Diabetes mellitus adversely affects cardiovascular outcomes in patients with coronary artery disease (CAD). Patients with diabetes mellitus undergoing percutaneous coronary interventions (PCIs) are at higher risk of developing major adverse cardiovascular events than nondiabetics.1,2 Poor glycemic control or higher hemoglobin A1c (HbA1c) is also associated with severity and progression of CAD.3 Elevated HbA1c levels in nondiabetic patients presenting with ST-segment–elevation myocardial infarction (STEMI) have been associated with adverse outcomes,4 and an increase in HbA1c after PCI among nondiabetics has been associated with an increase in restenosis rate.5 Although acute procedural hyperglycemia has been associated with worse outcomes in those undergoing PCI,6 the association of HbA1c and outcomes after PCI is unclear. Previous studies looking at the association of HbA1c and major adverse cardiovascular event among patients with diabetes mellitus undergoing PCI have provided conflicting results.7,8 With this background, we conducted a study to assess the association of preprocedural baseline HbA1c with long-term mortality among patients with diabetes mellitus undergoing PCI.

Methods

Patient Population

A total of 18,372 patients underwent PCI at our institution between January 1, 1998, and January 1, 2009. We retrospectively identified...
WHAT IS KNOWN

- Patients with diabetes mellitus undergoing percutaneous coronary interventions are at higher risk of developing major adverse cardiovascular events than those without diabetes mellitus.
- Acute preprocedural hyperglycemia has been associated with worse outcomes among patients undergoing percutaneous coronary interventions.

WHAT THE STUDY ADDS

- Higher baseline hemoglobin A1c at the time of percutaneous coronary interventions is associated with higher mortality among patients with diabetes mellitus.
- The association of higher baseline hemoglobin A1c with long-term mortality is most significant among noninsulin users.
- Insulin users have higher mortality as compared with noninsulin users, despite good glycemic control (ie, baseline hemoglobin A1c ≤7%).

6113 patients with self-reported diabetes mellitus (diet controlled, on oral hypoglycemic agents, and on insulin therapy) who underwent PCI. Of these, 3008 patients had HbA1c data available (within 3 months of index date of PCI) and were included in our study. A thorough electronic chart review was performed in this group to obtain baseline demographic and cardiovascular risk factors. Patients with stable and unstable coronary syndromes including patients with STEMI were included in the analysis.

Study Oversight

The authors designed this study; the data were assembled and analyzed by the authors who vouch for its accuracy. The study population was obtained from the prospective interventional database at our institution. The Cleveland Clinic Institutional Review Board approved the study and waived the requirement for informed consent. Baseline characteristics, pertinent history, risk factors, angiographic and periprocedural data were prospectively obtained and recorded in the registry by experienced research coordinators. An electronic chart review was performed using unique patient identifiers to extract additional information such as laboratory values and medication lists.

Statistical Analysis

All statistical analyses were performed using Stata 13.0 (Stata Corporation, College Station, TX). Continuous variables are presented as means±SD, and categorical variables are presented as proportions. Comparisons between study groups were drawn using the Student t test for continuous variables and χ² test for categorical variables. All statistical tests were 2-tailed and a P value of <0.05 was considered statistically significant.

Patients were divided into 5 categories according to their HbA1c levels (≤7, 7.1%–8.0%, 8.1%–9.0%, 9.1%–10.0%, and >10.0%). Baseline characteristics were compared between 5 categories using ANOVA for continuous variables and χ² test for categorical variables, with statistical significance for P value of <0.05. The primary end point was death at the time of PCI. Procedural characteristics included in the model were presentation with acute coronary syndrome (STEMI, non–STEMI), stable angina, heart rate, and systolic blood pressure at the time of PCI. Procedural characteristics included in the model were presence of multivessel disease, multivessel PCI, use of drug-eluting stent, severity of calcification, presence of chronic total occlusion, and procedural failure (described as the presence of >50% stenosis after PCI or postprocedural thrombolysis in myocardial infarction flow grade <3).

We performed stratified analysis for patients who were on insulin at the time of PCI as compared with those who were not on insulin therapy. To study the impact of glycemic control in the insulin and noninsulin groups, we subdivided these groups (insulin and noninsulin users) into the 5 prespecified HbA1c categories levels (≤7%, 7.1%–8.0%, 8.1%–9.0%, 9.1%–10.0%, and >10.0%). Long-term mortality was compared between these groups using multivariable Cox proportional hazards modeling using the same statistical approach outlined above.

Results

Baseline Characteristics

A total of 3008 patients with diabetes mellitus who underwent PCI were included in this study. Almost 44% patients had HbA1c ≤7%, 26% patients had HbA1c 7.1% to 8.0%, 13% had HbA1c 8.1% to 9.0%, 8% had HbA1c 9.1% to 10.0%, and 9% had HbA1c >10.0%. Those with lower HbA1c were older and had significantly higher incidence of chronic diseases such as chronic obstructive pulmonary disease, hypertension, and chronic renal failure (Table 1). Those with higher HbA1c had more severe presentation in terms of acute coronary syndrome, had higher total cholesterol, and low-density lipoprotein cholesterol, higher periprocedural heart rate, and lower systolic blood pressure. Most procedural characteristics were similar across the groups (Table 1). Although multivessel CAD was more common in those with high HbA1c (>10%), the use of multivessel PCI and use of drug-eluting stents were not significantly different across groups (Table 1).

Long-Term Mortality

After a mean follow-up of 5.4±3.0 years, 1104 patients died with an overall mortality rate of 36.7% in the study cohort. Age- and sex-adjusted analyses (Figure 1, top) showed higher hazard of death among those with baseline HbA1c of ≥10% (hazard ratio, 1.32; 95% confidence interval, 1.04–1.67; P=0.02). All adjusted long-term mortality analyses showed that those with highest HbA1c (>10%) had a 52% (95% confidence interval, 17%–99%) higher risk of long-term mortality (P=0.002) compared with the lowest HbA1c category (Figure 1, bottom). Figure 2 shows the adjusted cumulative hazard of death stratified by the HbA1c category. Independent predictors of long-term mortality were identified and besides the HbA1c category, they include age, race, acute coronary syndrome, heart rate on presentation, systolic blood pressure on presentation, history of cerebrovascular accidents, chronic obstructive pulmonary disease, renal failure, hypertension, peripheral vascular occlusive
disease, family history of CAD, left main trunk disease, calcification, use of drug-eluting stent, and final thrombolysis in myocardial infarction flow <3 (Figure 3). HbA1c was associated with mortality as a continuous variable (hazard ratio [95% confidence interval], 1.08 [1.04–1.12]; P<0.001), with a 7.9% increase in mortality per unit (% increment in HbA1c levels.

**Insulin and Noninsulin Users**

Compared with noninsulin users, those on insulin were younger, more frequently women, and had more prevalence of comorbid conditions such as chronic obstructive pulmonary disease, peripheral vascular disease, and renal failure (Table 2). The incidence of STEMI presentation, multivessel PCI, and the use of drug-eluting stents did not differ significantly between insulin and noninsulin users (Table 2). On adjusting for all variables, there was stepwise increment in mortality with higher levels of HbA1c among noninsulin users (Figure 4A). As compared with the reference group with baseline HbA1c of ≤7%, those with HbA1c >10.0% had a significantly higher risk of mortality (hazard ratio, 1.73; 95% confidence interval, 1.12–2.69; P=0.01) among noninsulin users. Among insulin users, however, there was no significant difference in mortality between the various HbA1c categories (Figure 4B). A nonsignificant U-shaped relationship was observed between HbA1c categories and long-term mortality among insulin users (Figure 4B). Furthermore, those patients who were on insulin had higher mortality as compared with patients not on insulin, even among the group with lower HbA1c (≤7%) as outlined in Figure 5.

**Discussion**

At a mean follow-up duration of 5.4 years, we observed a mortality rate of 36.7% among patients with diabetes mellitus undergoing PCI. We observed a significant association between increment in HbA1c and long-term mortality among patients undergoing PCI. In addition, there was a significantly higher mortality noted among patients using insulin as compared with those using oral agents for control of diabetes mellitus. Although HbA1c did not seem to have an effect on mortality in the cohort of insulin users, we observed a stepwise increase in long-term mortality among patients using oral hypoglycemic agents for diabetes mellitus control.

The relationship of level of HbA1c and mortality represents a complex interplay of several factors. It has been suggested previously that adverse outcomes may be associated with worse glycemic control or higher HbA1c in patients with diabetes mellitus. In a large population-based study, Currie et al demonstrated a U-shaped relationship between HbA1c and all-cause long-term mortality with a 79% increase in mortality in those with HbA1c in the highest quartile (median, 10.5; interquartile range, 10.1%–11.2%). Although the baseline mortality was different as compared with our study, they found similar trend of increasing hazard of death at high HbA1c of >10% as compared with those with HbA1c 7.5% to 7.6%. Diabetes mellitus is a complex disease affecting various organ systems involving micro- and macrovascular complications. Those with higher HbA1c may have more difficult to treat diabetes mellitus or longer duration of illness. Patients with higher HbA1c may have lower compliance with diabetic as well as other cardiac medications and nonpharmacological interventions including lifestyle modifications accounting for higher risk of mortality. Furthermore, there is evidence that atherosclerosis can be more aggressive with higher HbA1c as evidenced in a study by Berry et al, showing correlation between HbA1c and maximum percentage atheroma area at baseline and with change in plaque area using intravascular ultrasound. In several large clinical trials, tighter glycemic control has failed to show an improvement in macrovascular complications and death. Thus, it is likely that poor glycemic control is intrinsically linked to other confounders, which are associated with worse outcome. In any event, higher HbA1c levels in patients undergoing PCI should alert physicians and patients of the higher mortality risk.

Previous studies have shown seemingly conflicting data on the relationship between HbA1c and the risk of adverse cardiac outcomes in patients undergoing PCI. In a Japanese study, Ike et al divided patients according to HbA1c levels into those with <6.9% (n=212) and ≥6.9% (n=334). The mean values in both these groups were 6.3±0.4% and 8.2±1.2%, respectively. Incidence of major adverse cardiovascular event at a follow-up of 300 days was significantly lower in the <6.9% group (18.4% versus 26.2%; P<0.05). In another study, Lemesle et al divided patients into those with HbA1c ≤7% (n=429) and those with HbA1c >7% (n=523). The mean HbA1c in these groups were 6.2±0.7% and 9.3±5.2%, respectively. Incidence of major adverse cardiovascular event at 1 year was similar between groups (23.7% versus 20.8% P=0.45). In yet another smaller study, which had a prospective design, Corpus et al studied the relationship between glycemic control on target vessel revascularization after elective PCI. Patients with HbA1c >7% (mean, 8.8±1.6) had higher rate of target vessel revascularization (34% versus 15%; P=0.03) as compared with patients with HbA1c ≤7% (mean, 6.5±0.5). These discordant findings may partially be explained by differences in study methodology, patient selection, and the outcomes studied. Our study had a larger patient sample size (3008) and longer follow-up (up to 5.4±3 years as compared with ≥1 year in most other studies), and we divided the groups differently. In our study, those with highest risk of dying were those who had highest HbA1c, that is, >10%, which is higher than the mean HbA1c in the uncontrolled arm of these studies. Previous studies evaluating outcomes by dividing data near its mean may miss important differences among those at the extremes of this distribution.

We have studied the interaction between insulin therapy and HbA1c and its association with all-cause mortality in our analysis cohort. We observed that insulin users had significantly higher long-term mortality as compared with the noninsulin users, likely representing a higher prevalence of macrovascular complications and presumably a longer duration of diabetes mellitus. We observed that among insulin users, HbA1c failed to predict long-term mortality and this likely represents advanced disease, which may not be modifiable by further reductions in HbA1c. However, HbA1c had a significant impact on those patients with diabetes mellitus, who were not on insulin therapy. This may suggest a greater role of glycemic control among patients with diabetes mellitus, who do not
have advanced disease and likely lack significant macrovascular complications. Our study also demonstrated a high mortality rate (36.7% at mean follow-up of 5.4 years). This reflects on the severity of diabetes mellitus and other comorbidities in this high-risk patient population. These rates are similar to the high mortality rates seen in the analysis of National Cardiovascular Data Registry (NCDR) data among older patients with diabetes mellitus undergoing PCI. 

Follow-up data on control of known risk factors such as...
hypertension, hyperlipidemia, and recurrent cardiovascular disease were not evaluated in our study and may have contributed to such high mortality. The recently published

Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial showed that in patients with diabetes mellitus and advanced CAD, coronary artery bypass grafting provides lower rates of death and myocardial infarction as compared with PCI.16 A substantial proportion of patients included in our study had multivessel disease and underwent multivessel PCI (26% and 24% in insulin

Figure 1. Adjusted all-cause mortality. Top, Age- and sex-adjusted all-cause mortality stratified according to the hemoglobin A1c (HbA1c) level. Bottom, Respective estimates after multivariable adjustment using stepwise regression in a Cox proportional hazard model. All baseline demographic and clinical characteristics were entered into the model with a retention P value of 0.20. Besides the HbA1c category, the variables included in the final model were age, race, acute coronary syndrome, heart rate on presentation, systolic blood pressure on presentation, history of cerebrovascular accident, chronic obstructive pulmonary disease, renal failure, peripheral vascular occlusive disease, hypertension, family history of coronary artery disease, left main trunk disease, calcification, use of drug-eluting stent, and final thrombolysis in myocardial infarction flow <3. CI indicates confidence interval; and HR, hazard ratio.

Figure 2. Time to event curves depicting adjusted cumulative hazard of death according to hemoglobin A1c (HbA1c) category. The table below the graph depicts the number of patients in each category who were at risk of dying at each time interval (in days).

Figure 3. The figure demonstrates independent predictors of all-cause mortality derived from the multivariable Cox proportional hazard modeling, using backward stepwise elimination at a retention P value of 0.20. BP indicates blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DES, drug-eluting stent; HbA1c, hemoglobin A1c; HR, hazard ratio; LMT, left main trunk; PVD, peripheral vascular disease; and TIMI, thrombolysis in myocardial infarction.
and noninsulin groups). The choice of revascularization strategy may have contributed to the higher mortality rates observed in our study.

Ideal HbA1c in patients with diabetes mellitus has been a moving target, and most recent guidelines recommend individualizing target HbA1c in patients according to several important demographic, social, and comorbid risk factors. However, strict control (target HbA1c <6.5%) has been recommended by guidelines for patients with short disease duration, long life expectancy, and no significant cardiovascular disease, mainly to reduce microvascular complications. A less stringent goal (ie, HbA1c 7.5%–8.0% or even slightly higher) has been deemed appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, and extensive comorbid conditions. In a recently published study, authors showed that higher HbA1c was associated with better outcomes in patients with advanced heart failure. This finding raises concern on what is the optimal glycemic control in patients with diabetes mellitus and other cardiovascular disease such as those undergoing PCI.

In contrast to previous studies, our study showed an increased mortality in those with higher HbA1c at baseline among patients undergoing PCI.

Our study has several important strengths and limitations. Important limitations include an observational, single-center study design that is prone to bias and unintentional confounding. Important predictors that are known to be associated with worse outcomes in patients with diabetes mellitus, such as the duration of disease and use of other oral agents, could not be reliably extracted from the data set and likely resulted in confounding, especially among the insulin treated group. We selected mortality as the main outcome of our study, and although it is a reliable and valid outcome, it does not provide a mechanism of adverse outcomes. It is possible that death could be noncardiac from other comorbidities for which we could not adjust. However, we performed extensive chart reviews and even looked at malignancy at baseline as a potential cause of noncardiac death among these patients and found no significant differences among groups. The main strength of this study is the large number of patients with detailed clinical information, which provides statistical power to make comparisons among several groups.

**Conclusions**

This study demonstrated a significant association between baseline HbA1c and long-term all-cause mortality among patients with diabetes mellitus undergoing PCI. The incremental

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**Table 2. Baseline Characteristics of Insulin Users and Noninsulin Users Undergoing Percutaneous Coronary Intervention**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insulin Users</th>
<th>Noninsulin Users</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>64.1</td>
<td>65.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>58.7</td>
<td>67.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race, %</td>
<td>66.9</td>
<td>67.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index (mean±SD), kg/m²</td>
<td>32.1</td>
<td>32.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>COPD, %</td>
<td>18.5</td>
<td>14.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PVOD, %</td>
<td>21.6</td>
<td>14.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVA, %</td>
<td>10.4</td>
<td>9.9</td>
<td>0.618</td>
</tr>
<tr>
<td>Family history, %</td>
<td>28.9</td>
<td>28.4</td>
<td>0.783</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15.6</td>
<td>17.1</td>
<td>0.365</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>87.5</td>
<td>86.5</td>
<td>0.450</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>87.8</td>
<td>87.1</td>
<td>0.557</td>
</tr>
<tr>
<td>Renal failure, %</td>
<td>17.5</td>
<td>7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mean±SD), mg/dL</td>
<td>1.6</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit (mean±SD)</td>
<td>41.8</td>
<td>42.2</td>
<td>0.944</td>
</tr>
<tr>
<td>Hemoglobin A1c (mean±SD)</td>
<td>8</td>
<td>7.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin A1c &lt;7 (%)</td>
<td>30.5</td>
<td>52.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (mean±SD), beats per minute</td>
<td>75</td>
<td>73</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systolic BP (mean±SD), mm Hg</td>
<td>136</td>
<td>134</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>STEMI, %</td>
<td>5.4</td>
<td>6</td>
<td>0.107</td>
</tr>
<tr>
<td>Multivessel stent, %</td>
<td>26.6</td>
<td>24.3</td>
<td>0.187</td>
</tr>
<tr>
<td>Use of DES, %</td>
<td>20.7</td>
<td>22.6</td>
<td>0.228</td>
</tr>
<tr>
<td>Severe calcification, %</td>
<td>11.5</td>
<td>9.3</td>
<td>0.055</td>
</tr>
</tbody>
</table>

All continuous data are presented as mean±SD and categorical data are presented as percentages (%). BP indicates blood pressure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident (transient ischemic attack and stroke); DES, drug-eluting stent; PVOD, peripheral vascular occlusive disease; and STEMI, ST-segment–elevation myocardial infarction.

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**Figure 4. Adjusted hazard of death among (A) noninsulin and (B) insulin users stratified by hemoglobin A1c (HbA1c) category. CI indicates confidence interval; and HR, hazard ratio.**
long-term mortality with higher HbA1c was mainly seen among noninsulin users. Although the mortality among insulin users was significantly higher than that among noninsulin users, baseline HbA1c failed to predict long-term mortality among insulin users. These findings should be further explored in future studies to help understand the mechanisms underlying the differences in mortality that were observed among those on insulin therapy.

Disclosures

None.

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Association of Glycemic Control With Mortality in Patients With Diabetes Mellitus Undergoing Percutaneous Coronary Intervention
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