Prognostic Significance of Cerebrovascular and Peripheral Arterial Disease in Patients Having Percutaneous Coronary Interventions

Eugenia Nikolsky, MD, PhD, Roxana Mehran, MD, George D. Dangas, MD, PhD, Zoran Lasic, MD, Gary S. Mintz, MD, Manuela Negoita, MD, Alexandra J. Lansky, MD, Gregg W. Stone, MD, Issam Moussa, MD, Sriram Iyer, MD, Yingbo Na, MSc, Jeffrey W. Moses, MD, and Martin B. Leon, MD

This study shows that cerebrovascular and peripheral arterial diseases frequently co-exist in patients with coronary artery disease who undergo percutaneous coronary interventions. These 2 conditions are associated with adverse in-hospital and 1-year outcomes and independently predict early and 1-year mortality.

(Am J Cardiol 2004;93:1536–1539)

Peripheral arterial disease (PAD) is associated with worse outcomes after percutaneous coronary interventions (PCIs).[1,2] Whether cerebrovascular disease (CVD) alone or in combination with PAD influences prognosis after PCI is not known. Therefore, we compared the impact of symptomatic CVD and PAD on the outcomes of patients who underwent PCI.

• • •

All patients treated with PCI from January 1994 to December 1999 were included in the study. Data were entered into a database containing demographic, clinical, angiographic, and follow-up information. The study was approved by the institutional review board of the hospital.

Qualitative and quantitative coronary angiographic analyses were carried out according to standard methods and definitions.[3,4] PCI was performed using standard techniques.[5] All patients received aspirin 325 mg/day ≥24 hours before the procedure and continued indefinitely afterward. Patients who underwent stenting were treated with either ticlopidine 250 mg twice daily or clopidogrel 75 mg/day for 4 weeks. All other treatments were at the discretion of the physicians.

Information on end points (death, myocardial infarction, and target vessel revascularization) was collected by telephone at 1 year. End point definitions have been previously described.[5] Symptomatic PAD was a history of intermittent claudication or lower extremity vascular intervention. Intermittent claudication was based on accurate anamnesis using standardized World Health Organization Rose questionnaires and targeted clinical examinations.[6] Symptomatic CVD was a history of stroke or transient ischemic attack that resulted in visual, speech, or motor function abnormalities and/or prior carotid intervention.

Continuous variables are expressed as means ± 1 SD, and categorical data are presented as frequencies. Differences among groups were compared using analysis of variance and chi-square statistics for continuous and categorical variables, respectively. Pairwise p values were also calculated, and the Sidak method was used to control for multiple comparisons.

Multivariate regression analysis of predictors of mortality was performed using logistic regression with stepwise selection with entry and exit criteria of $p < 0.1$. A 2-sided 95% confidence interval (CI) was constructed around each point estimate of odds ratio (OR); $p \leq 0.05$ was considered statistically significant. Overall survival was estimated by the Kaplan-Meier method and compared by the log-rank test.

Of 10,428 patients, symptomatic CVD was present in 743 (7.1%), symptomatic PAD in 1,541 (14.8%), and CVD and PAD in 424 (4.1%). The remaining 7,720 patients (74%) had neither of these conditions (controls).

Compared with the controls, groups with CVD, PAD, or CVD and PAD were older, more frequently women, and had smaller body mass indexes and lower left ventricle ejection fractions ($p = 0.004$ to <0.0001, Table 1). In addition, hypertension, diabetes, chronic renal insufficiency (baseline plasma creatinine ≥2 mg/dl), and congestive heart failure were significantly more common in patients with CVD, PAD, or CVD and PAD compared with controls ($p = 0.03$ to <0.0001). More patients in the CVD, PAD, or CVD and PAD groups had histories of myocardial infarction and/or previous coronary artery bypass compared with controls ($p = 0.002$ to <0.0001).

Compared with patients with PAD, those with CVD had more systemic hypertension ($p = 0.003$) and less insulin-treated diabetes mellitus ($p = 0.002$), smoking history ($p < 0.0001$), prior PCI, and chronic renal insufficiency ($p = 0.01$). Compared with patients with CVD and PAD, those with only CVD had less hypercholesterolemia ($p = 0.001$), insulin-treated diabetes ($p < 0.0001$), smoking history ($p = 0.01$), prior coronary artery bypass, or chronic renal insufficiency ($p < 0.0001$). Patients with only PAD differed from those with PAD and CVD by less hypertension, prior coronary artery bypass, and chronic renal insufficiency (all $p \leq 0.0001$).

From the Cardiovascular Research Foundation; and the Lenox Hill Heart and Vascular Institute, New York, New York. Dr. Mehran's address is: Cardiovascular Research Foundation, 55 E. 59th Street, 6th Floor, New York, New York 10022. E-mail: rmehran@crf.org. Manuscript received December 22, 2003; revised manuscript received and accepted March 1, 2004.

0002-9149/04/$–see front matter
doi:10.1016/j.amjcard.2004.03.010

TABLE 1 Baseline Patient Characteristics

Characteristic	(+) CVD (–) PAD (n = 743)	(–) CVD (+) PAD (n = 1,541)	(+) CVD (+) PAD (n = 424)	(–) CVD (–) PAD (n = 7,720)	p Value*
Age (yrs), mean ± SD	68.5 ± 9.8	67.2 ± 9.9	68.4 ± 9.9	62.7 ± 11.5	<0.0001
Men	62.5%	65.1%	59.7%	71.8%	<0.0001
White	84.0%	87.4%	85.2%	83.2%	0.004
Hypercholesterolemia	67.4%	71.2%	77.5%	68.3%	<0.0001
Systemic hypertension	76.2%	69.2%	81.1%	59.9%	<0.0001
Diabetes mellitus	36.1%	44.1%	49.6%	26.7%	<0.0001
Insulin-treated	16.0%	21.2%	26.7%	10.3%	<0.0001
Treated with oral agents	15.8%	19.0%	19.4%	13.0%	<0.0001
Current smoker	12.7%	16.0%	17.5%	17.3%	0.01
Smoker history	54.4%	65.1%	63.7%	55.6%	<0.0001
Ejection fraction (mean ± SD)	0.44 ± 0.14	0.44 ± 0.14	0.43 ± 0.14	0.47 ± 0.13	<0.0001
Previous myocardial infarction	62.1%	59.0%	59.9%	54.1%	<0.0001
Previous PCI	46.2%	53.2%	52.5%	47.4%	<0.0001
Previous coronary bypass	50.7%	54.0%	64.1%	35.0%	<0.0001
Unstable angina pectoris	33.6%	35.5%	33.3%	34.0%	0.69
Congestive heart failure†	5.7%	7.9%	8.4%	3.3%	<0.0001
Chronic renal insufficiency	13.1%	18.1%	27.6%	6.0%	<0.0001
Body mass index (kg/m^2) (mean ± SD)	27.9 ± 5.4	27.9 ± 5.3	27.3 ± 5.1	28.3 ± 5.3	<0.0001
Medications					
Aspirin	96.8%	97.5%	96.3%	97.8%	0.12
Ticlopidine	53.5%	58.0%	59.3%	57.0%	0.18
Warfarin	22.3%	17.9%	23.7%	17.4%	0.0002
Persantine	1.4%	1.4%	2.2%	0.8%	0.009
Angiotensin-converting enzyme inhibitor	35.2%	33.2%	36.4%	25.2%	<0.0001

*Chi-square statistics for categorical variables and analysis of variance for continuous variables.
†New York Heart Association class III to IV.
ACE = angiotensin-converting enzyme.

Compared with controls, intervention on left anterior descending artery lesions was less frequent in patients with CVD, PAD, or CVD and PAD, whereas the opposite was true regarding saphenous vein graft interventions ($p = 0.003$ to <0.0001; Table 2).

The rates of procedural success (a final diameter stenosis of <50% by quantitative coronary angiography, without complications) in patients with CVD did not differ from controls. However, when PAD was present, procedural success was less than in the other groups ($p = 0.02$ to 0.0003). In general, procedural complications occurred with similar frequency in all groups, except that no reflow was more frequent in patients with CVD and PAD ($p < 0.0001$, compared with controls).

Alone or in combination, CVD and PAD were associated with increased in-hospital all-cause and cardiac mortality ($p = 0.01$ to <0.0001; Table 3). Stroke or transient ischemic attack was also more common in patients with only CVD or CVD and PAD compared with controls. Pulmonary edema, renal failure, hemodialysis, and limb ischemia complicated the in-hospital stay more frequently in patients with CVD, PAD, or CVD and PAD compared with controls (all $p < 0.0001$).

Compared with controls, the presence of CVD, PAD, or CVD and PAD was associated with a significant increase in the length of in-hospital stay (3.4 ± 9.9, 4.7 ± 7.4, 4.0 ± 4.6, and 4.0 ± 4.6 days, respectively; $p = 0.04$ to <0.0001).

One-year follow-up data are available on 94.6% of the patients (Table 4). Compared with controls, 1-year survival was less in all 3 study groups (all $p < 0.0001$; Figure 1). The greatest mortality was seen in patients with CVD and PAD, followed by the groups with only PAD, only CVD, and neither condition. Comparison among groups with CVD, PAD, and CVD and PAD showed that significant differences in 1-year mortality were confined to patients with CVD and PAD compared with patients with only CVD ($p = 0.007$). The rates of non–Q-wave myocardial infarction were higher than in controls only in patients with CVD and PAD ($p = 0.006$). Compared with controls, patients with only PAD had more target vessel revascularization at 1 year ($p = 0.01$).

Variables independently associated with in-hospital mortality included prior myocardial infarction (OR 2.69, 95% CI 1.68 to 4.30, $p < 0.0001$), older age (OR 1.07, 95% CI 1.05 to 1.09, $p < 0.0001$), chronic renal insufficiency (OR 1.87, 95% CI 1.11 to 3.17, $p = 0.02$), diabetes (OR 1.48, 95% CI 0.99 to 2.22, $p = 0.05$), and CVD (OR 2.33, 95% CI 1.35 to 4.03, $p = 0.003$), but not PAD.

One-year mortality, however, was predicted by either PAD (OR 1.72, 95% CI 1.38 to 2.14, $p < 0.0001$) or CVD (OR 1.40, 95% CI 1.03 to 1.91, $p = 0.03$) along with chronic renal insufficiency (OR 2.41, 95% CI 1.88 to 3.09, $p < 0.0001$), diabetes (OR 2.07, 95% CI 1.72 to 2.50, $p < 0.0001$), smaller body mass index (OR 0.95, 95% CI 0.93 to 0.97, $p < 0.0001$), prior myocardial infarction (OR 1.65, 95% CI 1.36 to 2.00, $p < 0.0001$), older age (OR 1.04, 95% CI 1.03 to 1.05, $p < 0.0001$), and saphenous vein graft intervention (OR 1.51, 95% CI 1.23 to 1.86, $p = 0.0001$).

TABLE 2 Lesion and Procedure Characteristics

Characteristic	(+) CVD (–) PAD (n = 1,393)	(–) CVD (+) PAD (n = 2,858)	(+) CVD (+) PAD (n = 799)	(–) CVD (–) PAD (n = 13,969)	p Value*
Restenosis lesion	18.9%	22.4%	19.0%	19.8%	0.009
Coronary lesion location					
Left main	3.3%	4.4%	3.5%	2.2%	<0.0001
Left anterior descending	26.1%	23.4%	22.3%	30.6%	<0.0001
Left circumflex	26.4%	23.2%	27.2%	24.4%	0.04
Right	25.6%	27.7%	23.3%	29.6%	<0.0001
Saphenous vein graft	18.6%	21.2%	23.7%	13.2%	<0.0001
Thrombolysis In Myocardial Infarction flow					
0–2	14.1%	12.5%	15.9%	12.0%	0.52
3	85.8%	87.5%	84.1%	88.0%	0.29
Lesion length (mm), mean ± SD	10.39 ± 8.16	11.23 ± 9.43	10.26 ± 7.98	11.08 ± 9.10	0.36
Bifurcation	6.5%	6.3%	5.5%	6.7%	0.91
Thrombus	6.9%	5.6%	6.2%	6.8%	0.72
Reference vessel size (mm) (mean ± SD)	2.82 ± 0.89	2.84 ± 0.79	2.83 ± 0.76	2.85 ± 0.73	0.94
Preminimal luminal diameter (mm) (mean ± SD)	0.98 ± 0.62	0.95 ± 0.61	1.00 ± 0.62	0.97 ± 0.60	0.75
Prediameter stenosis (%) (mean ± SD)	64 ± 21	66 ± 19	65 ± 17	66 ± 20	0.54
Final minimum lumen diameter (mm) (mean ± SD)	2.48 ± 0.84	2.51 ± 0.86	2.49 ± 0.91	2.54 ± 0.80	0.37
Final diameter stenosis (%) (mean ± SD)	15 ± 19	14 ± 21	17 ± 18	14 ± 19	0.17
Procedure characteristics					
Procedural success	94.9%	94.7%	92.4%	96.3%	<0.0001
No reflow	0.9%	0.6%	2.4%	0.8%	<0.0001
Stented lesions	48.0%	50.5%	50.6%	51.4%	0.86
Atheroablative devices	36.2%	32.3%	32.3%	32.5%	0.76
Glycoprotein IIb/IIIa receptor inhibitors	7.0%	6.0%	5.4%	6.5%	0.69

*Chi-square statistics for categorical variables and analysis of variance for continuous variables.
TIMI = Thrombolysis In Myocardial Infarction.

TABLE 3 In-hospital Complications

Variable	(+) CVD (–) PAD (n = 743)	(–) CVD (+) PAD (n = 1,541)	(+) CVD (+) PAD (n = 424)	(–) CVD (–) PAD (n = 7,720)	p Value*
Death	2.8%	2.0%	2.4%	0.9%	<0.0001
Cardiac death	2.0%	1.3%	2.4%	0.6%	<0.0001
Q-wave myocardial infarction	0.3%	0.4%	0.7%	0.4%	0.725
Non–Q-wave myocardial infarction	16.9%	15.3%	15.5%	14.3%	0.253
Coronary bypass surgery	1.1%	1.7%	2.6%	1.2%	0.051
Stroke	0.8%	0.5%	1.2%	0.2%	0.001
Transient ischemic attack	0.7%	0.3%	0.9%	0.1%	<0.0001
Recurrent ischemia	3.5%	5.2%	7.1%	2.8%	<0.0001
PCI to target lesion	0.9%	2.3%	2.6%	1.1%	0.0002
Pulmonary edema	6.3%	5.0%	7.1%	2.4%	<0.0001
Renal failure†	6.5%	6.2%	7.8%	2.2%	<0.0001
Hemodialysis	2.0%	1.8%	2.1%	0.4%	<0.0001
Limb ischemia	1.6%	3.0%	3.1%	0.6%	<0.0001

*Chi-square statistics.
†Increase ≥25% or absolute increase of ≥0.5 mg/dl in serum creatinine from baseline value.

The assessment of unadjusted ORs showed significantly (all p <0.0001) increased risk for 1-year death in patients with CVD, PAD, or CVD and PAD compared with controls (Figure 2). After adjusting for covariates, groups with CVD, PAD, and CVD and PAD still had a significantly increased risk for 1-year mortality than controls (p <0.0001, <0.0001, and 0.02, respectively).

• • •

Our study confirms that clinically evident PAD and CVD are frequent co-morbidities in patients with CAD who undergo PCI. One quarter (26%) of all patients in this study had CVD, PAD, or CVD and PAD. One third of patients with CVD (36.3%) also had PAD, whereas 1/5 (21.6%) of all patients with PAD also had CVD.

The main outcomes of patients with CVD, PAD, or CVD and PAD were similar in this study. Alone or in combination, CVD and PAD were associated with increased rates of in-hospital complications and mortality, prolonged hospitalization, and <1-year survival. Patients with CVD, PAD, or both had 2 to 3 times greater in-hospital mortality than controls and 2.5 to 9 times higher rates of neurologic events. Furthermore, renal failure after PCI was 3 to 4 times more common, and hemodialysis was required 4.5 to 5

TABLE 4 One-Year Follow-up

Variable	(+) CVD (–) PAD (n = 686)	(–) CVD (+) PAD (n = 1,381)	(+) CVD (+) PAD (n = 365)	(–) CVD (–) PAD (n = 7,433)	p Value*
Death	9.9%	12.6%	16.7%	4.7%	<0.0001
Q-wave infarction	1.5%	1.0%	2.3%	1.2%	0.196
Non–Q-wave myocardial infarction	6.6%	6.3%	9.4%	5.2%	0.004
Target vessel revascularization	21.5%	25.0%	23.1%	21.2%	0.02

*Chi-square statistics.

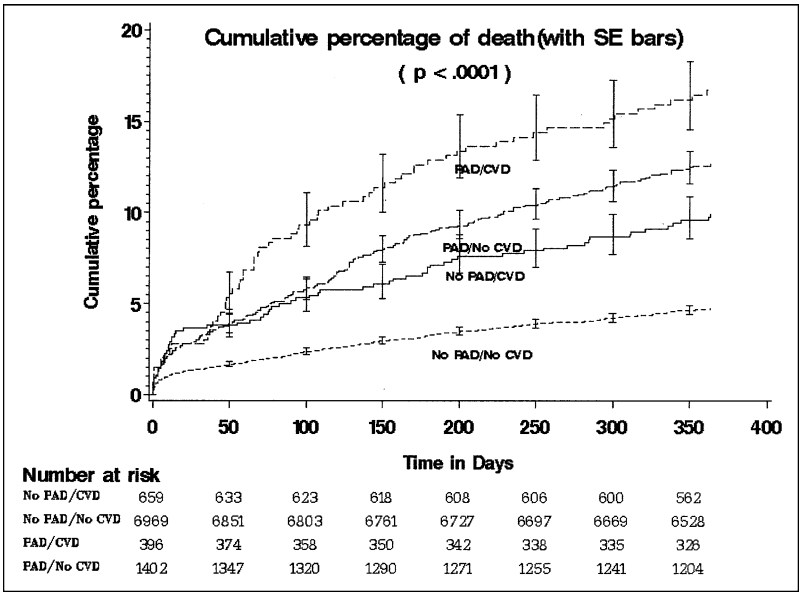

FIGURE 1. One-year survival after PCI in patients with CVD, PAD, CVD and PAD, or neither.

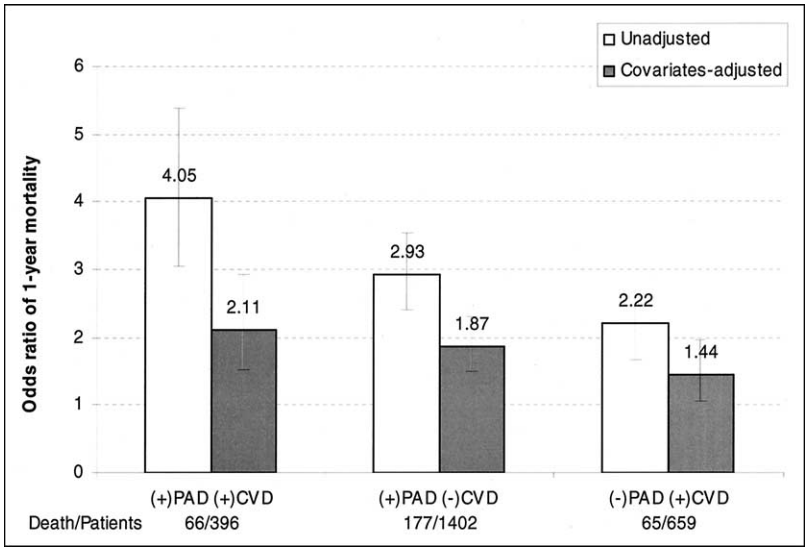

FIGURE 2. ORs of 1-year mortality in patients with CVD, PAD, or CVD and PAD, compared with controls, in patients treated with PCI.

times more frequently. Limb ischemia occurred with increased frequency in patients with either of these conditions. Finally, 1-year survival in patients with CVD, PAD, or CVD and PAD was 90.1%, 87.4%, and 83.3%, respectively, significantly less than in patients without these conditions (95.3%, p <0.0001).

To conclude, the results show that CVD and PAD are serious factors in the risk stratification of patients with CAD who undergo PCI. The outcomes of PCI in the general population cannot be extrapolated on a subset of patients with CVD, PAD, or their combination. This consideration should be specifically taken into account by physicians and properly explained to patients in the assessment of the risk-benefit ratio of different strategies (PCI vs medical therapy vs coronary artery bypass grafting). Further studies should prospectively address the best treatment for patients with CVD, PAD, or CVD and PAD. The high risk profile of these patients demands the aggressive targeting of risk factors for the secondary prevention of atherosclerotic disease.

1. Rihal CS, Sutton-Tyrrell K, Guo P, Keller NM, Jandova R, Sellers MA, Schaff HV, Holmes DR Jr. Increased incidence of periprocedural complications among patients with peripheral vascular disease undergoing myocardial revascularization in the bypass angioplasty revascularization investigation. *Circulation* 1999;100:171–177.

2. Nikolsky E, Mehran R, Mintz GS, Dangas GD, Lansky AJ, Aymong ED, Negoita M, Fahy M, Moussa I, Roubin GS, et al. Impact of symptomatic peripheral arterial disease on one-year mortality in patients undergoing percutaneous coronary interventions. *J Endovasc Ther* 2004;11:60–70.

3. Lansky AJ, Popma JJ. Quantitative angiography. In: Topol EJ, ed. Textbook of Interventional Cardiology. Philadelphia: WB Saunders, 1999:725–747.

4. TIMI Study Group. The Thrombolysis In Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med* 1985;312:932–936.

5. Gruberg L, Dangas G, Mehran R, Mintz GS, Kent KM, Pichard AD, Satler LF, Lansky AJ, Stone GW, Leon MB. Clinical outcome following percutaneous coronary interventions in patients with chronic renal failure. *Cathet Cardiovasc Intervent* 2002;55:66–72.

6. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation* 1997; 96:44–49.