# 研究成果の刊行物・別刷

**Title**

# Preoperative poor glycemic control is associated with worse outcomes after percutaneous coronary intervention compared with coronary artery bypass grafting - Insights from the CREDO-Kyoto Registry –

**Running Title**

Poor glycemic control as a predictor for worse PCI outcomes

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**ABSTRACT**

**AIMS:** Glucose metabolism disorders are associated with poor outcomes after coronary revascularization. HbA1c level is a recommended marker for long-term glycemic control. The aim of the present study was to investigate the impact of preoperative glycemic control on outcomes after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

**METHODS AND RESULTS:** Among the patients undergoing first PCI or CABG who were enrolled in the CREDO-Kyoto Registry, those with multivessel and/or left main coronary disease had preoperative HbA1c level obtained and enrolled into the present study (1975 PCI and 1175 CABG). Median follow-up was 3.5 years. Preoperative HbA1c levels were not different between patients undergoing PCI and CABG (6.4±1.5% vs. 6.4±1.5%, p=0.81). In good control patients (diabetes with preoperative HbA1c level of <7%, n=954), the incidences of propensity-matched all-cause death and composite events (cardiovascular death, stroke, or myocardial infarction) were similar between PCI and CABG (hazard ratio [95% confidence interval]: 1.14 [0.75-1.72], p=0.55 and 0.87 [0.62-1.23], p=0.44, respectively). Outcomes were similar in nondiabetic patients (n=1311). However, in poor control patients (diabetes with HbA1c level of ≥7%, n=885), the incidences of propensity-matched all-cause death and composite events were higher in the PCI compared with CABG (2.56 [1.54-4.26], p<0.01 and 1.75 [1.18-2.59], p<0.01, respectively).

**CONCLUSIONS:** Poor preoperative glycemic control, as measured by an elevated HbA1c level, is associated with poor outcomes after PCI compared with CABG. However, outcomes are similar in good control diabetes or nondiabetic patients. CABG may be a favorable revascularization strategy in patients with multivessel and/or left main disease, who suffer from

poor preoperative glycemic control.

**Key Words:** coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting (CABG), follow-up study, diabetes.

## INTRODUCTION

Diabetes mellitus has been recognized as an independent risk factor for poor outcomes following coronary revascularization [1]. Several studies have compared the outcomes between diabetic and nondiabetic patients after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [2-5]. However, outcomes may be different between patients with good and poor control diabetes. Namely, the influence of preoperative glycemic control on outcomes has not been well elucidated. Furthermore, there are few multicenter studies that investigated the impact of preprocedural glycemic control on outcomes of each treatment modality (PCI or CABG).

Hemoglobin A1c (HbA1c), known as glycosilated hemoglobin, indicates a patient's blood glucose control during the previous 3 to 4 months. The American Diabetes Association recommended that patients with diabetes achieve HbA1c level less than 7%, which is associated with a lower risk of diabetes-associated complications [6]. Thus, HbA1c level rather than the diagnosis of diabetes may be a good indicator for preoperative glycemic control.

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) is a multicenter registry in Japan enrolling consecutive 9877 patients undergoing first PCI or CABG [7]. In the present study, we sought to investigate the impact of preoperative glycemic control on outcomes after coronary revascularization by dividing the patients into following 3 groups using the preoperative HbA1c level; 1) Nondiabetes, 2) Good control diabetes (diabetes with HbA1c level of <7%), and 3) Poor control diabetes (diabetes with HbA1c level of ≥7%.

## PATIENTS AND METHODS

### *Study Population*

This study was approved by the institutional review boards or ethics committees of all participating institutions. Because the study subjects were retrospectively enrolled, written informed consent was not obtained, in concordance with the guidelines for epidemiologic studies issued by the Ministry of Health, Labor and Welfare of Japan. However, 73 patients were excluded because of their refusal to participate in the study when contacted for follow-up [7].

Between January 2000 and December 2002, 9877 patients were identified to have undergone either CABG or PCI without prior history of coronary revascularization. Among them, patients with multivessel and/or left main coronary artery disease whose preprocedural blood HbA1c level obtained were included in the present study. Patients undergoing concomitant valvular, left ventricular or major vascular operation were excluded from the current analysis.

### *Data Collection and Definitions*

Demographic, angiographic, and procedural data were collected from hospital charts or databases in each center by independent clinical research coordinators according to prespecified definitions. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians.

Elevated HbA1c was defined as that of 7% or greater, which is associated with a higher risk of diabetes-associated complications [6]. Elderly patients were defined as those patients 75 ≥ years of age. Left ventricular ejection fraction (LVEF) was measured either by contrast left ventriculography or echocardiography. Patients with LVEF of less than 40% were regarded as having left ventricular dysfunction. Chronic kidney disease was regarded as present when creatinine clearance estimated by Cockcloft-Gould formula was less than 60 mL/min. Anemia was defined as blood hemoglobin level less than 12 g/dL as previously described [7].

***Study groups***

Patients were divided into three groups according to their degree of glycemic control using preoperative HbA1c level: 1) poor control group (diabetic patients with HbA1c level of ≥7%), 2) good controlled group (diabetic patients with HbA1c level of <7%), 3) normal group (nondiabetic patients with HbA1c level of <7%). Subsequently, outcomes after PCI or CABG in each group were compared.

***Endpoints***

An independent clinical events committee adjudicated events. Death was regarded as cardiovascular in origin unless obvious noncardiovascular causes could be identified. (Any death during the index hospitalization was regarded as cardiovascular death.) Myocardial infarction was adjudicated according to the definition in the Arterial Revascularization Therapy Study [8]. Within 1 week of the index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. Stroke at follow-up was defined as symptomatic stroke.

Primary endpoint was death from any cause. Secondary endpoints were cardiovascular death, stroke, myocardial infarction, and composite cardiovascular event (cardiovascular death, stroke, and myocardial infarction), during the follow-up period.

### *Statistical Analyses*

After the descriptive statistical analysis, we used Kaplan-Meier estimates to plot survival curves in each group. The log-rank test was used to identify significant differences in unadjusted survival curves. The multivariable Cox proportional hazard models were used for adjustment for confounding factors; we included in the model the following risk factors for mortality confirmed previously [7]: age $\geq$ 75 years, chronic kidney disease, hemodialysis, history of heart failure, chronic obstructive lung disease, malignancy, anemia, peripheral vascular disease, stroke, left ventricular dysfunction, body mass index $\geq$ 25.0, diabetes with insulin, absence of statin use, and use of angiotensin converting enzyme inhibitors. Multivariate-adjusted hazard ratios and 95% confidence intervals are reported in this analysis. All analyses were conducted by a statistician with the use of SAS software version 9.2 (SAS Institute Inc) and S-Plus version 7.0 (Insightful Corp) and all reported p values were 2-sided. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

## RESULTS

### *Baseline Characteristics*

Among the 3150 patients with multivessel and/or left main disease, 1975 patients (63%) in the PCI and 1175 (37%) in the CABG group obtained preoperative HbA1c level. Baseline characteristics of the patients in the two groups are shown in Table 1. The PCI group included more elderly patients (≥ 75 years). The CABG group generally included more high-risk patients, such as those with left ventricular dysfunction, heart failure, prior myocardial infarction, chronic kidney disease, stroke, and anemia. Patient with diabetes, diabetes with any therapy, or diabetes with insulin therapy was more common in the CABG group. Preoperative HbA1c level and a ratio of patients with HbA1c of 7% or greater were not different between the groups (6.4 ± 1.5 vs. 6.4 ± 1.5, p=0.81 and 28% vs. 27%, p=0.56, respectively).

Regarding the complexity of coronary artery anatomy, the CABG group included more complex patients, such as those with triple-vessel disease, left main disease, involvement of proximal LAD, and total occlusion. In the PCI group, bare-metal stents were used in 83% of patients. None of the patients received drug-eluting stents. In the CABG group, internal mammary artery graft was used in 93% of patients. Thirty-four percent of CABG operations were performed without cardiopulmonary bypass.

Medications such as statins, thienopyridines, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and nitrates were more frequently used in the PCI group than the CABG group.

***Overall outcomes***

Clinical follow-up were completed in 99% at 1 year, and 95% at 2 years in the PCI group and 97% and 94% in the CABG group. The median follow-up period was 1291 days in the PCI group (interquartile range, 957 to 1583) and 1245 days in the CABG group (interquartile range, 930 to 1563).

In Kaplan-Meier analysis, freedom from all-cause death at 1, 3, and 5 years were 95.4%, 89.7%, and 86.7% in the PCI, and 95.2%, 91.5%, and 87.5% in the CABG group, respectively (Figure 1A). There were no significant differences in the incidence of the all-cause death between the groups ($p=0.19$). Similarly, there were no differences in the incidence of composite cardiovascular event between the PCI and the CABG groups ($p=0.89$, Figure 1B).

***Influence of preoperative glycemic control on outcomes after PCI and CABG***

Diabetic profiles of the three groups are summarized in Table 2. Preoperative HbA1c level was similar between PCI and CABG in each group ($p=0.15$, $p=0.67$, and $p=0.77$, respectively). Baseline characteristics of the three groups are shown in supplemental files. Patients' characteristics in each group were generally similar to those of whole population.

**Kaplan-Meier analysis:** In the poor control group, freedom from all-cause death at 1, 3, and 5 years, were 93.9%, 87.1%, and 82.6% in the PCI, whereas 95.9%, 93.5%, and 91.2% in the CABG group, respectively (Figure 2A). The incidence of all-cause death was lower in the CABG group ($p<0.01$). The incidence of composite events in the CABG group tended to be lower than the PCI group ($p=0.06$, Figure 2B). In the good control group, however, freedom from all-cause death and the incidence of composite event were not different between the PCI and CABG groups ($p>0.99$ and $p=0.32$, Figure 2A and B). In the normal group, freedom from all-cause death and the incidence of composite event were not different between the groups ($p>0.99$ and $p=0.96$, Figure 3A and B).

**Propensity-matched analysis:** Propensity-matched all-cause mortality after PCI was higher than CABG in the poor control group (Hazard ratio [95%CI]: 2.56 [1.54-4.26], $p<0.01$) (Table 3). On the contrary, all-cause mortality was similar between PCI and CABG in the good control and the normal group (1.14 [0.75-1.72], $p=0.55$ and 0.93 [0.59-1.46], $p=0.75$, respectively).

Significant interaction p-value (0.04) indicates the survival benefit of CABG is prominent particularly in patients with poor glycemic control. Propensity-matched cardiovascular mortality after PCI was also higher than CABG in the poor control group (3.11 [1.66-5.83], $p<0.01$). However, the all-cause and cardiovascular mortalities were similar between PCI and CABG in the good control or nondiabetic groups.

The incidence of stroke after PCI was lower than CABG, regardless of the degree of glycemic control. Insignificant interaction p-value (0.99) indicates treatment modality (PCI or CABG) rather than the degree of glycemic control influences the postoperative stroke rate. The incidence of myocardial infarction after PCI was higher than CABG in the poor control group (3.29 [1.54-7.01], $p<0.01$), but similar in the good control or nondiabetic group. Insignificant p-value (0.50) indicates that treatment modality (PCI or CABG) rather than the degree of glycemic control influences the incidence of myocardial infarction. The incidence of composite cardiovascular event after PCI was higher than CABG in the poor control group (1.75 [1.18-2.59], $p<0.01$), but similar in the good control and normal groups.

## DISCUSSION

### *Main findings*

To our knowledge, this is the first multicenter registry that investigated the influence of the preoperative glycemic control using HbA1c level on long-term outcomes after PCI and CABG in patients with multivessel and/or left main disease. In patients with poor glycemic control, propensity-matched multivariate analysis showed that CABG reduced the all-cause and cardiovascular mortality compared with PCI. On the contrary, in patients with good glycemic control or nondiabetes, there were no significant differences in those endpoints between PCI and CABG. The incidence of myocardial infarction was lower after CABG than PCI; however, that of stroke was lower after PCI regardless of the degree of preoperative glycemic control. It is noteworthy that in patients with poor glycemic control, treatment with CABG was associated with better outcomes than PCI although the patients undergoing CABG included more high-risk patients and less postoperative medication than those of PCI. These results indicate that CABG may be a favorable revascularization strategy in diabetic patients suffering from poor preoperative glycemic control, and that preoperative strict glycemic control is recommended in diabetic patients undergoing PCI.

***Diabetes and CABG outcomes***

Depending on the severity of diabetes and its associated disorders and comorbidities, long-term survival is lower in diabetic as compared with nondiabetic patients [9]. Aggressive treatment to achieve glycemic control is associated with reduced mortality in patients with diabetes undergoing CABG [10]. Thus, long-term glycemic control may improve outcomes after CABG. HbA1c is not affected by short-term glycemic control, and therefore allows better assessment of glucose control over 3 to 4 months. Halkos and associates reported that poor glycemic control, as assessed by elevated HbA1c level, was strongly associated with adverse events after CABG both in-hospital and long-term follow-up [11]. They demonstrated that higher HbA1c (measured as continuous value) was associated with reduced long-term survival for each unit increase with hazard ratio of 1.15/unit. They also conclude that preoperative HbA1c level rather than diagnosis of diabetes is a better predictor for long-term survival after CABG.

***Diabetes and PCI outcomes***

Chronic hyperglycemia, as assessed by HbA1c level, is associated with an increased risk of cardiovascular disease in patients with diabetes [12]. Preprocedural high blood glucose level is associated with adverse outcomes after PCI for acute myocardial infarction [13]. However, the influence of preprocedurel elevated HbA1c level on long-term outcomes has been controversial. Mazeika and associates demonstrated that high HbA1c increased the angiographic restenosis in patients with diabetes [14]. However, several studies have reported that HbA1c level is not a predictor for cardiac events in patients with diabetes [15, 16]. That may be due to the difference in rates of drug-eluting stent use in each study. In addition, these results could partially explain the recent findings of randomized clinical trials that suggest a benefit of intensive glucose control (target 6.5%) in microvascular complications but not in macrovascular complications and death from any cause [17].

***Optimal revascularization in patients with diabetes mellitus***

Optimal revascularization strategy in patients with diabetes still has been controversial. Several observational studies reported the superiority of CABG in patients with diabetes mellitus with multivessel coronary artery disease [18, 19]. The present study also indicates CABG may be a better option in patients with multivessel or left main disease with uncontrolled diabetes. However, to conclude the superiority of CABG, there are several points to be addressed.

First, the present study was conducted in bare-metal stent era. Contemporary PCI procedures have already shifted from bare-metal to drug-eluting stenting with variable penetration rates. The striking efficacy of drug-eluting stents in preventing both clinical and angiographic restenosis has led to a rapid expansion of PCI use particularly for patients with complex multivessel disease [20]; however, improvement of survival has not yet been reported patients with diabetes with use of drug-eluting stents [21]. In the ARTS-2 study, survival rates at

3 years were not significantly different among the 3 groups of ARTS-2, ARTS-1 CABG, and ARTS-1PCI, initial advantage with sirolimus-eluting stent appeared to diminish at 3 years follow-up [22]. Furthermore, the pooled analysis of the pivotal randomized trials of the sirolimus-eluting stents suggested excessive mortality in diabetic patients treated with the sirolimus-eluting stents as compared with those treated with bare-metal stents [23]. Thus, CABG may also be a better option in patients with diabetes in drug-eluting stent era, as shown in the bare-metal stent.

Second, the present study included patients with left main disease. Most of the comparative studies between the outcomes of PCI and CABG excluded left main disease because it has generally been recommended to CABG. Recently, however, SYNTAX study demonstrated that PCI achieved equivalent survival and event-free outcomes to CABG in patients with low or intermediate SYNTAX score although CABG was better in patients with high SYNTAX score [24]. In addition, rate of patients with left main disease in CABG (28%) was far higher than that of PCI (4%) in the present study (Table 1). Furthermore, including left main disease would reflect the "real-world" patients undergoing coronary revascularization. Thus we consider that including left main disease in the present study did not weaken the conclusions.

Finally, the present study is an observational study. The discrepancy in outcomes between randomized controlled trials and registries comparing PCI with CABG is commonly ascribed to usual enrollment in the former of very selected low-risk patients with multi vessel coronary artery disease who are suitable for PCI, a feature that limits the ability to generalize conclusions to many high-risk patient categories in real-world clinical practice. On the other hand, observational study may expand the indications of PCI to more complex subsets of patients who were not indicated to CABG. In the present study, however, the CABG group included more complex patients than PCI such as left ventricular dysfunction and chronic kidney disease. Thus, we believe CABG can be a better option in treating preoperative poor glycemic control than PCI.

***Study limitations***

There are several important limitations of this study. First, we evaluated the preprocedural HbA1c level, but did not confirm the postoperative blood glucose management. Although we decided principles of the management in each institution, there might be any differences between the institutions. Furthermore, important medications, statins in particular, to prevent cardiovascular events are obviously underused. More optimal use of medications might have changed the long-term outcome of both PCI and CABG.

***Conclusions***

Poor preoperative glycemic control, as measured by an elevated HbA1c level, is associated with poor outcomes after PCI compared with CABG. CABG may be a favorable revascularization strategy in patients with multivessel coronary or left main disease, who suffer from poor preoperative glycemic control. Further study with drug-eluting stent is warranted.


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## Disclosures

None

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## FIGURE LEGENDS

**Figure 1. Kaplan-Meier curves for each endpoint among all patients**

A: All-cause death

B: Composite cardiovascular event

**Figure 2. Kaplan-Meier curves for each endpoint among patients with preoperative poor glycemic control (diabetes with HbA1c ≥7%)**

A: All-cause death

B: Composite cardiovascular event

**Figure 3. Kaplan-Meier curves for each endpoint among patients with preoperative good glycemic control (diabetes with HbA1c <7%)**

A: All-cause death

B: Composite cardiovascular event

**Figure 4. Kaplan-Meier curves for each endpoint among nondiabetic patients**

A: All-cause death

B: Composite cardiovascular event

*CV: cardiovascular*

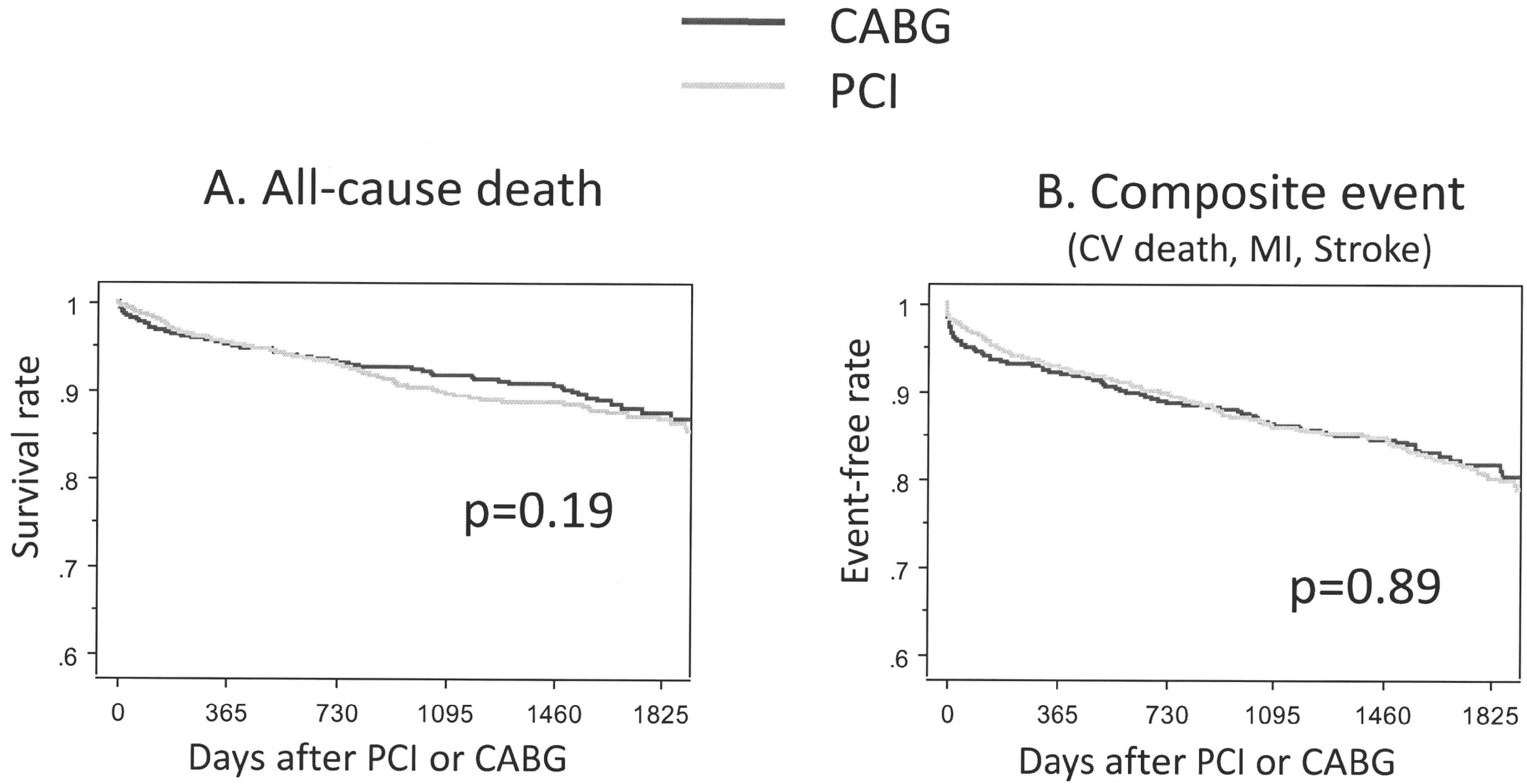
*MI: myocardial infarction*

**Table 1. Baseline characteristics**

| | PCI (n=1975) | CABG (n=1175) | p value |
|---|---|---|---|
| Age | 67.6 ± 9.9 | 66.9 ± 9.0 | 0.08 |
| ≥75 years | 26% | 21% | <0.01 |
| Male gender | 69% | 72% | 0.02 |
| Body mass index | 23.9 ± 3.4 | 23.5 ± 3.2 | <0.01 |
| ≥25% | 33% | 30% | 0.06 |
| No. of diseased vessels | 2.4 ± 0.5 | 2.6 ± 0.7 | <0.01 |
| Triple vessel disease | 38% | 70% | <0.01 |
| Left main disease | 4% | 28% | <0.01 |
| Proximal LAD disease | 41% | 61% | <0.01 |
| Total occlusion | 29% | 57% | <0.01 |
| Ejection fraction | 61.3 ± 13.6 | 59.1 ± 14.8 | <0.01 |
| <40% | 8% | 12% | <0.01 |
| Prior myocardial infarction | 30% | 37% | <0.01 |
| Heart failure | 16% | 28% | <0.01 |
| Atrial fibrillation | 6% | 6% | 0.43 |
| History of stroke | 14% | 22% | <0.01 |
| Peripheral vascular disease | 9% | 22% | <0.01 |
| Chronic pulmonary disease | 2% | 2% | 0.18 |
| Emergency procedure | 4% | 4% | 0.5 |
| Diabetes mellitus | 57% | 61% | 0.02 |
| Diabetes with any therapy | 38% | 45% | 0.01 |
| Diabetes with insulin therapy | 12% | 17% | <0.01 |
| Hemoglobin A1c (%) | 6.4 ± 1.5 | 6.4 ± 1.5 | 0.81 |
| ≥ 7.0% | 28% | 27% | 0.56 |
| Hypertension | 72% | 70% | 0.33 |
| Hyperlipidemia | 52% | 54% | 0.56 |
| Hemodialysis | 4% | 5% | 0.17 |
| Chronic kidney disease | 40% | 45% | <0.01 |
| Malignancy | 8% | 6% | 0.11 |
| Hemoglobin | 13.1 ± 2.0 | 12.7 ± 2.0 | <0.01 |
| < 12 mg/dl | 25% | 33% | <0.01 |
| Current smoker | 29% | 25% | <0.01 |
| Medication at discharge | | | |
| Statins | 37% | 18% | <0.01 |
| Aspirin | 86% | 87% | 0.02 |
| Thienopyridines | 74% | 10% | <0.01 |
| ACE inhibitor | 27% | 12% | <0.01 |
| ARB | 18% | 8% | <0.01 |
| β antagonist | 25% | 9% | <0.01 |
| Calcium antagonist | 60% | 55% | <0.01 |
| Nitrates | 711% | 48% | <0.01 |

LAD: left anterior descending artery
ACE: angiotensin converting enzyme
ARB: angiotensin receptor blockers

# Figure 1A, 1B (All patients)




No. at Risk (A)

| | 0 | 1yr | 2yrs | 3yrs | 4yrs | 5yrs |
|---|---|---|---|---|---|---|
| PCI | 1975 | 1842 | 1739 | 1299 | 705 | 249 |
| CABG | 1175 | 1089 | 1031 | 721 | 379 | 135 |

No. at Risk (B)

| | 0 | 1yr | 2yrs | 3yrs | 4yrs | 5yrs |
|---|---|---|---|---|---|---|
| PCI | 1975 | 1778 | 1684 | 1205 | 651 | 226 |
| CABG | 1174 | 1043 | 967 | 670 | 349 | 125 |