Title

Impact of diabetes and acute coronary syndrome on survival in patients treated with drug-eluting stents

Journal

Catheterization and Cardiovascular Interventions, 72(7)

ISSN

1522-1946

Authors

Lee, Michael S
Jurewitz, Daniel
Zimmer, Raymond
et al.

Publication Date

2008-12-01

DOI

10.1002/ccd.21795

Catheterization and Cardiovascular Interventions 72:909–914 (2008)

Impact of Diabetes and Acute Coronary Syndrome on Survival in Patients Treated With Drug-Eluting Stents

Michael S. Lee,* MD, Daniel Jurewitz, MD, Raymond Zimmer, MD, Antonio Pessegueiro, MD, Ravi Bhatia, Jesse Currier, MD, Larry Yeatman, MD, and Jonathan M. Tobis, MD

Background: Diabetics who undergo percutaneous coronary intervention (PCI) are at increased risk for death, myocardial infarction, repeat revascularization, and stent thrombosis. Methods: Our retrospective study includes 887 consecutive patients who underwent PCI with drug-eluting stents (DES) at UCLA Medical Center. The cohort was divided into four groups: group 1, no diabetes and no acute coronary syndrome (ACS); group 2, no diabetes and ACS; group 3, diabetes and no ACS; group 4, diabetes and ACS. Results: Survival at 1 year was the lowest in diabetics who presented with ACS (90% in diabetics with ACS, 95% in diabetics without ACS, 95% in non-diabetics with ACS, and 96% in the non-diabetics without ACS, $P = 0.03$). At 1 year, age, diabetes, chronic renal insufficiency, ejection fraction, and myocardial infarction were identified as independent predictors for mortality. Conclusion: In the DES era, diabetics who undergo PCI for ACS continue to have an excess risk of death and major adverse cardiac events at 1 year.

Key words: drug-eluting stents; diabetes; acute coronary syndrome

INTRODUCTION

Diabetes has reached epidemic proportions in the United States, with a prevalence of 20.8 million people, representing 7% of the population [1]. Despite improvements in the treatment of atherosclerosis and the subsequent reduction of mortality, diabetics who undergo percutaneous coronary intervention (PCI) are at increased risk for death, myocardial infarction, repeat revascularization, and stent thrombosis [2–6].

Acute coronary syndrome (ACS) represents a spectrum of presentations including unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction. In the United States, there are $\sim$ 2.3 million patients who develop ACS every year [7]. Diabetics are at increased risk for coronary artery disease and ACS when compared with non-diabetic patients [8]. Diabetes is also an independent predictor of increased mortality in non-ST-elevation ACS [9]. Among patients with a previous myocardial infarction, diabetics have almost a threefold greater long-term mortality compared with non-diabetics in the same group [10].

Drug-eluting stents (DES) have been shown to decrease in-stent restenosis when compared with bare-metal stents [11–13]. Similarly, in diabetic patients, DES decreased target vessel revascularization when compared with bare-metal stents, although diabetes was identified as an independent predictor of target lesion revascularization [14–17]. However, the randomized trials excluded patients with myocardial infarction. PCI with sirolimus-eluting stents in diabetic patients was associated with a higher 1-month mortality compared with non-diabetic patients [18]. We report our clinical outcomes of diabetic and non-diabetic patients with and without ACS who underwent PCI with DES.

Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California

Conflict of interest: Nothing to report.

*Correspondence to: Dr. Michael S. Lee, UCLA Medical Center, Adult Cardiac Catheterization Laboratory, 10833 Le Conte Avenue, Rm BL-394 CHS, Los Angeles, CA 90095-171715.
E-mail: mslee@mednet.ucla.edu

Received 27 June 2008; Revision accepted 16 August 2008

DOI 10.1002/ccd.21795
Published online 24 November 2008 in Wiley InterScience (www.interscience.wiley.com).

TABLE I. Baseline Demographic Data

	No diabetes		Diabetes		
	No ACS (n = 217)	ACS (n = 426)	No ACS (n = 85)	ACS (n = 159)	*P* value
Age (yrs)[a]	69 ± 12	66 ± 13	67 ± 11	68 ± 12	0.16
Male (%)	75	75	75	66	0.19
Hypertension (%)	69	65	87	86	<0.0001
Hypercholesterolemia (%)	76	71	90	81	0.0003
Current smoker (%)	3	15	10	9	<0.0001
Chronic renal insufficiency (Cr >1.5 mg/dL) (%)	10	10	25	30	<0.0001
Hemodialysis dependent (%)	1	1	4	9	<0.0001
Type of ACS					0.06
Unstable angina (%)	NA	48	NA	57	
Myocardial infarction (%)	NA	52	NA	43	
ST-elevation (%)	NA	45	NA	40	
Non-ST-elevation (%)	NA	55	NA	60	
Prior stroke (%)	8	7	10	8	0.70
Prior PAD (%)	16	10	24	23	<0.0001
Prior PCI (%)	29	25	37	30	<0.0001
Prior CABG (%)	23	14	32	26	<0.0001
Prior valve surgery (%)	1	2	5	2	0.19
Mean ejection fraction*	53 ± 11	50 ± 13	49 ± 11	49 ± 13	0.009

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; NA, not applicable; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.
[a]Data are presented as mean ± SD.

METHODS

Patient data was collected retrospectively on a dedicated PCI database from medical records or telephone interview with the patient's physician. Repeat angiography was performed if clinically indicated due to recurrent ischemia or surveillance angiography after unprotected left main coronary artery stenting or in orthotopic heart transplant patients. The Social Security Death Index, which lists more than 90% of people who die, was used to determine patient survival if hospital source documentation was not available.

The primary endpoint was survival at 1 year. The secondary endpoint was freedom from major adverse cardiac events. Death was defined as all causes of mortality. A myocardial infarction was defined as ischemic symptoms associated with cardiac enzyme elevation ≥three times the upper limit of the normal value. Target vessel revascularization was defined as a repeat revascularization to treat a vessel. Major adverse cardiac events were defined as a composite of death, myocardial infarction, and target vessel revascularization. ACS encompasses a spectrum of coronary artery diseases, including unstable angina, ST-elevation myocardial infarction, and non-ST-elevation myocardial infarction. Patients were diagnosed with unstable angina if they had symptoms of angina at rest, new onset (<2 months) of exertional angina, or acceleration of preceding angina.

Statistics

Continuous variables are presented as mean ± SD and were compared by the ANOVA or Kruskal-Wallis test. The χ^2 test or Fisher exact test was used to determine the significance of differences in categorical variables, as appropriate. Survival, target vessel revascularization, and major adverse cardiac event curves were generated by the Kaplan–Meier method, and the differences were assessed by the log-rank test. A multivariable Cox proportional hazard model was created with the use of baseline clinical and angiographic characteristics and procedure-related variables to identify independent predictors of survival. Variables entered into the multivariable models were age, gender, diabetes, hypertension, hypercholesterolemia, prior bypass surgery, prior PCI, smoker, chronic renal insufficiency (creatinine >1.5 mg/dL), hematocrit, presentation with myocardial infarction, peripheral arterial disease, prior mitral or aortic valve surgery, restenotic lesions, total stent length, number of diseased vessels, and use of glycoprotein IIb/IIIa inhibitors. A P value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS, version 10.0 (SPSS, Chicago IL).

RESULTS

Baseline Demographic, Angiographic, and Procedural Characteristics

Of the total 887 patients, ACS was present in 585 patients (66%), and diabetes was present in 244

TABLE II. Baseline Angiographic and Procedural Data

	No diabetes		Diabetes		
	No ACS (n = 217)	ACS (n = 426)	No ACS (n = 85)	ACS (n = 159)	P value
Number of diseased vessels[a]	1.2 ± 0.6	1.2 ± 0.4	1.4 ± 0.6	1.3 ± 0.5	0.002
Number of stents[a]	1.8 ± 1.1	1.6 ± 0.9	1.7 ± 0.8	1.9 ± 1.2	0.33
Total stent length (mm)	35 ± 24	33 ± 20	33 ± 17	38 ± 24	0.28
Restenotic lesion (%)	7	7	6	13	0.14
Intravascular ultrasound (%)	9	7	14	8	0.14
Intraaortic balloon pump (%)	2	8	5	8	0.02
GP IIb/IIIa inhibitors (%)	42	50	37	41	0.05

[a]Data are presented as mean ± SD.

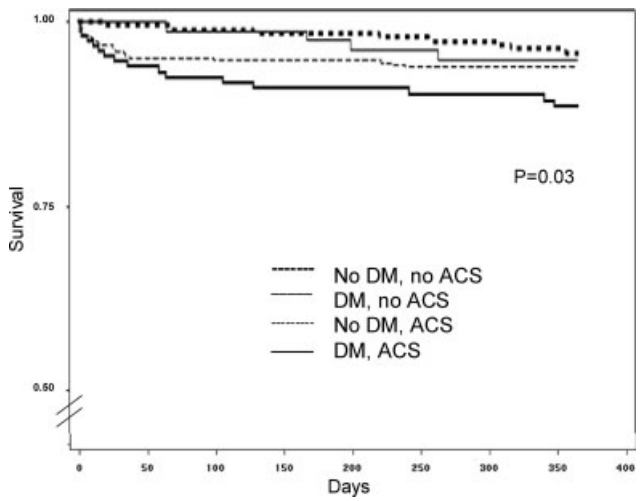

Fig. 1. Survival at one year.

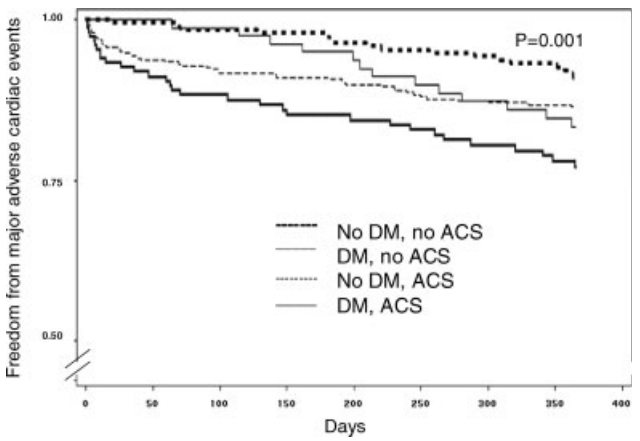

Fig. 2. Freedom from major adverse cardiac events at one year.

patients (28%). Baseline demographic data are presented in Table I, and baseline angiographic and procedural data are presented in Table II. There were significant differences between the four groups in baseline characteristics including hypertension, hypercholesterolemia, current smoking, chronic renal insufficiency, need for hemodialysis, peripheral arterial disease, prior percutaneous and surgical revascularization, mean ejection fraction, and mean number of diseased vessels.

One-Year Survival and Freedom From Major Adverse Cardiac Events

Survival at 1 year was the lowest in diabetics who presented with ACS (90% in the diabetics with ACS, 95% in diabetics without ACS, 95% in non-diabetics with ACS, and 96% in the non-diabetics without ACS, $P = 0.03$) (Fig. 1). Freedom from major adverse cardiac events was also the lowest in diabetics who presented with ACS (81% in the diabetics with ACS, 85% in diabetics without ACS, 89% in non-diabetics with ACS, and 92% in the non-diabetics without ACS, $P = 0.001$) (Fig. 2).

Multivariable analyses were performed to identify predictors of mortality and major adverse cardiac events at 1 year using the Cox proportional hazards model. Age, diabetes, chronic renal insufficiency, ejection fraction, and myocardial infarction were identified as independent predictors for 1-year survival (Table III). Age, chronic renal insufficiency, peripheral arterial disease, history of previous PCI, diabetes, and myocardial infarction were identified as independent predictors of 1-year major adverse cardiac events.

DISCUSSION

The main finding was that in a real-world experience with PCI with DES which included complex lesions and patients across the full spectrum of ACS, diabetics who presented with ACS had the highest 1-year mortality and major adverse cardiac event rate. Diabetes and myocardial infarction were also identified as independent predictors of mortality and major adverse cardiac events.

In the pre-DES era, diabetics had significantly lower rates of 1-year event-free survival compared with non-

TABLE III. Predictors of 1-Year Mortality and Freedom From Major Adverse Cardiac Events

	Hazard ratio (95% CI)	*P* value
One-year mortality		
Variable		
Age	1.10 (1.06–1.14)	<0.0001
Diabetes	2.10 (1.06–4.16)	0.03
Chronic renal insufficiency	2.71 (1.40–5.24)	0.003
Ejection fraction	0.97 (0.95–1.00)	0.004
Presentation with myocardial infarction	3.41 (1.37–8.45)	0.008
One-year risk of major adverse cardiac events		
Variable		
Age	1.02 (1.01–1.04)	0.009
Chronic renal insufficiency	2.07 (1.33–3.21)	0.001
Peripheral arterial disease	1.71 (1.10–2.68)	0.02
Diabetes	1.55 (1.03–2.30)	0.03
Myocardial infarction	2.33 (0.92–1.44)	0.0006

CI, confidence interval.

diabetics (73.1% vs. 78.5%, $P < 0.001$), lower rates of survival free of myocardial infarction (89.9% vs. 94.4%, $P < 0.001$), higher rates of restenosis (37.5% vs. 28.3%, $P < 0.001$), and higher rates of stent occlusion (5.3% vs. 3.4%, $P = 0.037$) [2]. Our study demonstrated a decrease in 1-year survival in ACS patients with diabetes compared with non-ACS patients without diabetes. This is similar to the results of a substudy analysis of the SYMPHONY and 2nd SYMPHONY trials [19] which reported nearly a twofold increase in 1-year mortality in diabetics with ACS (6.0% vs. 3.4%, $P < 0.001$), as well as the substudy analysis of the PAMI trials [20], which also reported a twofold increase in 6-month mortality in diabetics who underwent primary PCI for acute myocardial infarction (8.1% vs. 4.2%, $P < 0.001$). A pooled analysis of patients with ACS in 11 Thrombolysis in Myocardial Infarction (TIMI) Study Group clinical trials reported a significant association between diabetes and mortality [21]. Although randomized studies with sirolimus- and paclitaxel-eluting stents included single de novo lesions in native coronary arteries, our study included patients with long-complex lesions (mean total stent length ranged from 33 to 38 mm) as well as patients with myocardial infarction [11–13]. Our data provides insight into the outcomes of current treatment strategies for all-comers treated with DES rather than highly selected populations that are enrolled in clinical trials and which may not be representative of patients encountered in everyday clinical practice.

PCI in diabetics may be associated with poorer outcomes because of a greater prevalence of multivessel disease and atherosclerotic plaque burden, prothrombotic state, decreased antithrombotic factors, and an exaggerated process of neointimal proliferation [22–24]. In addition, influences from endothelial dysfunction, negative vascular remodeling, increased protein glycosylation, and increased vascular matrix deposition contribute to diabetes-associated coronary artery disease and poor outcomes following revascularization procedures [25,26]. The highest mortality was observed in diabetics with ACS which may be explained by important differences in several baseline characteristics. Diabetics with ACS were more likely to have chronic renal insufficiency, increased atherosclerotic burden (i.e., higher prevalence of peripheral arterial disease, previous percutaneous and surgical revascularization, and greater number of diseased vessels) and worse left ventricular function, all of which increase the risk of death after PCI. In addition, diabetes and presentation with myocardial infarction were also identified as independent predictors of survival.

Diabetics appear to be a group of patients who are likely to derive a survival benefit with glycoprotein IIb/IIIa inhibitors. Diabetics have larger platelets, express increased numbers of glycoprotein IIb/IIIa receptors, and have increased platelet binding to fibrinogen as well as increased platelet activation and aggregation [27–29]. In a pooled analysis of 6,458 diabetics who presented with non-ST-elevation ACS from six large clinical trials, treatment with glycoprotein IIb/IIIa inhibitors reduced 30-day mortality by 26% (4.6% vs. 6.2%, $P = 0.007$) [29]. Diabetics who underwent PCI with glycoprotein IIb/IIIa inhibition derived a marked reduction in 30-day mortality of 70% (1.2% vs. 4.0%, $P = 0.002$) [30]. Despite the extensive data supporting the clinical benefit of GP IIb/IIIa inhibition, the GRACE registry reported that glycoprotein IIb/IIIa inhibitors were used in only 21% of patients with non-ST-elevation ACS, and among those patients who underwent PCI, only 53% received glycoprotein IIb/IIIa inhibitors [31]. Diabetics who underwent primary PCI had increased 1-year mortality [32]. In our study, glycoprotein IIb/IIIa inhibitors were used in less than half of our patients with ACS, thus highlighting the underutilization of a therapy that reduces mortality. Although glycoprotein IIb/IIIa inhibitors have not been extensively studied in the DES era in randomized clinical trials, increased utilization, especially in diabetics with ACS, may provide better outcomes.

Two randomized clinical trials will help elucidate the optimal treatment strategies in diabetics. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) will not only compare insulin replacement with insulin-sensitizing agents but also evaluate medical therapy versus revascularization in diabetics with multivessel disease [33]. The FREEDOM trial will compare PCI with DES and bypass surgery in diabetics [34].

Limitations

Our study was a single center, retrospective, non-randomized registry with relatively small numbers. Follow-up angiography was not available on all patients. Although all efforts were attempted to obtain complete follow-up including contacting referring physicians and institutions, because of the retrospective nature of the study, all clinical events may not have been captured. The Social Security Death Index does not state the cause of death, and therefore, we were unable to determine whether patients died from cardiovascular or non-cardiovascular causes. Some patients with unknown diabetes may have been misassigned to the non-diabetic group. Glycated hemoglobin was not available in all patients, and therefore, the level of glycemic control of diabetes was not available for all patients.

CONCLUSION

Despite recent advances in technology and pharmacology, diabetics who undergo PCI for ACS continue to have an excess risk of death and major adverse cardiac events at 1 year, despite the utilization of DES. Diabetes was also an independent predictor of mortality. Newer and more effective therapeutics are needed to attenuate the negative impact of diabetes on cardiovascular disease. The results of randomized clinical trials with long-term follow-up are needed to clarify the optimal treatment strategies for these high-risk patients.

REFERENCES

1. Diabetes Statistics. National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Information Clearing House. Available at http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#7. Accessed March 8, 2008.
2. Elezi S, Kastrati A, Pache J et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. J Am Coll Cardiol 1998;32:1866–1873.
3. Safley DM, Marso SP. Diabetes and percutaneous coronary intervention in the setting of an acute coronary syndrome. Diabetes Vasc Dis Res 20052;128–135.
4. Kip KE, Faxon DP, Detrel KM, et al. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1996;94:1818–1825.
5. Marso SP, Giorgi LV, Johnson WL, et al. Diabetes mellitus is associated with a shift in the temporal risk profile of inhospital death after percutaneous coronary intervention: An analysis of 25,223 patients over 20 years. Am Heart J 2003;145:270–277.
6. Stein B, Weintraub WS, Gebhart SP, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979–989.
7. National Center for Health Statistics. 1999 National Hospital Discharge Survey: Annual Summary with Detailed Diagnosis and Procedure Data. Hyattsville, Maryland: US Dept of Health and Human Services; 2001: Series 13, No. 151.
8. Goraya TY, Leibson CL, Palumbo PJ, et al. Coronary atherosclerosis in diabetes mellitus: A population-based autopsy study. J Am Coll Cardiol 2002;40:946–953.
9. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation 2000;102:1014–1019.
10. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects and without prior myocardial infarction. N Engl J Med 1998;339:229–234.
11. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346:1773–1780.
12. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349:1315–1323.
13. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350:221–231.
14. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, et al. DIABETES Investigators. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: The Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. Circulation 2005: 112:2175–2183.
15. Hermiller JB, Raizner A, Cannon L, et al. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. J Am Coll Cardiol 2005; 45:1172–1179.
16. Abizaid A, Costa MA, Blanchard D, et al. Sirolimus-eluting stents inhibit neointimal hyperplasia in diabetic patients. Euro Heart J 2004;25:107–112.
17. Moussa I, Leon MB, Baim DS, et al. Impact of sirolimus-eluting stents on outcome in diabetic patients. Circulation 2004;109: 2273–2278.
18. Kuchulakanti PK, Torguson R, Canos D, et al. Impact of treatment of coronary artery disease with sirolimus-eluting stents on outcomes of diabetic and nondiabetic patients. Am J Cardiol 2005;96:1100–1106.
19. McGuire DK, Newby LK, Bhapkar MV, et al., SYMPHONY and 2nd SYMPHONY Investigators. Association of diabetes mellitus and glycemic control strategies with clinical outcomes after acute coronary syndromes. Am Heart J 2004;147:246–252.
20. Harjai KJ, Stone GW, Boura J, et al. for the Primary Angioplasty in Myocardial Infarction (PAMI) Investigators. Comparison of outcomes of diabetic and nondiabetic patients undergoing primary angioplasty for acute myocardial infarction. Am J Cardiol 2003;91:1041–1045.
21. Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndrome. JAMA 2007;298: 765–775.
22. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerotic epidemiology, pathophysiology, and management. JAMA 2002;287:2570–2581.
23. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy. I. Circulation 2003;108:1527–1532.
24. Schneider DJ, Sobel BE. Diabetes and thrombosis. In: Johnstone MT, Veres A, editors. Diabetes and Cardiovascular Disease. Totowa, New Jersey: Humana Press; 2001. pp 149–168.
25. Roffi M, Topol EJ, Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2004;25:190–198.

26. Smith SC, Faxon D, Cascio W, et al., Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing group VI: Revascularization in diabetic patients. Circulation 2002;105:e165–e169.
27. Colwell JA, Nesto RW. The platelet in diabetes: Focus on prevention of ischemic events. Diabetes Care 2003;26:2181–2188.
28. Tschoepe D, Roesen P, Kaufmann L, Schauseil S, Kehrel B, Ostermann H, Gries FA. Evidence for abnormal platelet glycoprotein expression in diabetes mellitus. Eur J Clin Invest 1990; 20:166–170.
29. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation 2001;104:2767–2771.
30. Théroux P, Alexander J, Jr., Pharand C, Barr E, Snapinn S, Ghannam AF, Sax FL. Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infarction: Results from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. Circulation 2000;102:2466–2472.
31. Budaj A, Brieger D, Steg PG, et al., GRACE Investigators. Global Patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2003;146:999–1006.
32. Mehra RH, Harjai KJ, Cox D, et al. Primary angioplasty in myocardial infarction (PAMI) investigators. Clinical and angiographic correlates and outcomes of suboptimal coronary flow in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. J Am Coll Cardiol 2003;42: 1739–1746.
33. Brooks MM, Frye RL, Genuth S, et al. Hypothesis, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Am J Cardiol 2006; 9G–19G.
34. Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes (FREEDOM). Available at http://www.clinicaltrials.gov/ct2/show/NCT00086450. Accessed on March 9, 2008.