Peripheral Arterial Disease, Diabetes, and Mortality

Cynthia L. Leibson, phd[1]
Jeanine E. Ransom, bs[1]
Wayne Olson, bs[1]
Bruce R. Zimmerman, md[2]
W. Michael O'Fallon, phd[1]
Pasquale J. Palumbo, md[3]

OBJECTIVE — The aims of this study were to provide estimates of *1*) the risk of mortality for individuals with both diabetes and peripheral arterial disease (PAD) relative to that for individuals with either condition alone and *2*) the association between PAD progression and mortality for individuals with diabetes, PAD, and both conditions.

RESEARCH DESIGN AND METHODS — This longitudinal cohort study was conducted in Rochester, Minnesota. Local residents age 50–70 years with a prior diagnosis of PAD and/or diabetes were identified from the Mayo Clinic diagnostic registry and invited to a baseline examination (1977–1978). Those who met inclusion criteria were assessed for PAD progression at 2 and 4 years and followed for vital status through 31 December 1999.

RESULTS — The numbers who met criteria for PAD, diabetes, and both conditions at baseline were 149, 238, and 186, respectively. Within each group, observed survival was less than expected ($P < 0.001$). The adjusted risk of death for both conditions was 2.2 times that for PAD alone. Among the 449 who returned at 4 years, the risk of subsequent death was greater for those whose PAD had progressed; among individuals with diabetes alone at baseline, 100% (17 of 17) who met criteria for PAD progression were dead by 31 December 1999 compared with 62% (111 of 178) of those who had not met criteria (adjusted relative hazard 2.29 [95% CI 1.30–4.02], $P = 0.004$). The increased mortality associated with PAD progression was significant only for individuals with diabetes (alone or with PAD).

CONCLUSIONS — Diabetes is a risk factor for both PAD and PAD-associated mortality, emphasizing the critical need to detect and monitor PAD in diabetic patients.

Diabetes Care 27:2843–2849, 2004

Up to 20% of elderly individuals have peripheral arterial disease (PAD) upon noninvasive testing (1–4). Because only a small percentage of these individuals are symptomatic, PAD is poorly recognized in primary care practice (1,3,5,6). This is disconcerting because both asymptomatic and symptomatic PAD contribute to increased mortality, and both have been associated with increased cardiovascular events, gangrene, revascularization, and amputation, leading to considerable disability and use of health care resources (6–10). As a consequence, numerous studies have attempted to assist physicians in identifying individuals at greatest risk of developing PAD. Such studies consistently identify diabetes as a key risk factor (1,2,4,11–15). The extent to which diabetes contributes to progression to disability and/or premature mortality in individuals with PAD, however, is less clear. A study from our institution prospectively determined the presence of diabetes and PAD in a cohort of individuals at baseline (i.e., 1977–1978) and again 4 years later (16–21). The study confirmed that individuals with diabetes were at significantly increased risk of developing PAD (21). However, among individuals who met criteria for PAD at baseline, the likelihood of progression at 4 years, measured as rate of change in postexercise ankle-brachial index (ABI), was unaffected by the presence of diabetes at baseline (20). The opportunity to compare these findings is limited because few studies have had serial measures of ABI and because most investigations of PAD progression have consisted of individuals who were symptomatic at baseline (22–24). There is also a shortage of data on the association between PAD progression and mortality, and to our knowledge, there are no investigations of whether the association between PAD progression and mortality differs between individuals with and without diabetes.

These are critical questions. The finding that individuals with asymptomatic PAD are at increased risk of adverse outcomes has resulted in recommendations that elderly individuals be screened for PAD (25). But a majority of individuals identified with asymptomatic PAD upon screening will compensate for the reduced perfusion with collateral circulation (26), and the risk of adverse outcomes in such individuals is likely to be low. To identify which individuals should be monitored more frequently and how often, it is important to understand the extent to which progression of PAD contributes to increased morbidity and mortality and in whom that risk is greatest. The present study begins to examine these issues by following members of the cohort initiated in 1977–1978 to determine vital status through 31 December 1999, for a maximum of 23 years of observation. The aims of the study were *1*) to estimate the risk of mortality for individuals with both diabetes and PAD relative to that for individuals with either condition alone and *2*) to estimate the association between PAD progression and mortality for individuals with diabetes alone, those with PAD alone, and those with both conditions at baseline.

From the [1]Department of Health Sciences Research, Rochester, Minnesota; the [2]Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and [3]Department of Internal Medicine, Mayo Clinic, Scottsdale, Arizona.

Address correspondence and reprint requests to Dr. Cynthia L. Leibson, Department of Health Sciences Research, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. E-mail: leibson@mayo.edu.

Received for publication 13 May 2004 and accepted in revised form 24 August 2004.

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; PAD, peripheral arterial disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

The present study is a follow-up to a 4-year longitudinal study initiated in 1977. The original study received Mayo Clinic Institutional Review Board approval. Separate institutional review board minimal risk approval was obtained for this follow-up. The identification and recruitment of subjects for the original study have been described in detail (16). Potential cases were identified from a registry maintained on all patients seen at the Mayo Clinic, Rochester, Minnesota, since 1945. The registry was used to generate a listing of all individuals who as of 1 January 1977 were age 50–70 years, had any clinical diagnosis of diabetes and/or PAD, and lived close enough to return to the clinic on a regular basis. Individuals were excluded who had a diagnosis of secondary diabetes, advanced renal failure, blood dyscrasias, liver disease, active malignancy, untreated endocrine dysfunction other than diabetes, previous peripheral arterial surgery, or any condition other than diabetes or PAD that might limit life expectancy <5 years. For the purpose of calibrating PAD progression, a healthy control group was also identified, consisting of individuals with no diagnoses of diabetes or PAD but at least one clinic encounter in the 2 years before 1977. Individuals who exhibited any of the above exclusion criteria were excluded as potential control subjects; those with evidence of hypertension or hyperlipidemia were also excluded. Eligible subjects were contacted, and examinations were scheduled from January 1977 through March 1978. Baseline clinical characteristics, physical examination findings, and laboratory results have been reported (16–21). Written informed consent was obtained from all subjects.

Determination of diabetes and PAD

The presence of PAD and diabetes at baseline were confirmed with *1*) review of complete Mayo Clinic medical records (hospitalizations and emergency department, urgent care, and office visits), *2*) a detailed medical history obtained by a trained interviewer, and *3*) a thorough physical examination by one of the investigators that included chemical, hematological, and vascular laboratory studies. Individuals were considered to have diabetes if taking antidiabetic medication and/or if their glucose values (mmol/l) exceed thresholds used by Mayo clinicians at the time of the original study (i.e., fasting of 6.66 or tolerance test values at 1 and 2 h, respectively, of 9.16 and 6.66 for age 50 years, 9.71 and 7.22 for ages 51–59 years, and 10.27 and 7.77 for ages 60–70 years). The definition of PAD incorporated the postexercise ABI values obtained at baseline. Baseline ABI was calculated as the mean ankle systolic blood pressure at 1, 3, 5, and 10 min postexercise divided by the mean of the arm systolic pressures at the same times. The lesser of the mean ABI values for the right and left legs was used to determine the presence of PAD (yes/no) (20). For the present study, individuals were categorized as having PAD at baseline if this value was below the 5th percentile of the distribution of lesser mean ABI values observed at baseline for subjects in the healthy control group (i.e., 0.89).

Determination of PAD progression

At enrollment, individuals were invited to return for follow-up examinations at 2 and 4 years. For each individual who returned at year 4, a weighted summary measure of the annual rate of change in postexercise ABI between baseline, year 2, and year 4 was calculated (summary rate). Details of the calculation are provided elsewhere (20). Individuals were categorized as exhibiting PAD progression who met both of the following: *1*) the summary rate value for either leg fell below the fifth percentile of the value for the healthy control group, i.e., <-0.032, and *2*) the 4-year ABI measure was <0.89. Individuals who had undergone peripheral arterial reconstructive surgery because of worsened clinical status (disabling claudication or development of ischemic rest pain) or amputation of part of the lower extremity as a result of gangrene produced by increasing ischemia were also classified as exhibiting PAD progression (20). Findings from the 4-year assessment were reported previously (21).

Determination of vital status as of 31 December 1999

Vital status as of 31 December 1999 and date of death for those who died was determined following review of Mayo Clinic medical records, Social Security death index, state of Minnesota death tapes, and with telephone and mail follow-up.

Statistical analysis

The three groups (PAD alone, diabetes alone, and PAD with diabetes) were compared for baseline characteristics using χ^2 tests for categorical variables and nonparametric ANOVA for continuous variables. For each group separately, Kaplan-Meier life table estimates of survival were obtained, and one-sample log-rank tests were used to compare observed mortality with that expected, based on West North Central white population rates for individuals of the same age, sex, and calendar year distribution. To assess the independent contribution of both conditions versus each condition alone to mortality (i.e., adjusted for baseline differences among the groups), we used multivariable Cox proportional hazards modeling. We first used forward stepwise regression to identify which baseline covariates (sex, age, BMI, smoking status [current and ever], history of hypertension, history of coronary heart disease [CHD], duration of diabetes, and duration of PAD) contributed significantly to mortality. When this modeling was complete, we then added the variables for group status to the model (coded as two indicator variables to distinguish diabetes alone and PAD alone from both conditions). Then, to test if baseline postexercise ABI had an additional influence on mortality, we entered it into the above model. Appropriate interaction and higher order terms were assessed as part of the model building process.

Among subjects who returned for the 4-year assessment, subsequent survival rates were estimated separately for those who progressed and those who had not progressed using the Kaplan Meier product limit method. Tests for significant differences between those who did and did not progress were performed using Cox proportional hazards, adjusted for sex, age, and baseline postexercise ABI. Comparisons were performed separately for each of the three groups as defined at baseline, that is, PAD alone, diabetes alone, and PAD with diabetes. In models that included all three groups, a process similar to that described above was used to identify covariates that contributed significantly to mortality. The independent contribution of 4-year progression of PAD to mortality was then assessed by adding progression (yes/no) to the variables found to be significant in the Cox models.

Table1 —*Comparison of baseline characteristics among individuals who met study criteria for PAD, diabetes, or both conditions at baseline (1977–1978)*

Group	Diabetes	PAD	Both	*P*
n	238	149	186	
Men (%)	62	72	57	0.019
Current smoker (%)	11	38	22	0.001
Ever smoked (%)	45	83	60	0.001
CHD (%)	12	30	26	0.001
Hypertension (%)	42	50	41	0.205
Newly identified diabetes (%)	3	—	3	0.9
Newly identified PAD (%)	—	17	82	<0.001
Median duration diabetes (years)	6.2	—	12.2	<0.001
Median duration PAD (years)	—	3.1	0	<0.001
Age (years)	60.3 ± 5.3	61.8 ± 5.4	60.8 ± 5.2	0.031
BMI (kg/m^2)	28.5 ± 4.8	26.7 ± 4.3	28.8 ± 5.2	<0.001
ABI	1.06 ± 0.10	0.53 ± 0.28	0.75 ± 0.26	<0.001

Data are means ± SD unless otherwise indicated.

RESULTS — There were 583 individuals enrolled in 1977–1978 who met criteria for PAD and/or diabetes. In accordance with a 1997 Minnesota privacy law (27), three subjects who subsequently refused authorization for medical records research were excluded, as were seven subjects who had vascular surgery before enrollment. Of the remaining 573, 149 had PAD only, 238 had diabetes only, and 186 had both conditions.

The three groups differed significantly with respect to baseline characteristics (Table 1). At baseline, the proportion of individuals with newly discovered diabetes was 3% in the group with diabetes alone and 3% in the group with both PAD and diabetes. Because diabetes is a risk factor for PAD, duration of diabetes in individuals with diabetes alone was shorter than that for individuals with both conditions. By contrast, duration of PAD in individuals with PAD alone was longer than that for individuals with both diabetes and PAD. This difference reflects the manner in which potential subjects were identified (see RESEARCH DESIGN AND METHODS), such that the proportion of individuals newly discovered as having PAD at the baseline examination was only 17% for individuals with PAD alone versus 82% for individuals with both PAD and diabetes. This also explains the lower mean postexercise ABI values for individuals with PAD alone compared with those with both conditions.

Information on vital status as of 31 December 1999 was available for 98% of subjects (559 of 573). For each group, the observed number of deaths between baseline and 31 December 1999 was greater than expected based on rates for the West North Central white population of similar age, sex, and calendar year distribution (111 versus 80 for individuals with PAD alone, 163 versus 123 for individuals with diabetes alone, and 152 versus 72 for individuals with both conditions) ($P <$ 0.001 for each comparison).

Survival as a function of baseline status

Stepwise Cox proportional hazards modeling was used to estimate the hazard of death associated with each of the baseline characteristics, exclusive of group variables and postexercise ABI (a marker of PAD severity). Only age, male sex, ever having smoked, history of hypertension, history of CHD, and duration of diabetes contributed independently to mortality, with no other factors entering the model. Addition of the two group variables to this model revealed that individuals with both PAD and diabetes had an adjusted risk of death 1.55 times that for individuals with diabetes alone (95% CI 1.22–1.95, $P <$ 0.001) and 1.67 times that for individuals with PAD alone (1.24–2.26, $P < 0.001$).

The addition of baseline postexercise ABI (range 0.03–1.65) to the model revealed a strong association ($P < 0.01$) between this measure and the risk of death, with every 0.1-unit decrease in ABI resulting in a 13% increase in the risk of death. With this measure of PAD severity in the model, the risk of death for the three groups was still significant, but the risk for individuals with both PAD and diabetes no longer differed from those with diabetes alone (hazard ratio [HR] 1.12 [95% CI 0.85–1.48], $P = 0.41$). The risk of death for individuals with both PAD and diabetes versus those with PAD alone remained highly significant (HR 2.21 [1.59–3.07], $P < 0.001$).

Survival as a function of PAD progression at year 4

Of the 573 individuals enrolled at baseline, 449 (78%) returned for the 4-year assessment. The numbers by category status at baseline were 110 with PAD only, 195 with diabetes only, and 144 with both PAD and diabetes. Of the 110 individuals with PAD alone at baseline, only two (1.8%) had developed diabetes by year 4. The numbers with progression of PAD at year 4 were 31 (28.2%) for individuals with PAD alone at baseline, 17 (8.7%) for individuals with diabetes alone at baseline, and 31 (21.5%) for individuals with both PAD and diabetes at baseline.

The subsequent risk of mortality for individuals who at year 4 exhibited PAD progression relative to those who did not is displayed graphically for each group (Fig. 1). Among individuals with PAD alone at baseline, the proportions who died by 31 December 1999 were 77% (24 of 31) for progressors versus 66% (52 of 79) for nonprogressors (age, sex, and baseline ABI adjusted HR 0.91 [95% CI 0.55–1.51], $P = 0.72$). By contrast, among individuals with diabetes alone at baseline, 100% (17 of 17) of those who exhibited PAD progression at year 4 had died by 31 December 1999 versus 62% (111 of 178) of nonprogressors (2.29 [1.30–4.02], $P = 0.004$). Among individuals with both conditions at baseline, the proportions who died by 31 December 1999 were 94% (29 of 31) for progressors versus 75% (85 of 113) for nonprogressors (1.85 [1.18–2.90], $P =$ 0.008). Thus, among individuals with PAD alone at baseline, progression of PAD at year 4 was not a significant predictor of mortality. But among individuals with diabetes at baseline (either alone or with PAD), PAD progression at year 4 was a significant predictor of mortality.

In a model that included all 449 individuals who returned for the 4-year assessment, we used forward stepwise regression in the manner described above to test whether PAD progression at year 4 contributed significantly to mortality.

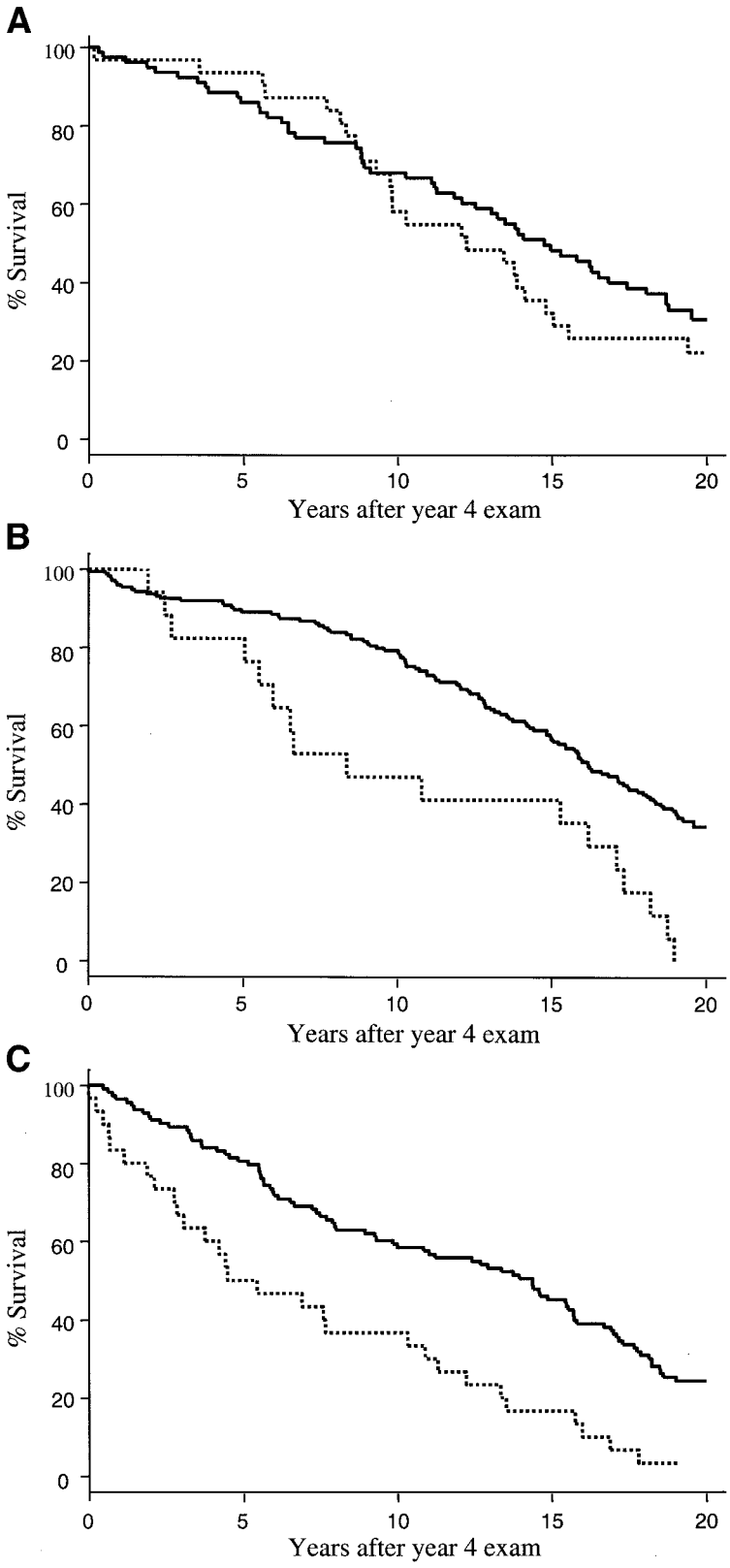

Figure 1—*Subjects were local residents registered at the Mayo Clinic (Rochester, MN) who met criteria for PAD* (A)*, diabetes* (B)*, or both conditions (C) at the baseline examination (1977–1978). For each group, those who did (- - -) and did not (—) exhibit progression of PAD at year 4 are compared for subsequent survival through 1999 with Kaplan-Meier survival curves.*

The final model included age, male sex, current smoking, history of hypertension, history of CHD, BMI, duration of diabetes, the group variables, and baseline postexercise ABI. Baseline postexercise ABI remained an independent predictor of mortality; and the risk of death for individuals with both diabetes and PAD at baseline remained greater than that for individuals with PAD alone at baseline (data not shown). The risk of death for individuals with PAD progression at 4 years was 46% greater than that for individuals who did not exhibit progression (95% CI 1.08–1.96, $P = 0.012$).

CONCLUSIONS — This prospective cohort study with >20 years of follow-up revealed marked increases in the risk of death for individuals who met criteria for either PAD or diabetes at baseline relative to that for the general population. This is consistent with a large body of evidence demonstrating that each condition is associated with substantial reductions in survival. In analyses limited to individuals with either or both conditions, we observed a significant inverse association between baseline ABI and mortality that was independent of other CHD risk factors. The latter is compatible with previous reports that individuals with low ABI (both symptomatic and asymptomatic) are at increased risk of death relative to individuals with normal ABI (8,9,11). There is less agreement across these studies regarding the independent contribution of diabetes to the risk of death. The unique estimates provided here reveal that individuals with both PAD and diabetes have a risk of death approximately twice that for individuals with PAD alone, even after adjusting for between-group differences in baseline ABI, history of heart disease, and other risk factors. In investigations of subjects, all of whom had arteriographically proven CAD, Barzilay et al. (28,29) observed that the adjusted risk of death for individuals with both lower extremity arterial disease (defined as pain in the calf muscles on ambulation that subsided with rest, self-reported diagnosis of vascular disease or surgical repair, or absent pedal pulses on examination), and self-reported diabetes was 40% greater than that for individuals with lower extremity arterial disease and no diabetes, a smaller difference than the twofold increase found here. Between-study comparisons are complicated by differences in the populations under investigation, determination of PAD and diabetes, and choice of adjusting variables.

Increasing age, diabetes, and diabetes duration are important risk factors for PAD. Because the population is aging (30), the incidence of diabetes is rising, and individuals with diabetes are living longer (31), it is likely that the burden of PAD will increase. In a "call to action," members of the Prevention of Arterothrombotic Disease Network emphasized early detection of PAD (25). The authors recognized that for any screening protocol to be clinically and cost effective, it must target individuals at high risk. This is because up to 20% of the elderly population meet criteria for PAD based on noninvasive examination, yet relatively few asymptomatic individuals develop intermittant claudication, and only a small proportion of claudicants experience disease progression (9,32). In addition, the characteristics consistently identified to date as predictive of adverse PAD outcomes are very similar to those associated with the development of PAD (11). Thus, these characteristics are of limited use in identifying, among individuals with these characteristics who screen positive for PAD, those who are at high risk of experiencing adverse outcomes.

Very few other studies that include asymptomatic individuals have afforded assessment of PAD progression as measured by change in ABI over time (24,33). To our knowledge, this is the only study to demonstrate that PAD progression, measured as rate of change in ABI, is a risk factor for mortality. Perhaps the most important study finding was that, although individuals who exhibited progression of PAD were at significantly increased risk of death compared with nonprogressors, the risk was significantly elevated only for individuals who had diabetes at baseline (either alone or with PAD). This finding emphasizes the need to identify PAD clinically and/or by vascular laboratory studies (ABI) in individuals with diabetes and highlights the importance of periodic assessment of PAD progression in individuals with diabetes.

Not surprisingly, we observed that male sex, increasing age, hypertension, and CHD contributed independently to mortality, even after adjusting for the effects of diabetes, PAD, and PAD progression. These findings suggest that detection and aggressive control of cardiovascular risk factors remain the core of management for both diabetic and nondiabetic individuals with PAD.

Interpretation of study findings is limited to the extent that the sample was not population based but rather consisted of individuals residing in the area who were registered at the Mayo Clinic, Rochester, Minnesota. Previous studies have demonstrated that, due to the unique geographic setting and the limited number of health care providers in this community, essentially all local residents are registered at the Mayo Clinic in any 5-year period (34). Subjects were also not identified from a random sample of registrants. Although the final categorization as to PAD, diabetes, or both was based on objective criteria, the list of potential subjects was drawn from individuals who had come to clinical attention for PAD and/or diabetes or who were initially selected as potential healthy control subjects. Thus, the distribution, severity, and duration of disease differed from that within the population generally (35). In addition, the study population was 98% white. Thus, the generalizability of study findings to nonwhite populations cannot be assessed. The extent to which the findings hold for ethnic minorities has important implications because these populations have both a higher prevalence of diabetes and PAD and an increased risk of adverse outcomes (4,8,36).

The determination of PAD progression was based on assessments at baseline, year 2, and year 4. Importantly, the extent to which these measures were representative of the entire follow-up period cannot be assessed. The determination of both PAD and PAD progression relied on the ratio of lower extremity to arm systolic blood pressures. In the group of 238 with diabetes only, there were four individuals with a baseline and/or subsequent ratio >1.5, which was a value 4 SD above the control mean. These values may have been falsely elevated due to sclerotic, noncompressible arteries; therefore, analyses were also performed excluding these few individuals. The results were virtually identical (data available on request).

The advantages of this study include a well-characterized sufficiently large sample, objective determination of both PAD and diabetes, serial measurements of ABI, a definition of PAD progression based on distributions for a healthy control group, and a cohort design with extensive fol-

low-up. This study reinforces the need to closely monitor PAD progression in individuals with diabetes and emphasizes the importance of diabetes prevention and management for reducing the burden of PAD.

Acknowledgments— This study was financially supported by the A.J. and Sigismunda Palumbo Charitable Foundation and the American Diabetes Association.

We thank Karen Tennison for help with manuscript preparation.

References

1. Novo S: Classification, epidemiology, risk factors, and natural history of peripheral arterial disease. *Diabetes Obes Metab* 4:S1–S6, 2002
2. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE: Peripheral arterial disease in the elderly: the Rotterdam Study. *Arterioscler Thromb Vasc Biol* 18:185–192, 1998
3. Stoffers HEJH, Rinkens PELM, Kester ADM, Kaiser V, Knottnerus JA: The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol* 25:282–290, 1996
4. Cardiovascular Health Study (CHS) Collaborative Research Group: Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. *Circulation* 88:837–845, 1993
5. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286:1317–1324, 2001
6. McDermott MM, Kerwin DR, Liu K, Martin GJ, O'Brien E, Kaplan H, Greenland P: Prevalence and significance of unrecognized lower extremity peripheral arterial disease in general medicine practice. *J Gen Intern Med* 16:384–390, 2001
7. McDermott MM, Ferrucci L, Simonsick EM, Balfour J, Fried L, Ling S, Gibson D, Guralnik JM: The ankle brachial index and change in lower extremity functioning over time: the Women's Health and Aging Study. *J Am Geriatr Soc* 50:238–246, 2002
8. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D: Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 19:538–545, 1999
9. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, Ruckley CV: Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 25:1172–1181, 1996
10. Phillips DE, Mann JI: Diabetes-inpatient utilization, costs and data validity: Dunedin 1985–1989. *N Z Med J* 105:313–315, 1992
11. Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA: Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol* 153:666–672, 2001
12. Barzilay JI, Spiekerman CF, Kuller LH, Burke GL, Bittner V, Gottdiener JS, Brancati FJ, Orchard TJ, O'Leary DH: Prevalence of clinical and isolated sub-clinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care* 24:1233–1239, 2001
13. MacGregor AS, Price JF, Hau CM, Lee AJ, Carson MN, Fowkes FG: Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease: the Edinburgh Artery Study. *Diabetes Care* 22:453–458, 1999
14. Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF: Intermittent claudication: a risk profile from the Framingham Heart Study. *Circulation* 96:44–49, 1997
15. Uusitupa MI, Niskanen LK, Siitonen O, Voutillainen E, Pyorala K: Five-year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin dependent diabetic and non-diabetic subjects. *Circulation* 82:27–36, 1990
16. Zimmerman BR, Palumbo PJ, O'Fallon WM, Osmundson PJ, Kazmier FJ: A prospective study of peripheral occlusive arterial disease in diabetes. I. Clinical characteristics of the subjects. *Mayo Clin Proc* 56:217–222, 1981
17. Osmundson PJ, Chesebro JH, O'Fallon WM, Zimmerman BR, Kazmier FJ, Palumbo PJ: A prospective study of peripheral occlusive arterial disease in diabetes. II. Vascular laboratory assessment. *Mayo Clin Proc* 56:223–232, 1981
18. Zimmerman BR, Palumbo PJ, O'Fallon WM, Ellefson RD, Osmundson PJ, Kazmier FJ: A prospective study of peripheral occlusive arterial disease in diabetes. III. Initial lipid and lipoprotein findings. *Mayo Clin Proc* 56:233–242, 1981
19. Kazmier FJ, Bowie EJW, O'Fallon WM, Zimmerman JBR, Osmundson PJ, Palumbo PJ: A prospective study of peripheral occlusive arterial disease in diabetes. IV. Platelet and plasma functions. *Mayo Clin Proc* 56:243–253, 1981
20. Osmundson PJ, O'Fallon WM, Zimmerman BR, Kazmier FJ, Langworthy AL, Palumbo PJ: Course of peripheral occlusive arterial disease in diabetes: vascular laboratory assessment. *Diabetes Care* 13:143–152, 1990
21. Palumbo PJ, O'Fallon M, Osmundson PJ, Zimmerman BR, Langworthy AL, Kazmier FJ: Progression of peripheral occlusive arterial disease in diabetes mellitus. *Arch Intern Med* 151:717–721, 1991
22. Nicoloff AD, Taylor LM Jr, Sexton GJ, Schuff RA, Edwards JM, Yeager RA, Landry GJ, Moneta GL, Porter JM: Homocysteine and progression of atherosclerosis study investigators: relationship between site of initial symptoms and subsequent progression of disease in a prospective study of atherosclerosis progression in patients receiving long-term treatment for symptomatic peripheral arterial disease. *J Vasc Surg* 35:38–46, 2002
23. Aquino R, Johnnides C, Makaroun M, Whittle JC, Muluk VS, Kelley ME, Muluk SC: Natural history of claudication: long-term serial follow-up study of 1244 claudicants. *J Vasc Surg* 34:962–970, 2001
24. Smith I, Franks PJ, Greenhalgh RM, Poulter NR, Powell JT: The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. *Eur J Vasc Endovasc Surg* 11:402–408, 1996
25. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton D, Gavin JR, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA: Critical issues in peripheral arterial disease detection and management. *Arch Intern Med* 163:884–892, 2003
26. Vogt MT, Wolfson SK, Kuller LH: Lower extremity arterial disease and the aging process: a review. *J Clin Epidemiol* 45:529–542, 1992
27. Melton LJ III: The threat to medical records research. *N Engl J Med* 337:1466–1470, 1997
28. Barzilay JI, Kronmal RA, Bittner V, Eaker E, Evans C, Foster ED: Coronary artery disease in diabetic patients with lower extremity arterial disease: disease characteristics and survival: a report from the Coronary Artery Surgery Study (CASS) Registry. *Diabetes Care* 20:1381–1387, 1997
29. Barzilay JI, Kronmal RA, Bittner V, Eaker E, Foster ED: Coronary artery disease in diabetic and nondiabetic patients with lower extremity arterial disease: a report from the Coronary Artery Surgery Study Registry. *Am Heart J* 135:1055–1062, 1998

30. Arias E: United States life tables, 2000. *Natl Vital Stat Rep* 51:1–38, 2002
31. Leibson CL, Obrien PC, Atkinson E, Palumbo PJ, Melton LJ: Relative contributions of incidence and survival to increasing prevalence of adult-onset diabetes mellitus: a population-based study. *Am J Epidemiol* 146:12–22, 1997
32. Dormandy J, Heeck L, Vig S: The natural history of claudication: risk to life and limb. *Semin Vasc Surg* 12:123–137, 1999
33. Whiteman MC, Deary IJ, Fowkes FG: Personality and social predictors of atherosclerotic progression: Edinburgh Artery Study. *Psychosom Med* 62:703–714, 2000
34. Melton LJ III: History of the Rochester Epidemiology Project. *Mayo Clin Proc* 71:266–274, 1996
35. Ogren M, Hedblad B, Janzon L: Biased risk factor assessment in prospective studies of peripheral arterial disease due to change in exposure and selective mortality of high-risk individuals. *J Cardiovasc Risk* 3:523–528, 1996
36. Zheng ZJ, Sharrett AR, Chambless Le, Rosamond WD, Nieto FJ, Sheps DS, Dobs A, Evans GW, Heiss G: Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* 131:115–125, 1997