Impact of Perioperative Glycemic Control Strategy on Patient Survival After Coronary Bypass Surgery

A. Thomas Pezzella, MD, Sari D. Holmes, PhD, Graciela Pritchard, BS, Alan M. Speir, MD, and Niv Ad, MD
Cardiac Surgery Research, Inova Heart and Vascular Institute, Inova Fairfax Hospital, Falls Church, Virginia

Background. Glycemic control in the perioperative period decreases mortality and morbidity, but data are scarce with regard to the effects of glucose control approaches on survival. We assessed long-term survival in patients treated with 2 strategies of glucose control after first-time isolated coronary artery bypass graft.

Methods. In a previously published trial, patients were prospectively randomized to strict (90-120 mg/dL) or liberal (121-180 mg/dL) glucose control protocols. The aim of this study was to assess long-term data on survival and health-related quality of life based on the original prospective randomized study population.

Results. No differences were found in cumulative survival between the strict (95.5%) and liberal (93.5%) target range groups (log-rank = 0.32, p = 0.57) over a mean follow-up of 40.0 ± 4.4 months. Physical health-related quality of life significantly improved in all patients from baseline to 6 months after surgery (F = 17.73, p < 0.001), and there were no differences in improvement of health-related quality of life between the 2 target range groups (F = 0.15, p = 0.70).

Conclusions. These results support our previous findings and indicate that a liberal glycemic control strategy after coronary artery bypass leads to survival rates and improvements in health-related quality of life that are similar to those achieved with a strict target range. In addition, the liberal strategy is superior in glucose control and target range management.


Perioperative hyperglycemia after coronary artery bypass graft (CABG) and other cardiac surgery has been shown to be associated with increased morbidity and mortality [1]. The application of tight glycemic control during the perioperative period in both cardiac and noncardiac surgery patients results in improved operative outcomes [2–7]. Recent studies have shown that after CABG, the maintenance of glucose levels in a liberal target range (121 to 180 mg/dL) is safer and more advantageous than a tight target range (90 to 120 mg/dL) in both diabetic and nondiabetic patients [8, 9]. Our prior experience with a liberal glycemic control protocol in a prospective randomized controlled trial supports these findings [10]. In that study, we demonstrated that maintenance of blood glucose in a liberal range of 121 to 180 mg/dL immediately after CABG in both diabetic and nondiabetic patients led to perioperative outcomes similar to those achieved with a strict target range of 90 to 120 mg/dL and was superior in glucose control and target range management [10].

Data are conflicting with regard to midterm and long-term morbidity and mortality associated with various glycemic control strategies in the perioperative period. In this study, we sought to determine the effects of a liberal (121 to 180 mg/dL) and a tight (90 to 120 mg/dL) target glucose range on long-term survival after first-time isolated CABG.

Patients and Methods

The follow-up data analyzed in this study were collected from patients who participated in our previous study [10] as part of our center’s prospective postsurgery follow-up program. The study was approved by our institutional review board (IRB no. 09.11 and no. 12.039). Patient selection and eligibility criteria were determined as described previously [10]. Survival information was obtained through the Social Security Death Index and the National Death Index [11]. Data on health-related quality of life (HRQL) were available for a subset of the original patients in the prior randomized controlled trial (n = 41) and were collected with the Short Form-12 (SF-12) [12]. All patients were given standard discharge instructions according to their diabetic status. Patients with a history of diabetes were returned to their presurgery diabetic control method before discharge. Patients with previously undiagnosed diabetes were referred to their primary care physician or endocrinologist for further assessment and treatment. Patients without a history of diabetes were instructed to maintain a controlled diet. After discharge there was no further study intervention for glucose management.
**Statistical Analysis**

Descriptive statistics and group comparison analyses for preoperative characteristics in this sample of patients were described previously [10]. Survival rates in the strict (90 to 120 mg/dL) and liberal (121 to 180 mg/dL) target range groups were compared by using Kaplan-Meier survival analysis and Cox proportional hazards regression, adjusting for age and Society of Thoracic Surgeons (STS) predicted operative risk score. Changes in HRQL from before surgery to 6 months after surgery in the strict and liberal groups were compared by using repeated-measures analysis of variance.

The main format for analyses was intention-to-treat unless otherwise noted. As described previously [10], due to crossover between the 2 treatment arms, we also conducted completers analyses and per-protocol analyses when examining long-term outcomes. In completers analyses, patients were compared according to the actual treatment they received. In per-protocol analyses, patients were included only if their actual treatment matched their randomly assigned treatment.

### Results

The sample examined in this study comprised patients enrolled in our previous randomized controlled trial (Table 1). Therefore, all preoperative characteristics remained the same as those previously described [10]. The mean age of the patients at the time of surgery was 62.7 ± 9.8 years, 16% were female, and there were no differences in preoperative characteristics, including presence of diabetes mellitus, between patients who had strict glucose control and those who had liberal glucose control (41% vs 45%, *p* = 0.56).

#### Survival

Regardless of which group comparison method was used, there was no difference in cumulative survival between the strict and liberal control groups (mean follow-up, 40.0 ± 4.4 months; median [interquartile range], 40.9 [38.0 to 43.2] months). Specifically, intention-to-treat analysis found a cumulative survival rate of 95.5% in the strict group and 93.5% in the liberal group (log-rank = 0.32, *p* = 0.57; Fig 1). Completer analysis found a cumulative survival rate of 94.3% in the strict group and 94.8% in the liberal group (log-rank = 0.05, *p* = 0.82), whereas per-protocol analysis found a cumulative survival rate of 94.8% in the strict group and 94.0% in the liberal group (log-rank = 0.04, *p* = 0.84).

After adjustment for age and STS score, Cox proportional hazard modeling indicated no difference in survival between the 2 glucose control groups. Hazard ratios for the glucose control groups (reference group = strict control) were 1.42 (95% confidence interval [CI] = 0.40 to 5.06, *p* = 0.59) in the intention-to-treat analysis, 0.81 in the completer analysis (95% CI = 0.22 to 2.98, *p* = 0.76), and 1.21 (95% CI = 0.30–4.96, *p* = 0.79) in the per-protocol analysis.

#### Health-Related Quality of Life

In the subgroup of patients with SF-12 data at baseline and 6 months after surgery (*n* = 41), intention-to-treat analyses indicated that physical HRQL improved significantly (*F* = 17.73, *p* < 0.001), and there was no difference between the glucose control groups in HRQL improvement (*F* = 0.15, *p* = 0.70). Similarly, in completer analyses, physical HRQL improved significantly (*F* = 16.57, *p* < 0.001) and there was no difference between the 2 groups in HRQL improvement (*F* = 0.13, *p* = 0.72).

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Strict (n = 91)</th>
<th>Liberal (n = 98)</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.5 ± 10.2</td>
<td>62.8 ± 9.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Female</td>
<td>10 (11)</td>
<td>20 (20)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37 (41)</td>
<td>44 (45)</td>
<td>0.56</td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>20 (54)</td>
<td>15 (34)</td>
<td>0.07</td>
</tr>
<tr>
<td>Noninsulin dependent</td>
<td>17 (46)</td>
<td>29 (66)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>6.64 ± 1.52</td>
<td>6.48 ± 1.28</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>75 (82)</td>
<td>84 (86)</td>
<td>0.56</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>12 (13)</td>
<td>9 (9)</td>
<td>0.49</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.57 ± 0.08</td>
<td>0.56 ± 0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>Aspirin</td>
<td>84 (92)</td>
<td>92 (94)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>77 (85)</td>
<td>91 (93)</td>
<td>0.10</td>
</tr>
<tr>
<td>ACE/ARB inhibitors</td>
<td>46 (51)</td>
<td>46 (47)</td>
<td>0.62</td>
</tr>
<tr>
<td>Lipid-lowering medications</td>
<td>84 (92)</td>
<td>92 (94)</td>
<td>0.78</td>
</tr>
<tr>
<td>STS risk percentage</td>
<td>1.4 ± 2.2</td>
<td>1.1 ± 2.1</td>
<td>0.36</td>
</tr>
<tr>
<td>EuroSCORE (additive)</td>
<td>3.97 ± 2.98</td>
<td>3.67 ± 2.65</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard deviation or frequency (percent) unless otherwise indicated.*

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EuroSCORE = European system for cardiac operative risk evaluation; STS = Society of Thoracic Surgeons.

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**Fig 1.** Kaplan-Meier survival curves comparing strict and liberal glucose target range groups.
Comment

Our present study assessed management of hyperglycemia in both diabetic and nondiabetic patients who had undergone CABG, focusing on long-term mortality. Because early and late mortality rates were not significantly different in the 2 target range groups, it appears that cumulative survival rates over a mean follow-up period of 40.0 ± 4.4 months were not different for cardiac surgery patients with either strict or liberal control, regardless of the presence of diabetes. This study lends support to the appropriate and systematic early control of glucose levels, whether liberal or strict. Further long-term evaluation of glucose control measures in diabetic CABG patients, along with the degree of target organ dysfunction, may add insight into the postoperative course of these patients.

In our study physical HRQL improved significantly and comparably in both protocol groups. Our results with regard to HRQL reflect those of other studies showing that intensive intraoperative insulin therapy improves outcomes [13] and is associated with sustained outcome benefits, particularly for cardiac surgery patients with prolonged illness [14].

The early perioperative control of hyperglycemia has been well studied [2–4, 15–17]. Current STS practice guidelines support the beneficial effects of a more liberal glycemic control strategy [8]. The current STS recommendation is continuous insulin infusions in the operating room and for at least 24 hours postoperatively with target maintenance glucose levels of less than 180 mg/dL [8]. Our experience, as well as that of others, supports this approach, given the potential negative consequences of hypoglycemia associated with tight control [18–20]. This has also become a quality assurance measure [21, 22].

Although recent literature has shown that perioperative survival is improved with glycemic control (whether tight or liberal) long-term data are scarce [14, 15, 23–31]. Diabetic patients with coronary artery disease reputedly have worse long-term outcomes than nondiabetic patients [15]. Yet the retrospective data are difficult to analyze because the definition of diabetes mellitus is not universal and details regarding hyperglycemic control during follow-up are not well documented. Prior studies have acknowledged the difficulty of achieving consistent control of glucose [22], and the literature is variable with regard to definitions of mean glucose control values in postsurgery diabetic patients. In our original manuscript [10], we reported that the strict glucose control protocol took longer for patients to reach target range, had greater readings outside of the target range, and a greater number of patients with hypoglycemic events. The liberal target protocol was easier to maintain adequately. Although variability in glucose readings was found, particularly around the introduction of solid food, it was found to be lower with the liberal protocol compared with the strict protocol. In fact, because the original randomized trial showed such promise for the liberal target protocol without increasing morbidity, our center switched to the liberal protocol as the standard of care for glucose management in all cardiac surgery patients. A new study by our center has evaluated the effectiveness of this change in standard of care, finding implementation of the liberal protocol on a large scale was not associated with increased morbidity and was easier to maintain [32].

There is no uniform consensus regarding the preoperative definition or classification of diabetes mellitus. Definitions include the following: type 2 diabetes only; diabetes controlled with diet, oral drugs, or insulin; prediabetes with hemoglobin A1C levels of greater than 6.5; and metabolic syndrome. In addition, studies in this area have examined patients with diabetes alone as well as those with diabetes and comorbid organ disease, including coronary artery disease, heart failure, renal failure, peripheral vascular disease, and stroke. In our study, the STS definition was used for the 43% of patients with diabetes [10]. The STS defines diabetes as a history of diabetes diagnosed or treated by a physician and documented in the medical record or HgbA1c (glycated hemoglobin), is greater than or equal to 6.5, regardless of duration of disease or need for antidiabetic agents [33]. Further long-term comparisons should better define diabetic and nondiabetic cohorts to strengthen comparative analyses. In addition, as noted in the Surgical Care Improvement Project [22], the postoperative definition of hyperglycemic control is not standardized. Thus it is not possible to give an accurate assessment of diabetes as a preoperative risk factor [30, 31].

Limitations

The limitations of this study include the fact that it is a retrospective analysis of prospectively collected data rather than a prospective randomized controlled study. However, patients were initially randomly assigned to the glycemic control treatment groups. The proportion of patients with diabetes, particularly insulin-dependent diabetes, was relatively small within this study sample, which may limit the generalizability of these results from a mixed sample to individual groups of patients across various levels of diabetic status.

Another potential limitation for this study is the relatively small sample size available for follow-up survival analyses. Although the observed power for Cox regression analyses was only around 60%, there were 10 events that were modeled in these analyses. This “events per predictor variable” ratio is sufficient for the univariate association between target range and survival given traditional rule of thumb, but the addition of adjustment for age and European system for cardiac operative risk evaluation (EuroSCORE) does put a strain on the power for these analyses. However, the association of target range to survival was comparable with or without adjustment for age and EuroSCORE. Power analyses for HRQL analyses indicated high observed power (> 85%) for the main effect of time, but the interaction of time by target range group had very low power (< 10%). Therefore, the results for HRQL should be interpreted with caution and viewed as secondary hypothesis-generating analyses.
Another practical limitation is that smaller centers, particularly those without computerized glucose management, may find it impractical to apply the rigorous blood and glucose management that is employed at our center. In addition, detailed information regarding long-term follow-up events outside of mortality was outside the scope of this study and was not captured. A review of readmissions within 30 days of surgery did indicate a trend toward fewer short-term readmissions for the liberal target range (4% vs 9%), but these analyses did not reach significance.

Conclusions

Our previous prospective randomized controlled study suggested that maintaining glucose levels in the range of 120–180 mg/dL in post-CABG patients led to perioperative outcomes that were non-inferior to those achieved with a strict target range of 90 to 110 mg/dL [10]. In this follow-up study, we found no differences in cumulative survival or HRQL in patients who had undergone CABG and whose glucose levels were maintained in a strict (90 to 120 mg/dL) or a liberal (121 to 180 mg/dL) target range. The STS guidelines recommend the maintenance of blood glucose below 180 mg/dL for all patients after cardiac surgery, regardless of their diabetic status [8]; that recommendation is based on data showing that glycemic control is associated with reduced perioperative mortality and morbidity and, more specifically, fewer infections and shorter length of stay. Our findings demonstrate the safety and efficacy of a liberal approach to glycemic control for all adult patients undergoing cardiac surgery.

References

INVITED COMMENTARY

Although the optimal target for perioperative blood glucose levels in diabetic patients undergoing coronary artery bypass grafting (CABG) is unknown, there is evidence to suggest that aggressive protocols to achieve glucose levels between 90 and 120 mg/dL do not improve short-term outcomes. In this edition of *The Annals*, Pezzella and colleagues [1] now report that more aggressive glycemic control (90 to 120 mg/dL) results in no better long-term survival or improvements in health-related quality of life that can be achieved with more liberal glycemic control (121 to 180 mg/dL).

To determine the effects of more aggressive glycemic control in patients with diabetes undergoing CABG, my colleagues and I prospectively randomized patients to either an aggressive (90 to 120 mg/dL) or a moderate (120 to 180 mg/dL) protocol [2]. There was no difference in the incidence of 30-day mortality, myocardial infarction, neurologic events, deep sternal wound infection, or atrial fibrillation between the groups. Patients with aggressive control had a higher incidence of hypoglycemic events, but this did not result in any clinical sequelae. These results were consistent with the results of other studies [3], including the initial work by the current authors [4]. Although we found no difference in short-term outcomes, more aggressive control did significantly lower markers of inflammation, such as free fatty acids. In our earlier studies, this reduction in free fatty acids resulted in improved long-term survival [5]. It is conceivable that this reduction in the inflammatory response may ultimately enhance vein graft patency, inasmuch as patients with lower free fatty acid levels had more freedom from recurrent angina and need for revascularization procedures [5].

In their study, Pezzella and colleagues report only data on survival but fail to tell us whether there were any differences in cardiac-related issues, such as the incidence of myocardial infarction, recurrent angina, need for repeated coronary revascularization procedures, or long-term readmissions for acute coronary syndromes. In our follow-up study, we plan to report not only long-term survival but the incidence of cardiac events over a 5-year period from the time of operation. Although more aggressive control may not prolong survival, these data will help us determine whether more aggressive perioperative glycemic control will translate into superior long-term freedom from cardiac-related events.

Harold Lazar, MD

Department of Cardiothoracic Surgery
Boston Medical Center
88 E Newton St, B404
Boston, MA 02118
e-mail: harold.lazar@bmc.org

References