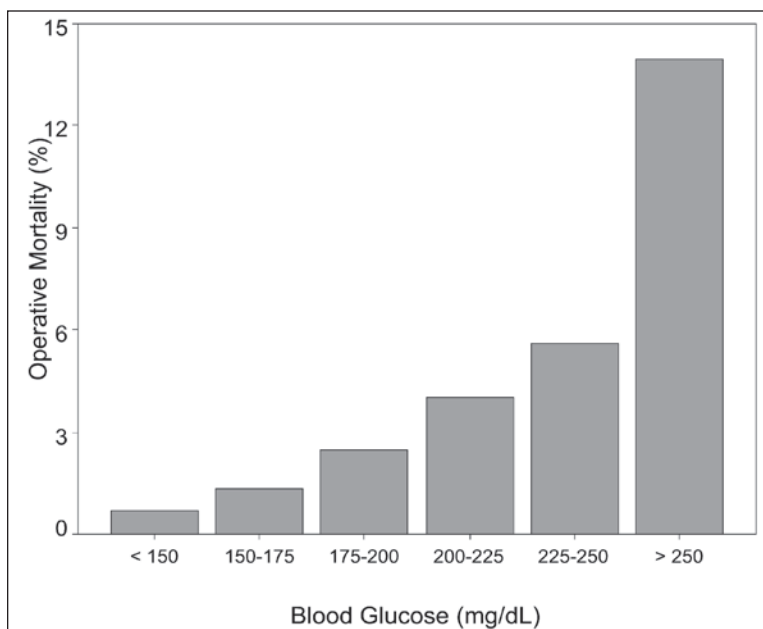
2.0 per 50 mg/dL increase in 3-BG) and does so independently of the use of epinephrine and of 9 other variables previously known to influence this outcome.

A similar multivariable analysis demonstrated that the use of CII *independently* reduced the risk of death by 60% (RR = 0.4,  $P < 0.001$ ). This reduction in postoperative mortality occurred mainly through a marked reduction in cardiac-related causes of death, namely acute heart failure (pump failure) and arrhythmias. Comparison of cause of death between the SQI and CII groups showed a 75% reduction in the incidence of cardiac-related death (4.4% versus 1.1%, respectively;  $P < 0.0001$ ).

Annual mortality rates for both our diabetic and non-diabetic patient populations are shown in Figure 3. As glycemic control in our institution grew tighter and tighter over the course of this study, and as our use of intravenous infusions on the floor became more pervasive, our annual CABG mortality for diabetics at first equaled, and now has been lowered beyond, that of our nondiabetic population. To our knowledge, this is a feat unequaled in any other cardiac surgery center to date, anywhere in the world. Moreover, at our institution, “diabetes” is no longer considered a risk factor for death following CABG.

**Infection**

We analyzed perioperative infectious complications by focusing on deep sternal wound infections (DSWI), or “mediastinitis,” in all patients enrolled in the study who underwent median sternotomy (n = 5,510). 3-BG was found to affect DSWI both directly and independently ( $P < 0.0001$ ,



**Fig. 2.** Operative mortality rates for isolated CABG by 3-BG extile. Note the direct relationship between increasing 3-BG and increasing in-hospital mortality ( $P < 0.0001$ ).

OR = 1.73 per 50 mg/dL increase in 3-BG). Because of the physiologic and biochemical reasons elucidated previously, this effect becomes significant only at 3-BG levels above 175 mg/dL. At 3-BG >175 mg/dL, the risk of DSWI increases by 3.4-fold overall ( $P<0.007$ ) and can be subcategorized into a twofold increase from 175 to 225 mg/dL; a fourfold increase from 225 to 250 mg/dL; and a sixfold increase for 3-BG levels above 250 mg/dL. Again, CII was shown to reduce the incidence of DSWI from 2.0% in the SQI group to 0.6% in the CII group ( $P<0.001$ ). Multivariable analysis showed that CII independently reduces DSWI by 77% (RR = 0.23,  $P<0.0001$ ).

### Other Complications

Through separate multivariable analyses, several other complications were shown to be directly and significantly affected by increases in 3-BG. For every 50-mg/dL increase in 3-BG, the following risks were apparent: requirement for transfusion was increased 2.2 times ( $P<0.0001$ ); risk of new-onset atrial fibrillation was increased 1.2 times ( $P<0.001$ ); inotropic use for >48 hours (a surrogate for acute postoperative heart failure) was increased 1.6 times ( $P<0.03$ ); and risk of infections other than DSWI was increased 1.2 times ( $P<0.02$ ).

### Length of Stay

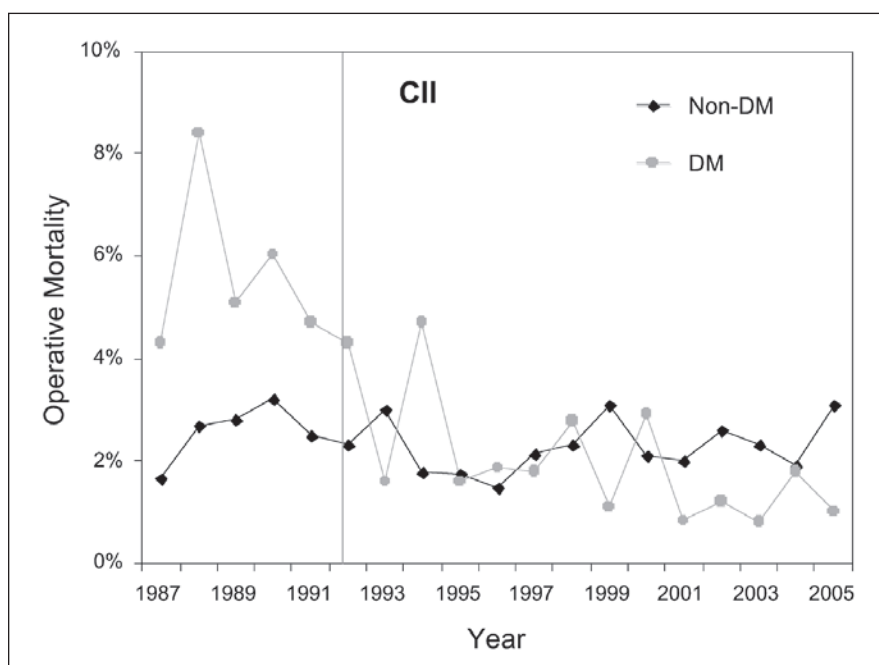
Length of stay (LOS) was analyzed in the isolated CABG population, again to maintain a homogenous ex-

pected outcome. There was a direct relationship between increasing 3-BG and increasing LOS. Multivariable analysis showed that LOS in the CABG population increases by 1 day for every 50-mg/dL increase in 3-BG ( $P<0.01$ ).

### DURATION OF 3-BG EFFECT AND CII THERAPY ON OUTCOMES

Detailed multivariable analyses of the interrelationship between the various components of 3-BG and LOS, mortality, and DSWI were performed to determine the time-related impact of hyperglycemia on these outcomes. A summary of these findings is shown in Table 1. Results showed that hyperglycemia on the day of surgery, and the first and second postoperative days, significantly affects mortality. Hyperglycemia also has a significant affect on DSWI outcomes throughout the perioperative period studied, and even elevated hemoglobin A1c on admission indicates increased risk. The hyperglycemic affect on LOS is significant until the third postoperative day.

Thus, the impact of time-related treatment and control of hyperglycemia with CII should be matched to maintain euglycemia throughout the period for which BG remains an independent outcome risk. We applied this knowledge by expanding our protocol and CII treatment to include both intraoperative control as well as control for patients who had been transferred from the ICU into general telemetry wards. Note that when this was done, and *only* when this



**Fig. 3.** Annual CABG mortality rates for both the diabetic and nondiabetic populations through the course of the study. *Vertical line* indicates initiation of the CII protocol in 1992. Note that the mortality rate for diabetics was normalized to that of nondiabetics only when CII use was expanded to include a full 3 postoperative days (1995), with CII use even on non-ICU floors.

**Table 1**  
**Independent Significance of Daily Glucose Parameters on Outcomes\*†**

	HbA1C	Preoperative BG	DOS BG	POD 1 BG	POD 2 BG	POD 3 BG
Mortality	NS	NS	<0.001	<0.001	0.004	NS
DSWI	0.019	0.008	0.021	<0.001	<0.001	0.008
LOS	NS	0.025	<0.001	<0.001	<0.001	NS

\*DSWI = deep sternal wound infection (mediastinitis); LOS = length of stay; NS = not significant ( $P>0.05$ ).

†All calculations were performed as part of separate multivariable analyses for each outcome listed.

was done, did our outcomes for diabetics normalize to those of the nondiabetic population (Fig. 2).

The importance of these time-related observations should not be underestimated. The duration of CII therapy is just as important as target range in achieving optimal outcomes. Hospitals that utilize CII to control patients' glucose levels only in the ICU likely will not achieve the dramatic reductions in adverse outcomes observed in the present study. If these patients are transferred to the non-ICU ward prior to the third postoperative day, CII should be continued to ensure maintenance of euglycemia and thus optimization of surgical outcomes.

## CONCLUSION

Our data suggest that diabetes itself is not a risk factor for adverse outcomes following cardiac surgery. Rather, hyperglycemia, as defined by 3-BG, is the true risk factor for increases in mortality, DSWI, LOS, and other complications. Importantly, both the "3" and the "BG" are essential components of that risk. Because of these findings, CII should become the accepted gold standard of care and should be utilized to maintain euglycemia for 3 full days in all hyperglycemic cardiac surgery patients.

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