

Effect of Diabetes on Long-Term Mortality Following Contemporary Percutaneous Coronary Intervention

Analysis of 4,284 cases

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OBJECTIVE — Diabetic patients are known to have reduced long-term survival following percutaneous transluminal coronary angioplasty compared with nondiabetic patients. However, it is unknown whether this survival disadvantage has persisted in the era of contemporary percutaneous coronary intervention (PCI) techniques, which include the widespread use of stents and the availability of platelet glycoprotein (GP) IIb/IIIa inhibitors.

RESEARCH DESIGN AND METHODS — Three hospitals in New York City contributed prospectively defined data on 4,284 patients undergoing PCI. The primary end point was all-cause mortality following hospital discharge for PCI.

RESULTS — Hypertension, renal insufficiency, and renal failure requiring dialysis were all more common in diabetic patients, whereas active smoking was less frequent. Congestive heart failure on admission was more common in diabetic than nondiabetic patients (7.7 vs. 4.0%, $P < 0.001$). Stents were placed in 78% of nondiabetic patients and 75% of diabetic patients ($P = 0.045$). Platelet GP IIb/IIIa antagonists were administered to 23% of nondiabetic and 24% of diabetic patients ($P = NS$). At a mean follow-up of 3 years, mortality was 8% among nondiabetic patients and 13% for diabetic patients ($P < 0.001$). After adjustment for differences in baseline characteristics between nondiabetic and diabetic patients, diabetes remained a significant independent hazard for late mortality (hazard ratio 1.462, 95% CI 1.169–1.828; $P = 0.001$).

CONCLUSIONS — Following contemporary PCI, diabetic patients continue to have worse survival than nondiabetic patients.

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D iabetes is an independent risk factor for the development of coronary artery disease (CAD) (1). When diabetic patients develop clinical manifestations of CAD, their prognosis for survival is worse than that of similar patients without diabetes (2–5). Diabetic patients treated for CAD with percutaneous transluminal coronary angioplasty (PTCA) appear to have a particularly un-

favorable prognosis compared with nondiabetic patients. Subgroup analysis of the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial demonstrated that diabetic patients with multivessel coronary disease treated with PTCA had a 5-year mortality rate of 35% compared with 9% for patients without diabetes (6). Subsequent randomized trials and observational studies have con-

firmed the reduced survival of diabetic patients compared with nondiabetic patients undergoing PTCA (7–10). Since the acquisition of these data, coronary stents have become standard treatment for patients with obstructive coronary disease undergoing percutaneous coronary intervention (PCI). Stents reduce the acute risks related to abrupt vessel closure associated with PTCA (11) as well as the long-term adverse outcomes associated with the development of restenosis (12,13). In addition, inhibitors of the platelet glycoprotein (GP) IIb/IIIa receptor were not available at the time of the BARI. These agents reduce the composite end point of mortality and myocardial infarction (MI) following PCI (14–19), and abciximab, in particular, has been reported (20) to reduce long-term mortality in diabetic patients following PCI. There are little data available to assess the survival of unselected diabetic patients undergoing PCI outside the setting of randomized clinical trials in the stent and GP IIb/IIIa era. The purpose of the current study was thus to determine whether contemporary techniques have eliminated the difference in long-term survival between diabetic and nondiabetic patients undergoing PCI for CAD.

RESEARCH DESIGN AND METHODS

The study population was drawn from a cohort of 4,284 consecutive patients undergoing PCI from 1 January 1998 to 1 October 1999 at three tertiary medical centers in New York City.

Data collection

Patient data were recorded prospectively on standardized forms and entered into a computerized database. The data fields are identical to those of the standardized reports submitted to the New York State Department of Health on every PCI performed in New York state. The defined elements in these reports include information on patient demographics, clinical

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Abbreviations: BARI, Bypass Angioplasty Revascularization Investigation; CAD, coronary artery disease; GP, glycoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

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Table 1—Baseline characteristics according to diabetes status

| | No diabetes | Diabetes | P |
|---------------------------|-------------|-----------|--------|
| Demographics | | | |
| n | 3,142 | 1,142 | — |
| Mean age (years) | 63.4 ± 12 | 63.6 ± 11 | 0.645 |
| Age >75 years | 19 | 18 | 0.333 |
| BMI (kg/m ²) | 28.2 | 29.5 | <0.001 |
| Female | 27 | 43 | <0.001 |
| Non-white | 19 | 32 | <0.001 |
| Clinical History | | | |
| Current smoking | 15 | 8.8 | <0.001 |
| Hypertension | 67 | 78 | <0.001 |
| Cerebrovascular disease | 2.1 | 3.0 | 0.080 |
| Aortoiliac disease | 3.1 | 3.8 | 0.270 |
| Femoral/popliteal disease | 2.9 | 7.0 | <0.001 |
| Creatinine >2.5 mg/dl | 1.2 | 3.9 | 0.002 |
| Dialysis | 0.9 | 3.9 | <0.001 |
| Previous CHF | 4.9 | 8.7 | <0.001 |
| Prior MI | 34 | 36 | 0.363 |
| Prior stroke | 2.3 | 4.0 | 0.002 |
| Prior CABG | 15 | 22 | <0.001 |
| Prior PCI | 26 | 26 | 0.529 |

Data are means ± SD or percent, unless noted otherwise. CABG, coronary artery bypass graft; CHF, coronary heart failure.

characteristics, preintervention risk factors, procedural information, in-hospital outcome, and discharge status.

End points

The primary end point was all-cause mortality following discharge from the hospital for the index PCI as determined from the Social Security Death Index. This index has been shown to be highly specific and unbiased (21,22). Follow-up was for a mean of 3 years for nondiabetic as well as diabetic patients.

PCI

All procedural decisions, including device selection and adjunctive pharmacotherapy, were made at the discretion of the individual physician performing PCI. Stents were deployed at high pressure, and patients were maintained on ticlopidine or clopidogrel for 4 weeks in addition to aspirin following implantation unless contraindicated. Angiographic assessments were made at the individual hospital and generally were obtained by visual assessment. Cardiac enzymes (creatinine kinase and creatine kinase MB isoenzyme or troponin) were obtained by protocol before and at 8 and 24 h following PCI.

Definitions

At the time of the procedure, patients were classified as having diabetes if they were being treated with oral hypoglycemics or insulin or if they had a history of elevated fasting blood glucose (>140 mg/dl) on more than two separate occasions in conjunction with ongoing dietary measures. Ejection fraction was recorded before the cardiac procedure. A coronary vessel was considered diseased when it contained at least one lesion with >50% stenosis. Intravenous GP IIb/IIIa inhibitor treatment was administration of abcix-

imab, eptifibatide, or tirofiban during or within 3 h following PCI. Postprocedural MI was defined as creatine kinase values >2.5 times the upper limit of normal and the development of new Q-waves on the electrocardiogram following PCI.

Statistical analysis

Differences between diabetic and nondiabetic patients were compared using χ^2 statistics for categorical variables and *t* tests for continuous variables. Survival curves were constructed by the Kaplan-Meier method with differences in survival assessed with the log-rank test. Survival curves were constructed using only patients who survived to be discharged from the hospital following their index PCI. Diabetes was related to all-cause mortality using multivariable Cox proportional hazard regression analyses to adjust for differences in baseline characteristics. Potential confounders were entered into models if they were clinically relevant (age, stent use, and GP IIb/IIIa inhibitor treatment) or showed univariable differences between groups with a *P* < 0.10. All analyses were performed with SPSS software. All *P* values are two tailed. A *P* value of <0.05 was considered significant.

RESULTS— Baseline characteristics of nondiabetic and diabetic patients are presented in Table 1. Diabetic and nondiabetic patients were similar in age. Diabetic patients were more often female, had a greater mean BMI, and were less commonly white than nondiabetic patients. Hypertension, femoral/popliteal atherosclerotic disease, renal insufficiency (creatinine >2.5 mg/dl), renal failure requiring dialysis, and prior congestive

Table 2—Clinical presentation according to diabetes status

| | No diabetes | Diabetes | P |
|-------------------------|-------------|----------|--------|
| n | 3,142 | 1,142 | — |
| MI <6 h | 3.9 | 3.8 | 0.786 |
| MI 6–24 h | 6.5 | 5.6 | 0.272 |
| Thrombolysis ≤6 h | 0.6 | 0.7 | 0.818 |
| Thrombolysis >6 h | 3.6 | 2.1 | 0.014 |
| Unstable angina | 42 | 43 | 0.861 |
| CHF on admission | 4.0 | 7.7 | <0.001 |
| Ventricular arrhythmias | 2.0 | 1.7 | 0.433 |
| IABP | 1.2 | 1.9 | 0.063 |
| Shock | 0.3 | 0.1 | 0.233 |
| Unstable hemodynamics | 1.1 | 1.3 | 0.469 |

Data are percent. CHF, coronary heart failure; IABP, intra-aortic balloon pump.

Table 3—Angiographic and procedural characteristics of patients according to diabetes status

| | No diabetes | Diabetes | P |
|-----------------------------------|-------------|-------------|--------|
| n | 3,142 | 1,142 | — |
| One-vessel CAD | 51 | 41 | <0.001 |
| Two-vessel CAD | 29 | 29 | 0.914 |
| Three-vessel CAD | 16 | 24 | <0.001 |
| LAD disease | 68 | 70 | 0.099 |
| LCX disease | 44 | 54 | <0.001 |
| RCA disease | 54 | 61 | <0.001 |
| Ejection fraction (mean \pm SD) | 51 \pm 10 | 50 \pm 10 | 0.002 |
| Heparin prior to PCI | 28 | 31 | 0.110 |
| Nitroglycerin prior to PCI | 13 | 14 | 0.387 |
| Stent | 78 | 75 | 0.045 |
| Atherectomy | 13 | 15 | 0.058 |
| GP IIb/IIIa inhibitor treatment | 23 | 24 | 0.877 |
| Procedural success | 97 | 97 | 0.349 |

Data are percent. LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

heart failure were all more common in diabetic patients. However, a history of stroke was more common in diabetic patients. Prior bypass surgery had been performed more commonly in diabetic patients.

Features of the clinical presentation are summarized in Table 2. The frequency of presentation with acute MI or unstable angina was similar in nondiabetic and diabetic patients, whereas congestive heart failure on admission was more common in diabetic than nondiabetic patients (7.7 vs. 4.0%, $P < 0.001$).

Procedural information is displayed in Table 3. One-vessel CAD was more common in nondiabetic patients (51 vs. 41%, $P < 0.001$), whereas three-vessel CAD was more common among diabetic patients (24 vs. 16%, $P < 0.001$). The mean ejection fraction was 51% in nondiabetic patients and 50% in diabetic patients ($P = 0.002$). Stents were placed slightly less commonly in diabetic patients (75 vs. 78%, $P = 0.045$), whereas

atherectomy was somewhat more common in diabetic patients (15 vs. 13%, $P = 0.058$). Platelet GP IIb/IIIa antagonists were administered with about the same frequency in nondiabetic and diabetic patients. Procedural success was 97% for both groups. Complications of PCI were uncommon and not significantly different between groups. However, in-hospital mortality was greater for diabetic patients (1.0 vs. 0.3%, $P = 0.004$) (Table 4).

During 3 years of follow-up, mortality was 8.0% (252 deaths) for nondiabetic patients and 13% (146 deaths) for diabetic patients who were alive when discharged following PCI (log-rank $P < 0.001$) (Fig. 1). After adjustment for baseline differences between nondiabetic and diabetic patients, diabetes remained independently associated with an increased mortality hazard (hazard ratio [HR] 1.462, 95% CI 1.169–1.828; $P = 0.001$) (Table 5). Stent use and GP IIb/IIIa inhibitor treatment were not associated with a reduction in the hazard for late mortality.

Table 4—In-hospital outcomes following PCI according to diabetes status

| | No diabetes | Diabetes | P |
|--------------------------|-------------|----------|-------|
| n | 3,142 | 1,142 | — |
| Death | 0.3 | 1.0 | 0.004 |
| Emergency bypass surgery | 0.1 | 0.0 | 0.228 |
| Postprocedure MI | 0.2 | 0 | 0.110 |
| Abrupt closure | 0.5 | 0.5 | 0.842 |
| Stent thrombosis | 0.2 | 0.2 | 0.915 |
| Vascular complications | 0.1 | 0.2 | 0.500 |

Data are percent.

CONCLUSIONS— The most important finding of this analytical cohort study was a significantly increased hazard of mortality following contemporary PCI in diabetic patients compared with nondiabetic patients when identifiable confounders were controlled for by multivariate modeling. The ~50% increase in mortality risk among diabetic patients was entirely due to deaths that occurred following discharge from the hospital. Of concern, this survival disadvantage occurred in a population in whom 70% had single- or double-vessel CAD. Furthermore, two of the most important recent advances in interventional cardiology, coronary stents and GP IIb/IIIa inhibitors, did not appear to impact long-term survival. These findings are of considerable public health significance because the prevalence of diabetes is expected to double by the year 2025 (23).

The presence of diabetes has long been associated with higher rates of long-term adverse events for patients undergoing PTCA. High restenosis rates, persistent hemostatic abnormalities, and uninterrupted progression of atherosclerosis potentially contribute to the poor outcomes seen among diabetic patients treated with PTCA.

The risk of restenosis is significantly greater for diabetic than nondiabetic patients following PTCA (8,10,24–30). Among diabetic patients, a unique feature of restenosis is its frequent association with complete occlusion of the previously treated coronary artery (31). In its occlusive form, restenosis in diabetic patients is a major determinant of long-term mortality (31). Compared to PTCA, coronary stent implantation has been demonstrated to reduce restenosis and the subsequent requirement for revascularization for patients with a relatively narrow spectrum of coronary lesions (12,13). Although stents appear to achieve a reduction in restenosis compared to PTCA in diabetic patients (32), even with stents, diabetic patients appear to have increased restenosis when compared with nondiabetic patients (33,34).

Altered hemostasis may also contribute to the increase in adverse outcomes among diabetic patients with CAD. Platelets from diabetic patients demonstrate abnormal aggregation and enhanced shear-induced adhesion (35). These functional abnormalities of the platelet in diabetic patients have been linked to

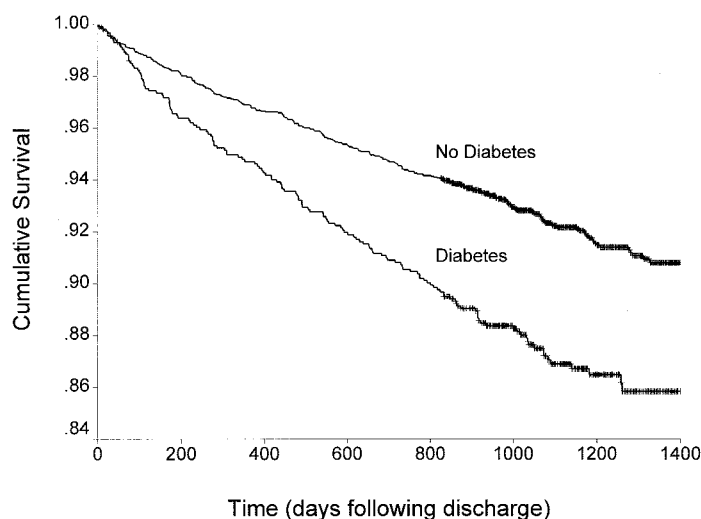


Figure 1—Kaplan-Meier curves for out-of-hospital survival in diabetic and nondiabetic patients following PCI.

increased levels of cell surface adhesion molecules, including the GP IIb/IIIa receptor (36). Thus, inhibitors of the GP IIb/IIIa receptor have been advocated for treatment of diabetic patients undergoing PCI (20). A retrospective analysis (20) of abciximab-treated diabetic patients enrolled in three randomized trials demonstrated reduced 1-year mortality. In contrast, a large single-center study found no effect of abciximab on late mortality following PCI in unselected diabetic patients (37). GP IIb/IIIa inhibitor treatment was not associated with improved survival among diabetic patients in this study (data not shown). However, these agents were used uncommonly, and the possibility remains that the sample size was too small to detect a protective effect.

Diabetic patients appear to have a greater volume of atherosclerotic plaque and an increased propensity for atherosclerotic plaque rupture than nondiabetic patients. The progressive separation of the survival curves in this study supports the concept of ongoing coronary events after PCI. Focal treatments of atherosclerosis, such as those that are achieved by all percutaneous approaches, may leave behind many untreated, potentially vulnerable plaques in diabetic patients. On the other hand, bypass surgery has the potential advantage of providing an alternative conduit to myocardium in the event of rupture of a vulnerable plaque, most of which occur in proximal portions of the coronary arteries. Thus, the choice of revascularization procedures is especially

important in populations with accelerated atherosclerosis and plaque instability, such as diabetic patients. The reduced survival of diabetic patients with predominantly one- and two-vessel CAD in this study raises the question of whether bypass surgery should be considered for diabetic patients with less extensive CAD. Regardless of the revascularization modality, aggressive attempts to control progression of atherosclerosis by addressing not only hyperglycemia, but also smoking cessation and the dyslipidemias, obesity, and hypertension, which frequently accompany diabetes, should be implemented in all diabetic patients with CAD (38).

Limitations

Several limitations should be borne in mind when interpreting the results of the

current study. First, as this was not a randomized trial, unidentifiable confounders may have been responsible for the increased mortality in diabetic patients rather than diabetes itself. Thus, inferences about causation in any observational study must be made with caution. Second, our database does not allow the identification of the specific type of diabetes therapy each patient received. Several studies have suggested that the outcome of insulin-dependent diabetic patients undergoing PCI is worse than that of diabetic patients treated with oral agents or dietary restriction (6,8,33). Third, we measured only mortality as our outcome of interest. As a result, we cannot speculate on the mechanism of the increased mortality observed in diabetic patients. Fourth, our study antedated the availability of drug-eluting stents, which have the potential to improve long-term patency of stents in diabetic patients. Finally, our database does not contain information on other important secondary prevention interventions, such as lipid-lowering and antihypertensive medications, that may impact long-term survival.

Summary

In one of the largest series of diabetic patients to date we found that patients with diabetes and moderate CAD treated with contemporary PCI techniques have significantly reduced survival after 3 years compared with nondiabetic patients. A randomized trial of surgical revascularization versus PCI using drug-eluting stents may be required to determine the optimum treatment for diabetic patients with less extensive CAD than those enrolled in the BARI.

Table 5—Independent predictors of long-term mortality

| Characteristic | HR (95% CI) | P |
|---------------------------|---------------------|--------|
| Age | 1.067 (1.055–1.078) | <0.001 |
| Creatinine >2.5 mg/dl | 3.458 (2.402–4.977) | <0.001 |
| Dialysis | 4.715 (3.138–7.083) | <0.001 |
| Ejection fraction | 0.961 (0.952–0.970) | <0.001 |
| Diabetes | 1.462 (1.169–1.828) | 0.001 |
| History of CHF | 1.607 (1.198–2.154) | 0.002 |
| Intra-aortic balloon pump | 1.896 (1.113–3.230) | 0.019 |
| CHF during admission | 1.427 (1.027–1.981) | 0.034 |
| Cerebrovascular disease | 1.784 (1.138–2.796) | 0.012 |
| Stent | 0.965 (0.762–1.223) | 0.769 |
| GP IIb/IIIa inhibitor | 0.843 (0.657–1.080) | 0.176 |

CHF, coronary heart failure.

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