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Effect of glycemic control on mortality and infections in patients undergoing coronary artery bypass grafting: a Genesee County experience

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ABSTRACT

Background: We report post-coronary artery bypass outcomes and factors affecting the outcomes from the Genesee County, MI, where the population is distinctly characterized by a higher prevalence of renal failure (RF), diabetes, obesity and smoking than the national average.

Methods: We performed a retrospective cohort study on 1133 patients undergoing isolated CABG at our hospital from June 2012 to July 2017. Primary outcome was the association between preoperative hemoglobin A1c (HbA1c) and all-cause postoperative mortality after CABG, secondary outcomes included the association between HbA1c and a composite of postoperative infections including sternal-wound infections, leg harvest-site infections, pneumonia or sepsis. Logistic Regression analyses were also performed.

Results: There was no difference in the mortality rate (OR 1.0, 95% CI 0.4–2.3) and composite of all infections (OR 1.0, 95% CI 0.7–1.6) between the controlled (HbA1c ≤7%) and uncontrolled (HbA1c >7%) groups. However, RF (OR 5.9, 95% CI 1.5–22.9), smoking (OR 3.7, 95% CI 1.3–11.2) and ejection fraction <35% (OR 3.4, 95% CI 1.4–8.3) were independently associated with increased mortality after CABG. Additionally, low EF (OR 2.4, 95% CI 1.4–4.1) and smoking (OR 2.3, 95% CI 1.2–4.1) were associated with an increased rate of composite of all infections after CABG.

Conclusion: Although not different in controlled and uncontrolled diabetic groups, mortality, in our population was associated with comorbidities like RF, smoking and congestive heart failure that are highly prevalent, emphasizing the need for interventions at primary care level to improve the postoperative outcomes after CABG.

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Hemoglobin a1c; coronary artery bypass graft; mortality; infections

1. Introduction

In the USA, approximately one-third of patients undergoing percutaneous coronary intervention (PCI) and 25% of patients undergoing coronary artery bypass grafting (CABG) have DM [1]. American Diabetic Association recommends the use of glycosylated hemoglobin as an assessment method for long-term glycemic control in DM. HbA1c is more reliable than a spot glucose test as a marker of diabetic control, since the latter is associated with more variability. Data on association of preoperative glycemic control with post-CABG outcomes have been conflicting, with studies conducted in populations with inconsistent demographic characteristics [2–4]. Therefore, we conducted a study in a patient population of the Genesee County of Michigan (MI) with a total population of 407,385 persons [5]. We report an association of glycemic control in terms of HbA1c and other comorbidities with post-operative CABG outcomes. Our study is unique as our sample comes from an under-privileged population with unique social demographics (Table 1) that has one of the highest incidences and prevalence of end-stage renal disease (ESRD) in the USA along with higher prevalence of obesity, heart disease and DM as compared to the national average [6].

2. Methods

We performed a retrospective chart review of consecutive patients who underwent isolated CABG between 1 June 2012 and 13 July 2017 at our academic community hospital. A total of 1218 patients underwent isolated CABG at our institute during the above-mentioned dates, those who underwent emergent surgery or who did not have pre-operative hemoglobin A1C levels checked were excluded and a total of 1133 were included in final analysis.

Based on preoperative HbA1c our cohort was stratified into two groups i.e., Group A (controlled) with an Hba1c of ≤7% and Group B (uncontrolled) with an HbA1c of >7%. We used the ARMUS database (a data warehouse and reporting services provider for the

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Table 1. Comparison of population characteristics of Genesee County with U.S. national average.

Demographics	U.S. average	Genesee County
Race		
White	76.6%	75.4%
Black	3.4%	20.3%
Hispanic	18.1%	3.4%
Education		
High school graduate or higher in >25 year-old	87.0%	89.6%
Bachelor degree or higher in >25 year-old	30.3%	19.9%
Economy and Health		
Housing – median gross rent (2012–2016)	$949	$720
Median household income (2012–2016)	$55,322	$43,246
Percent in Poverty	12.7%	20.3%
With a disability, <65-year-old (2012–2016)	6.4%	10.1%

Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative) to obtain all patients' characteristics. Data was assessed for outliers and out of range values by performing a series of frequencies, proportions, descriptive statistics (e.g., mean, median, and standard deviation) and figures (e.g., histograms and box and whisker plots).

The following characteristics were included in our analysis: age, body mass index (BMI), gender, smoking status, DM, hypertension (HTN), peripheral arterial disease (PAD), preoperative renal failure (RF) (defined as dialysis-dependent RF), left ventricular (LV) ejection fraction (EF) < 35%, prior CABG, preoperative placement of intra-aortic balloon (IABP) and the duration of aortic cross-clamp time. Primary outcome of interest was all-cause mortality after CABG whereas secondary outcome of interest was the association between uncontrolled DM (HbA1c value of >7%) and all postoperative infections, including sternal wound infections, leg harvest site infections, postoperative sepsis, pneumonia and a composite outcome of all the above-mentioned infections. Sternal wound infection was defined as evidence of sternal/parasternal tissue infection requiring antibiotics or incision and drainage (I&D). Pneumonia was defined as a presence of cough/purulent tracheobronchial secretions, temperature >38.3°C or leukocytosis and the presence of one of (a) chest x-ray showing new pulmonary infiltrates for >48, (b) positive blood/trachea-bronchial secretion cultures or (c) difficulty in extubation. Leg harvest site infection was defined as clinical or microbiologic evidence of the venous harvest site requiring I&D or antibiotics. Post-op sepsis was defined as positive blood cultures after surgery with signs of systemic inflammatory response syndrome (SIRS).

We compared baseline characteristics between the two groups (Table 2). Descriptive statistics like mean ±SD were used to describe continuous variables and categorical variables were described with frequencies and percentages. Chi-square test was used to analyze the differences between the categorical variables and Student's t-test was used to study the differences between continuous variables. To control for confounders, a multivariate logistic regression analysis was conducted to examine the effect of our main study explanatory variable on our primary and secondary study outcomes. Age, gender, smoking status, DM, RF, EF<35% and aortic cross-clamp time were included in our final adjustment model for primary and secondary outcomes individually as they have been previously reported to influence outcomes [7,8]. All analyses were done using Stata statistical software package version 11.2 (Stata Corporation, College Station, TX). The usual two-sided 0.05 Type I error threshold for statistical significance was used for all analyses.

Table 2. Selected characteristics of postoperative patients with and without hemoglobin a1c defined glycemic control (≤7% and >7%).

Variable	Total (n = 1133)	Controlled (n = 818)	Uncontrolled (n = 315)	p-value
Age (mean ± SD)	65.0 (10.4)	66.2 (10.4)	62.1 (9.9)	< 0.001
Male (%)	68.8	71.3	62.2	0.003
Smoking Status (%)				
Never	56.2	57.1	54.0	0.112
Current-Some days	26.8	25.2	31.1	
Current-Every day	17.0	17.7	14.9	
Body Mass Index (kg/m^2) (mean ± SD)	30.8 (6.6)	29.8 (6.3)	33.3 (6.7)	< 0.001
Diabetes Mellitus (%)	48.3	28.3	100.0	< 0.001
Hypertension (%)	93.5	92.3	96.5	0.010
1 missing value				
Peripheral Artery Disease (%)	29.7	27.1	36.5	0.002
8 missing values				
Low Ejection Fraction (%) ≤35%	12.8	12.1	14.7	0.274
1 missing value				
Previous CABG (%)	3.9	4.0	3.5	0.735

n = number of patients included in the study.
CABG = coronary artery bypass grafting, SD = standard deviation.

3. Results

We included 1133 patients in our study sample. Of the 545 diabetic patients, 315 (57.7%) had preoperative HbA1c greater than 7%. As compared to the controlled HbA1c group, patients in the uncontrolled HbA1c group were relatively younger (66.1 ± 10.4 years vs 62.1 ± 9.9 years respectively), more likely to be males (71.3%), had a higher mean BMI and a slightly higher prevalence of HTN and PAD. Both groups were similar in terms of smoking status, prevalence of RF and, decreased EF (<35%), and the use of IABP (Table 2).

On an unadjusted analysis (Table 3), the incidence of postoperative mortality was similar in both controlled and uncontrolled groups (OR 1.0, 95% CI 0.4–2.3). Furthermore, no statistically significant difference was found between the two groups for our secondary outcomes i.e., composite of all infections and each of the individual infections in the unadjusted analysis (Table 3). After adjusting for various confounders, no statistically significant correlation was found between HbA1C and postoperative mortality (OR 1.7, 95% CI 0.5–6.1). On multivariate logistics regression analysis, age, sex, BMI, HTN, PAD and the presence of DM were not statistically significantly related to all-cause mortality. However, preoperative RF (OR 4.8, 95% CI 1.2–18.6), EF <35% (OR 3.5, 95% CI 1.4–8.7), use of IABP (OR 2.9, 95% CI 1.1–7.9) and smoking status (OR 2.8, 95% CI 1.1–7.4 and OR 3.7, 95% CI 1.3–11.2 for current -some days and every-day smokers, respectively) were significantly associated with all-cause mortality. Interestingly, smoking frequency had a positive and statistically significant association with all-cause mortality (Table 4). Variables independently associated with an increased risk of composite of all infections on multivariate analyses included every-day smoking and EF <35% (Table 5).

Table 4. Adjusted Odds Ratio[a] (OR) for relationship between preoperative characteristics and postoperative mortality (primary outcome) in patients undergoing CABG.

Variable	Odds ratio, 95% confidence interval	p-value
Hemoglobin a1c >7%	1.7 (0.5, 6.1)	0.404
Age >65	1.0 (1.0, 1.1)	0.052
Male gender	0.5 (0.2, 1.1)	0.066
Diabetes Mellitus	0.6 (0.2, 1.8)	0.321
Preoperative Renal Failure	5.9 (1.5, 22.9)	0.010
Smoking Status		
Current-Every day	2.8 (1.1, 7.4)	0.034
Current-Every day	3.7 (1.3, 11.2)	0.018
Ejection Fraction ≤35%	3.4 (1.4, 8.3)	0.007
Cross-clamp time >80 min	1.2 (0.5, 2.7)	0.683

[a]Adjusted for all other variables in the table.

Table 5. Adjusted Odds Ratio[a] (OR) for relationship between preoperative characteristics and composite of postoperative infections in patients undergoing CABG.

Variable	Adjusted OR (95% CI)	p-value
Hemoglobin A1c >7%	1.1 (0.6, 2.1)	0.843
Age	1.0 (1.0, 1.1)	0.017
Male gender	0.6 (0.4, 1.0)	0.062
Smoking Status		
Current-Some days	1.6 (1.0, 2.7)	0.076
Current-Every day	2.3 (1.2, 4.1)	0.008
Diabetes	1.0 (0.5, 1.7)	0.901
Cross-clamp time >80 min	1.2 (0.8, 1.9)	0.460
Preoperative Renal Failure	1.6 (0.5, 4.7)	0.426
Ejection Fraction ≤35%	2.4 (1.4, 4.1)	0.002

[a]Adjusted for all other variables in the table.

4. Discussion

The patient population in Genesee County has several characteristics that differentiate it from the rest of MI and USA. In 2012, the prevalence of DM in the Genesee County was 11.6%, compared to 9.48% in MI and 9.11% in the USA, prevalence of smoking was 28.1% compared to 18.9% in Michigan and 18.1% in the USA. Additionally, the prevalence of obesity, dyslipidemia and heart disease in the Genesee County was 35.7%, 42.4% and 6.6% compared to the national average of 26.6%, 38.5% and 4.4% respectively. In addition to the above-mentioned morbidities, the patient population in the Genesee County has distinct social characteristics (Table 1) that differentiate it from the average USA population.

For patients undergoing CABG at our hospital, a protocol for blood sugar control derived from updated literature is followed to ensure optimal outcomes. Preoperatively for elective surgery, all patients undergo standardized preoperative testing including HbA1c, thyroid stimulating hormone, urine culture and sensitivity and nasal swab for MRSA screen. Beta-blockers and statins are administered preoperatively while angiotensin converting enzyme inhibitors are held 48-hours prior to surgery. Intra-operatively and post-operatively in the intensive care unit, diabetes is managed with an insulin infusion to maintain a blood glucose level between 80–150 mg/dl. Endocrinology consultation

Table 3. Incidence of mortality and infections after CABG in patients with controlled or uncontrolled diabetes mellitus.

Outcome	Total n = 1133	Controlled n = 818	Uncontrolled n = 315	p-value
Mortality (%)	2.5	2.5	2.5	> 0.999
Pneumonia (%)	5.7	5.4	6.7	0.395
Sternal Wound Infection (%)	1.1	1.1	1.0	> 0.999
Leg Harvest site infection (%)	0.8	0.9	0.6	> 0.999
Sepsis (%)	2.6	2.3	3.2	0.407
Composite of all infections (%)	8.4	8.3	8.6	0.905

is obtained on all patients with diabetes. After transfer to the telemetry unit, the control is variable and includes scheduled-insulin in addition to a correction scale. The interventions have shown to have improved both postoperative mortality [9,10] and infections [11].

In our analysis, there was no difference in mortality between patients with preoperative HbA1c ≤7.0% and >7.0%. However, factors such as age, RF, smoking and preoperative LVEF ≤35% were associated with an increased mortality. In terms of infection, there was no statistical difference between the two patient groups in the incidence of composite of all infections and superficial/deep sternal wound infections, leg harvest site infections, pneumonia and sepsis, individually.

Total incidence of all-cause mortality in our population is 2.5% which is comparatively higher than previously reported studies [3,12,13]. Our analysis, however, did not report a statistically significant mortality difference between controlled and uncontrolled HbA1c groups. Literature from various regions of the world has shown conflicting results in this regard. Halkos et al. [12] reported a linearly increasing mortality with increasing HbA1c and a four-fold increase in mortality in patients with HbA1c >8.6%. Similarly, Narayan et al [4] reported an increased mortality with Hba1c >6.5% on a univariate analysis, which was eventually not statistically significant after a multivariate analysis. A multicenter study by Kuhl et al. [14] also reported an increasing in 30-day and long-term mortality associated with increasing preoperative Hba1c levels. On the contrary, several studies failed to show a statistically significant difference in terms of mortality between controlled and uncontrolled diabetic groups [3,13]. The patients with uncontrolled DM have more comorbidities and/or advanced cardiac disease than patients with controlled DM, and hence, it is possible that even after adjusting for known factors affecting postoperative mortality there was residual confounding. Practice changes overtime including improved surgical technique [15] and strict perioperative glycemic control with insulin infusion [9,10] have led to better postoperative outcomes, with a down trend in overall mortality from CABG. It can therefore be argued that a discrepancy in mortality between uncontrolled and controlled DM that had existed in the past might have been improved with modern techniques [15,16], improved perioperative management [9,10,17] and secondary prevention [11,18]. Also highlighting that perioperative glycemic control might have a closer association with postoperative mortality rather than the preoperative HbA1c levels. However, patients with uncontrolled diabetes do have an impaired insulin sensitivity that require a higher quantity of intraoperative insulin infusion than patients with controlled diabetes [19].

On multivariate logistic regression analysis, we found a 5.9 times increased mortality after CABG in patients with preoperative renal failure after adjusting for suspected confounders. RF is a known risk factor associated with increased mortality after CABG [20,21] and has been included in the surgical risk scores calculators [7]. Accelerated atherogenesis in hemodialysis patients occurs primarily through the development and a subsequent sustained state of uremia [22] that consequently leads to an increase in inflammatory responses, such as proinflammatory mediators like C-reactive protein (CRP). CRP, which is indicative of enhanced atherosclerotic risk can also cause vascular injury directly and indirectly by elevating proinflammatory cytokines such as interleukin 18 (IL-18) [23]. After adjusting for age, sex and race, the prevalence of ESRD in the Genesee County was reported as 2621 cases/million people, which was considerably higher than the national U.S. reported average i.e. 1913 cases/million people [24]. It is therefore likely that the increased mortality in our analysis compared to prior data might have been influenced by a much higher number of patients with RF (4.8% and 2.9%in uncontrolled and controlled DM group respectively) in our study population.

Smoking also had a significant association with mortality and a composite of all postoperative infections in our study. The increase in short and long-term mortality after major surgery in smokers is well documented. It can be explained by a higher incidence of pulmonary complications (up to 2.41 times) in smokers [25–27]. Also, smoking has been implicated in increased duration of mechanical ventilation, hospital stay, readmissions and a higher risk of postoperative infections. Smoking can lead to alteration in pulmonary macrophage phenotypes and decrease in pro-inflammatory cytokines with resultant compromise in pulmonary immune function [28,29].

We also found higher mortality and postoperative infections in patients with systolic heart failure with EF ≤35% as compared to their counterparts. LV systolic impairment has a predictive value during the postoperative period of CABG with highest mortality being associated with severely reduced EF [30]. Of note, patients with low EF tend to have a concomitant high-risk profile compared to others due to advanced age, severe symptoms, extensive coronary or left main disease and the need for urgent or emergent operation [31]. Also, hospitalization in these patients could be prolonged due to respiratory, renal and vascular complications after CABG [31], leading to a greater burden on health-care systems.

Our study is the first of its type that reports patient outcomes from the unique population of Genesee County in MI. Our findings are in conformity with several prior studies studying the effect of preoperative

HbA1c on postoperative outcomes. We have also corroborated, that factors such as preoperative renal insufficiency, LV systolic dysfunction and cigarette smoking that have been associated with adverse outcomes previously are also significant in our study population. This reinforces the need of adequate public health services and interventions at the primary care level to tackle the risk factors at the grass-root level, potentially improving morbidity and mortality in general, also impacting postoperative outcomes after CABG.

Our study had limitations. Being a retrospective chart review, our study has the inherent biases of a retrospective study. Even after adjusting for various confounders, there is a chance that the results might have been confounded by other unmeasured factors. Despite including a total of 1133 patients and 315 patients with a HbA1c of >7%, there was a small number of adverse events resulting in low statistical power to estimate the risks after correcting for potential confounders. Greater than two-thirds of the patients in the controlled HbA1c group were non-diabetics, which might have increased heterogeneity in the control arm as factors such as insulin resistance, metabolic syndrome and whole blood viscosity contribute to cardiovascular disease risk in diabetics. In order to include more patients to increase the power of the study, we would have had to include patient data for the past 8–10 years, which would have introduced further bias as outcomes of CABG performed 10-years ago and now would not have been comparable due to different practices. As our study was not an interventional study, it does not provide definitive causal association between preoperative HbA1c and postoperative outcomes.

To conclude, preoperative HbA1c was not predictive of postoperative mortality and infections in our study population. However, factors such as preoperative renal insufficiency, LV systolic dysfunction and cigarette smoking that occur more frequently in our population were significantly associated with higher mortality, suggesting the need for interventions at a public-health level.

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