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Diagnosed Diabetes and In-Hospital Mortality after Coronary Artery Bypass Grafting

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Background—Data are conflicting over whether patients with diagnosed diabetes mellitus (DM) have higher in-hospital mortality than patients without diabetes after coronary artery bypass grafting (CABG) surgery. Long-term survival is decreased in patients with diabetes after CABG. We hypothesized that patients with diabetes have higher in-hospital mortality rates after CABG.
Methods and Results—We studied 11,001 patients (38.8% with diagnosed DM) included in the Society of Thoracic Surgeons database who received CABG at 3 clinical centers January 1, 2002 and December 31, 2010. Patients with DM were more likely to be non-white, obese, and female. DM diagnosis was related to in-hospital mortality after CABG, but this relationship was dependent on age and race. Non-white individuals under 55 years of age were 14 times more likely to die in-hospital post-CABG if they were diagnosed with DM than if the were not diagnosed with DM (AOR= 14.10, 95% CI 1.77-112.28). White individuals under 55 years of age were no more likely to die in-hospital dependent on positive DM diagnosis (AOR= 1.25, 95% CI 0.25-8.01). Diagnosed DM in individuals between 55 and 69 years of age was not associated with increased likelihood of in-hospital mortality (AOR= 0.86, 95% CI 0.49-1.51) or in individuals over 70 years of age (AOR 0.88, 95% CI 0.56-1.38).
Conclusions— Diagnosed DM was associated with higher in-hospital mortality, but this association was limited to young (under 55 years of age) non-whites. Diagnosed DM was not associated with increased in-hospital mortality in whites, and individuals over 55 years of age. Additional investigation is needed to determine why in-hospital mortality is higher in those diagnosed with diabetes after CABG, with particular focus on younger non-white individuals.

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in both men and women in the United States. Common risk factors for CVD include increased age, male gender, hypertension, dyslipidemia, obesity, smoking, physical inactivity, and diabetes mellitus (DM).[1] While white non-Hispanic men have higher incidence of CVD, black men and women have higher death rates from the disease, especially at younger ages.[2] Coronary artery disease (CAD) is the most common subtype of cardiovascular disease accounting for 67.4% of all CVD deaths.[3] Narrowing, hardening, and/or complete occlusion of the arteries that supply oxygenated blood to the heart characterize CAD, which can lead to angina, arrhythmia, myocardial infarction, heart failure, and death.[3]

Coronary artery bypass grafting (CABG), a surgical revascularization treatment for coronary artery disease, was developed in 1967 by René Favaloro and has become a common medical procedure.[3] It was estimated that 232,000 patients underwent 408,000 CABG procedures in 2007.[1] Patients with CAD that undergo revascularization procedures in combination with medical therapy have significantly improved survival times compared to individuals that only receive medical therapy.[4] Furthermore, individuals with DM and CAD have significantly increased survival times when CABG is used as the revascularization technique instead of precutaneous interventions such as angioplasty and stents.[5,6]

Approximately 75% of deaths among individuals with diabetes mellitus are attributable to cardiovascular disease.[7] Data from the Framingham Heart Study indicated that DM elevates the risk of CVD. In the “early” Framingham cohort, diabetes was found to increase the risk of CVD by two-fold in men and almost three-fold in women.[8] This difference in gender-specific association between DM and CVD, which has been replicated in other studies, negates the higher prevalence of CVD usually seen in men.[9] Young adults with diabetes have rates of CAD 12 to 40 times higher than individuals of the same age that do not have diabetes. Having diabetes has been shown to be the risk equivalent of adding 15 years to the age to a person without diabetes.[10]

The prevalence of diagnosed diabetes in the United States has been increasing. Between 1990 and 2001 it increased by 65%.[1] Additionally, data from the National Health and Nutrition Examination Survey found that the overall prevalence of diagnosed diabetes increased significantly from 1999 to 2006, from 6.5% to 7.8% ($p<0.05$). The highest burdens of diabetes have been shown in the obese, non-whites, women, individuals 60 or over, the least educated, and the poor.[11,12]

Given the association between cardiovascular disease and diabetes, the prevalence of diagnosed DM is expected to be higher among CAD patients treated with CABG than in the general population. The prevalence of diagnosed type 2 DM in the general population is estimated to be around 7.8% but the corresponding estimate in patients undergoing CABG is generally between 20-30%.[13, 14]

CABG has been largely proven to be a safe and effective means of treating CAD, but it is not without risk. According to the American Heart Association the in-hospital mortality for all individuals undergoing CABG, is 1.9%.[1] Previous studies have investigated how patient demographic characteristics impact the risk of in hospital post-CABG death. Increased patient age, non-white race, and female gender have consistently been found to be associated with increased risk of in-hospital mortality following CABG.[15, 16, 17,18] Additionally, other patient-related factors such as obesity and smoking have been shown to be associated with greater in-hospital morbidity, but not in-hospital mortality.[19,20, 21]

Diabetes mellitus is associated with increased risk of CAD, and DM is associated with increased rates of infection and longer recovery times.[22] Therefore, DM has also been investigated as a risk for in-hospital mortality after CABG. While the data on long-term survival after CABG clearly show a disadvantage for patients with DM compared to their disease-free counterparts, the evidence on in-hospital mortality is less clear. Carson et al. (2002) found diabetes to significantly increase the risk of in-hospital death after CABG when compared to risk for individuals without diabetes (3.7% and 2.7% respectively) using multivariable logistic regression.[13] Thourani et al. came to similar conclusions after observing 3.9% post-CABG in-hospital mortality among DM patients versus 1.6% in patients without diabetes using multivariable logistic regression.[23] In contrast Szabo et al. (2002) did not find diabetes to be associated with increased in-hospital mortality, but they only conducted univariate analysis.[24] Rajakaruna et al. (2006) used multivariable logistic regression and diabetes was not an independent predictor of in-hospital mortality. [25] In a more recent study, Filsoufi et al. (2007) also reported no significant difference in post-CABG in-hospital mortality between the patients with DM compared to patients without DM using multivariable logistic regression.[26]

The apparent disagreement across study results and the continuous improvements in operative technology and diabetes control underscore the need for additional research investigating the relation of DM to in-hospital mortality following CABG procedure. Many of the previous studies are now out-of-date, and used relatively small sample sizes. Moreover most studies failed to fully explore the role of non-diabetes related patient characteristics that may confound or modify the effect of diabetes on in-hospital mortality in the post-CABG population. The present study seeks to address the above gaps in knowledge by evaluating the relation between diabetes mellitus and in-hospital mortality risk after CABG in a large cohort, with recent data, and through the use of multivariable models that take into consideration both confounding and effect modification by extraneous factors.

METHODS

Subjects and Sample: This study was conducted using a retrospective cohort design. The primary aim of this study was to compare in-hospital mortality following primary isolated CABG procedure in patients with and without diagnosed diabetes. The Society of Thoracic Surgeons (STS) Adult Cardiac institutional database was queried for all patients who underwent primary isolated CABG between January 1, 2002 and December 31, 2010 (n= 11,073) at all Atlanta area hospitals affiliated with Emory University. Patients that needed emergency surgery and resuscitation on the way to surgery (n=24) were excluded from the analysis because these individuals have extremely high likelihood of imminent morbidity and mortality. After additional exclusions of all patients with missing data (n= 20 for height or weight, and n=28 for race), the final study cohort consisted of 11,001 patients. Information from medical records was included in the STS database and this was used to obtain data pertaining to patient demographics, comorbidities, and clinical outcomes. The study was approved by Emory University's Institutional Review Board, and followed HIPPA guidelines.

Analysis Our exposure of interest was doctor-diagnosed diabetes as noted in the patient's medical records and the STS database. Our outcome of interest was in-hospital death during the CABG procedure, or during the patient's hospital stay following the CABG procedure. This too was obtained from patient's medical records and recorded in the STS database. Pre-operative risk and demographic factors of interest were selected using *a priori* knowledge about their potential association with both diabetes and in-hospital death. These included patient age, race, gender, body mass index (kg/m^2), and current self-reported smoking status.

Unadjusted comparisons of pre-operative risk factors and patient demographics between diabetic and non-diabetic patients were carried out using chi-square tests for categorical variables and t-tests for continuous variables. Multivariable logistic regression models were used to evaluate the association between diagnosed diabetes and in-hospital death after controlling for extraneous factors. The initial model included age (<55, 55-69, 70+), sex, race (Caucasian or not), hospital of procedure, and obesity status (BMI of >30 kg/m^2 versus other values). All possible two-way interaction terms involving the main exposure variable (diabetes status) were also included. The results of multivariable analyses were expressed as adjusted odds ratios (AOR) with 95% confidence intervals (CI). Models were checked for collinearity. Assessment of interactions was completed via likelihood ratio tests and non-significant interaction terms were removed using a backward elimination strategy to determine the most appropriate model. Statistically significant interactions were further evaluated by comparison of stratum specific results to determine if a meaningful difference was present. Final models considered interactions that were both statistically significant and meaningful. All statistical analyses were conducted using SAS version 9.3 (SAS Inc, Cary, NC). Statistical significance level was set based on the two-sided α-error of 0.05.

RESULTS

Overall, 38.8% of patients in the study had diagnosed diabetes prior to the CABG procedure. As shown in Table 1, there was no appreciable difference between diabetes and non-diabetes groups with respect to age (mean 62.7 years vs. 62.8 years, $p = 0.5$); however, diabetes patients were more often non-Caucasian (28.6% vs. 19.7%, $p < .001$), female (33.2% vs. 26.4%), and had higher BMI (30.8 vs. 28.3 kg/m^2, $p < .001$). Participants without diabetes were also more likely to report being current smokers (58.9% vs. 51.9%, $p < .001$). Results from the initial multivariable analysis using a full logistic regression model demonstrated significant interaction, between diabetes status and age (Table 2). For this reason all subsequent analyses were conducted separately for three groups: 1) participants under the age of 55, 2) 55 to 69-year olds, and 3) those 70 years of age and older. These age-specific models were further examined for two-way interactions between diabetes and model covariates. The model for the youngest age group (under 55 years old) showed a significant interaction between race and diabetes status; and thus this model was further stratified on race. The results of the analyses for participants under the age of 55 are presented in Table 3. For white individuals, there was no discernable association between diabetes in-hospital mortality and diabetes (AOR= 1.25, 95% CI 0.25-8.01). By contrast among non non-whites in this age group the association with diabetes was large and statistically significant (AOR= 14.10, 95% CI 1.77-112.28). No other independent variables in this age group demonstrated statistically significant associations with in-hospital death.

The corresponding analyses for the middle (55-69 years) and the highest (70+ years) age groups revealed no significant interactions involving the diabetes variable. Therefore, the final models for these age groups did not require further stratification (Table 4). The associations between diagnosed diabetes and in-hospital mortality for the 55-69 age group was not significantly different from the null (AOR= 0.86, 95% CI 0.49-1.51). Caucasian individuals in this age group were less likely to die in the hospital following CABG compared to non-Caucasians (AOR= 0.44, 95% CI 0.25-0.77).

The final adjusted model for patients 70 years of age and older also showed no difference in post-CABG mortality between patients with and without diabetes (AOR 0.88, 95% CI 0.56-1.38). No significant associations were observed for any other variables in this age group (Table 4).

DISCUSSION

This study of 11,001 CABG patients confirmed that diabetes is a risk factor for post-surgery in-hospital mortality, but the effect is most pronounced in (and, in fact, limited to) one particular group of patients – young (under the age of 55) non-whites. By contrast, having a diagnosis of diabetes did not significantly increase the odds of in-hospital mortality for white individuals (regardless of age) or persons over 55 years of age (irrespective of race).

As seen in our study, the likelihood of adverse outcome, such as in-hospital mortality, may vary extremely by subpopulation. While research on diabetes, race, and age being independently associated with in-hospital mortality exists in the CABG literature, information on diabetes/race/age interaction is missing.

Individually, a patient's race and a patient's age have proven to be related to both the diabetes and in-hospital mortality. The older the individual is, the more likely they are to have type 2 DM, with individuals 40-59 having a prevalence of 8.2%, and individuals over 60 years old having a prevalence of 16.9%.[11] Increased age also confers increased risk of in-hospital mortality post-CABG.[17,1,15] The relationship between race and diabetes, and race and in-hospital mortality post-CABG is also fairly well described. Type 2 DM is more prevalent in blacks, and (more broadly) among non- whites, and the incidence of type 2 DM is increasing at faster rates amongst minorities.[14] Even though African-Americans have higher prevalence of risk factors for both CHD and diabetes, they less frequently undergo CABG.[27] When they do receive CABG, evidence from prior studies has highlighted persistently higher rates of in-hospital mortality for non-Hispanic blacks versus all other races after CABG.[28] Results from our study indicate that the relationship between diabetes, race, and age to in-hospital mortality is interconnected, and should be evaluated accordingly.

Our study had several limitations. First, our data lacked information on the socioeconomic status (SES) of the CABG patients. As SES and race are interconnected, SES data are necessary to clarify the relation between race and in-hospital mortality. Secondly, our dichotomization of race into white and non-white individuals may contribute to a biased estimate of risk if a subset of the group had substantially different rates of in-hospital mortality. Thirdly, we were not able to take into consideration treatment type for diabetes or the blood concentrations of hemoglobin A1c. Because treatment type and A1c offer information about both the severity of diabetes and how well it is being controlled, it is possible that using these variables could have provided more discernment in the relationship between severity of diabetes and in-hospital mortality. However, this level of detail may be more appropriate for long-term survival analysis where there are sufficient mortality events by each small subgroup to build effective models.

Despite these limitations our study is novel and important for a number of reasons. We had a relatively large cohort representing a more contemporary population than those described in previous studies of in-hospital mortality. Atlanta area hospitals provide a suitable setting to study race, diabetes, and CHD-related surgery because of the large minority population, and the high prevalence of diabetes and heart disease in the south. The vast majority of previous research on in-hospital mortality post-CABG used multivariable logistic regression without consideration of interaction.

As seen in our study, likelihood of adverse outcome/event can vary extremely by subpopulation. Odds ratios that are averaged across whole population may be effectively meaningless because they fail to accurately describe the relationship between patient characteristics and likelihood of event. While the majority of contemporary medical research uses multivariable logistic regression when evaluating dichotomous outcomes, less than half of studies in several prominent medical journals that reported using multivariable logistic regression even considered interaction terms during analysis.[29]

Our study emphasizes the need for further research on the interaction between risk factors for in-hospital mortality, morbidity, and long-term survival after CABG. The dearth of information on the interactions between risk factors for diabetes, including patient age and race represent an important knowledge gap. Our study findings underscore the need for further research on the intertwined roles of social, environmental, and biological factors that contribute to the persistent racial disparities in health care outcomes.

TABLES

Table 1. Patient Characteristics by Diabetes Status

	No Diabetes n=6,732	Diabetes n=4,269	p-value
Age (SD)	62.7 (11.5)	62.8 (10.4)	0.5
Caucasian Race (%)	5405 (80.3)	3046 (71.4)	<0.001
Female (%)	1774 (26.4)	1417 (33.2)	<0.001
BMI (kg/m^2) (SD)	28.3 (5.5)	30.8 (6.4)	<0.001
Height (cm) (SD)	172.4 (10.2)	171.7 (10.7)	<0.001
Weight (kg) (SD)	84.4 (18.6)	90.8 (20.6)	<0.001
Current Smoker (%)	3963 (58.9)	2216 (51.9)	<0.001

Table 2. Full logistic regression model for the multivariable analysis of the association between in hospital death and variables relating to patient characteristics, clinical profile, and hospital completing CABG procedure (n=11,001)

Patient Characteristics		Adjusted OR (95% CI)
Diabetes	No	1
	Yes	**5.26 (1.47-18.77)**
Sex	Male	1
	Female	1.35 (0.88-2.05)
Race	Non-White	1
	White	0.98 (0.58-1.67)
Age	<55	1
	55-69	**3.22(1.25-8.32)**
	70+	**3.07 (1.93-4.88)**
BMI (kg/m^2)	<30	1
	>30	0.66 (0.40-1.10)
Smoker	Not Current	1
	Current	0.97 (0.65-1.46)
Diabetes*Age	<55	1
	55-69	**0.26 (0.08-0.86)**
	70+	**0.49 (0.28-0.88)**
Diabetes*Sex	Male	1
	Female	0.76 (0.39-1.49)
Diabetes*Race	Non-White	1
	White	**0.46 (0.22-0.96)**
Diabetes*Smoker	Not Current	1
	Current	0.90 (0.47-1.72)
Diabetes*BMI	≤30	1
	>30	**2.07 (1.01-4.24)**

Table 3. Multivariable Analysis of the association between in-hospital death and various patient characteristics for individuals under 55 years of age; data stratified by race

		White Adjusted OR (95% CI)	Non-White Adjusted OR (95% CI)
Diabetes	No	1	1
	Yes	1.42 (0.25-8.01)	**14.10 (1.77-112.28)**
Sex	Male	1	1
	Female	0.79 (0.09-6.83)	1.45 (0.42-4.99)
BMI	≤30	1	1
	>30	0.20 (0.02-1.80)	1.54 (0.43-5.5)
Smoker	Not Current	1	1
	Current	2.26 (0.26-19.69)	0.99 (0.29-3.37)

Table 4. Multivariable Analyses of the association between in-hospital death and various patient characteristics for 55 to 69-year olds and for those 70 years of age and older

		Ages 55-69 Adjusted OR (95% CI)	Ages 70+ Adjusted OR (95% CI)
Diabetes	No	1	1
	Yes	0.86 (0.49-1.51)	0.89 (0.57-1.38)
Sex	Male	1	1
	Female	1.10 (0.61-2.0)	1.30 (0.85-1.99)
BMI	≤30	1	1
	>30	1.56 (0.90-2.70)	0.67 (0.40-1.14)
Race	Non-White	1	1
	White	**0.44 (0.25-0.77)**	1.20 (0.68-2.11)
Smoker	Not Current	1	1
	Current	0.88 (0.51- 1.52)	0.95 (0.62- 1.44)

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