Association of Asymptomatic Peripheral Arterial Disease With Vascular Events in Patients With Stroke or Transient Ischemic Attack

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Background and Purpose—Patients with stroke and patients with transient ischemic attack (TIA) are at high risk for vascular events and may not exhibit the signs and symptoms of peripheral arterial disease (PAD). We investigated if asymptomatic PAD detected by ankle brachial index <0.9 is independently associated with recurrent vascular events in patients with stroke or TIA.

Methods—In this prospective longitudinal hospital-based cohort study, asymptomatic PAD was detected by ankle brachial index measurement in consecutive patients with stroke and patients with TIA. They were assessed for stroke risk factors, ankle brachial index measurement, and laboratory parameters known to be associated with stroke risk. These patients were followed for composite vascular events, including stroke, TIA, myocardial infarction, and vascular death.

Results—In a 1-year period, 102 patients were evaluated, of whom 26% had asymptomatic PAD. All patients were followed for a median period of 2.1 years from the index stroke/TIA (range, 1.0 to 2.7 years) for vascular events. Kaplan–Meier curve showed fewer patients with asymptomatic PAD remained free of composite vascular events (48% compared with 84% in the no-PAD group; log rank, P=0.0001). Asymptomatic PAD was significantly associated with composite vascular events before (hazard ratio, 4.2; 95% CI, 1.9 to 9.3; P=0.0003) and after adjustment for confounders (hazard ratio, from Model 1, 2.8; 95% CI, 1.1 to 7.2; P=0.03 and Model 2, 3.4; 95% CI, 1.4 to 8.2, P=0.006). Asymptomatic PAD was also significantly associated with stroke before (hazard ratio, 6.5; 95% CI, 2.1 to 19.9; P=0.001) and after adjustment for confounders (hazard ratio from Model 1, 4.8; 95% CI, 1.5 to 15.3; P=0.009 and Model 2, 5.2; 95% CI, 1.5 to 17.6; P=0.008).

Conclusions—In patients with stroke or TIA, asymptomatic PAD is independently associated with recurrent vascular events and stroke. (Stroke. 2009;40:00-00.)

Key Words: claudication • peripheral vascular disease • propensity score • stroke

Patients with cerebrovascular disease are at substantially higher risk of mortality than the general population, primarily from cardiovascular disease.1 Peripheral arterial disease (PAD) is an atherosclerotic syndrome in which the lumen of the arteries in the extremities becomes progressively obstructed by plaque. Recent epidemiological studies estimate a prevalence of PAD of 11% to 16% in the population aged ≥55–4 and a prevalence as high as 20% to 30% in specific high-risk populations.3–7 Several prospective and cross-sectional studies have shown that PAD is a marker for arterial disease in other vascular beds8,9 and is associated with a 6-fold increase in fatal and nonfatal myocardial infarction10 and a 2- to 3-fold increase in risk of incident ischemic stroke.11 In addition, the presence of PAD is a strong predictor of overall mortality.12 Hence, detection of PAD may be essential to screen patients with cerebrovascular disease who may be at a very high risk of subsequent cardiovascular morbidity and mortality.

Intermittent claudication is the most common manifestation of symptomatic PAD.13 The Framingham Heart Study initially described the association between intermittent claudication with coronary heart disease, stroke, and death.14 However, up to one third of patients did not even alert a physician to their leg symptoms,15 and fewer than half of general medicine physicians reported routinely obtaining a history of claudication.16 The ankle brachial index (ABI) is an objective noninvasive method used to assess the lower extremity arterial system and is considered to be the best
screening test for PAD. However, the US Preventive Services Task Force currently recommends against PAD screening by ABI testing in the general population due to low prevalence and harm posed by false-positive results. Despite the recommendation, the PAD management guidelines suggest screening ABIs in high-risk patients in the primary care setting. Because major barriers currently prevent widespread implementation of this practice, it is of utmost importance to determine if patients with stroke and patients with transient ischemic attack (TIA) constitute a high-risk patient group that may benefit from screening for PAD using ABI measurement. We undertook this study to investigate if asymptomatic PAD detected by ABI is independently associated with recurrent vascular events in a high-risk population of patients with stroke or TIA.

Materials and Methods
In this prospective longitudinal hospital-based cohort study, consecutive patients admitted ≤1 month from their stroke/TIA were screened for eligibility. Eligible patients consented to a protocol for ABI measurement and phone follow-up approved by the Institutional Review Board. All patients had CT/MRI of the brain to confirm stroke and had stroke risk factors assessed. Complete blood count, fasting lipid profile, high-sensitivity C-reactive protein, and homocysteine level were measured as part of their stroke risk assessment. Exclusion criteria were: age <18 years, intracerebral hemorrhage, subarachnoid hemorrhage, coma and conditions limiting life expectancy to <12 months (example end-stage cancer), and symptomatic PAD as noted by the Rose PAD questionnaire.

Baseline Measurements
Stroke risk factors, stroke, and TIA were defined based on previously described criteria. Stroke risk factors and laboratory parameters were assessed at the time of initial qualifying event (stroke or TIA). Each participant also underwent a bilateral carotid duplex ultrasound to evaluate for carotid stenosis as a part of their standard diagnostic workup. Carotid stenosis (≥50%) was graded based on recommendations from The Society of Radiologists in Ultrasound Consensus Conference. ABI measurement was calculated using standard method. Systolic pressure was detected with a handheld 5-MHz Bidirectional Doppler probe (Hokanson MD6 Doppler with MD6VR Chart Recorder; Bellevue, Wash). Pressures in each leg were measured and ABI calculated separately for each leg. An ABI <0.90 in either leg was considered as evidence of PAD, and an ABI ≥0.90 was considered as normal. Elevated ABI (≥1.40) suggestive of poorly compressible leg arteries was excluded from the analysis.

Follow-Up
Follow-up phone calls were conducted at 6-month intervals from study inclusion for 2.5 years. During the follow-up phone calls, patients were asked about hospitalization occurring since the previous phone call. Patients were asked about their health and the occurrence of recurrent myocardial infarction or stroke. For patients with outcome events, the clinical records were collected for verification and characterization of outcome event. Date and cause of death were recorded for patients who died during the study.

Outcome Events
The primary outcomes of the study were nonfatal acute myocardial infarction, nonfatal ischemic stroke, TIA, and death from any cardiovascular cause during a study period of at least 1 year from the index event. Nonfatal acute myocardial infarction was defined as the presence of symptoms consistent with the World Health Organization criteria associated with abnormal levels of necrosis markers (including troponin) or diagnostic electrocardiographic changes. Ischemic stroke was defined as the presence of a new focal neurological deficit lasting for ≥24 hours. MRI/CT was required to confirm stroke. TIA was defined as the presence of a new focal neurological deficit lasting <24 hours. Death from myocardial infarction or stroke, or sudden otherwise unexplained death, was considered to be a vascular death. All outcome events and deaths were reviewed by a physician who was unaware of the results of ABI measurements.

Statistical Analysis
Statistical analysis was performed using SAS Version 9.1.3 (SAS Institute, Cary, NC). Intergroup difference was assessed by the χ² test for categorical variables, t test for normally distributed continuous variables, and log-transformed values for continuous variable that were not normally distributed. Initially, the cumulative event-free rates for the time to composite vascular events (myocardial infarction, ischemic stroke, TIA, and vascular death) and time to recurrent cerebrovascular event (ischemic stroke) were estimated by Kaplan–Meier product limit method and the 2 groups with and without asymptomatic PAD were compared by the log rank test. Subsequently, Cox proportional hazards multivariable analysis was used to identify risk factors for composite vascular events and stroke after adjusting for significant confounders using methods discussed subsequently. Asymptomatic PAD was defined by ABI <0.90 with no clinical symptoms. Covariates assessed for confounding included stroke risk factors and laboratory parameters known to be associated with stroke risk (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, leukocyte count, and homocysteine levels). Of these, in Model 1, only the covariates that were noted to change the effect measure (hazards ratio) by ≥5% were selected as confounders and used to generate propensity score. In Model 2, confounders were selected based on association with PAD (P<0.20; Tables 1 and 2). Propensity score was used because the number of confounders was large in relation to the composite vascular outcomes. To generate propensity scores, a logistic regression model was first created in which the confounders were the independent variables and asymptomatic PAD was the dependent variable. Propensity scores were calculated for each study subject by applying the subject’s values to the logistic model. The propensity score reflected each subject’s conditional probability of being exposed (PAD based on ABI <0.90) given the confounding variables. The c statistics for the propensity score model was 0.71 (Model 1) and 0.74 (Model 2), indicating an acceptable discrimination between the PAD and the no-PAD group. Cox proportional hazards models were used to examine the association between asymptomatic PAD and time to composite vascular events and stroke adjusting for propensity score generated individually as a continuous variable in lieu of adjusting for the multiple confounders. The assumption of proportional hazards and a linear association between propensity scores and evalu-
ated outcomes were ascertained. The results were expressed as adjusted hazard ratios (HRs) and corresponding 95% CIs. Statistical significance was considered to be a probability value $<$ 0.05.

**Results**

Of the 117 consecutive patients assessed, 106 met the eligibility criteria, of whom 2 refused to participate. Among the 11 that were excluded, 8 had symptomatic PAD; 2 had intracerebral hemorrhage, and one had a terminal illness. Of the 104 patients who consented to a protocol mandated ABI measurement, in one patient the ABI was elevated ($\geq 1.40$) and another patient was lost to follow-up. All the remaining 102 patients had ABI measured $\leq 7$ days of their index event. Of these, 26 (26%) had evidence of asymptomatic PAD (ABI $< 0.90$). Although most characteristics between patients with and without PAD were not statistically different, the 26 patients who did exhibit asymptomatic PAD were approximately 4 years older (67 ± 12 versus 63 ± 15 years, $P = 0.17$), more likely to be black (39% versus 20%, $P = 0.06$), hypertensive (89% versus 71%, $P = 0.08$), have hypercholesterolemia (73% versus 49%, $P = 0.03$), and have $\geq 50$% carotid stenosis (39% versus 16%, $P = 0.02$) when compared with the 76 patients without asymptomatic PAD (Table 1). There were no significant differences in laboratory parameters, including complete blood count, fasting lipid profile, plasma homocysteine, and high-sensitivity C-reactive protein between the asymptomatic PAD and the no-PAD group (Table 2).

Over a median of 2.1 years from the ABI measurement (range, 1.0 to 2.7 years), 25 (25%) patients exhibited composite vascular events, including 13 strokes, 3 TIAs, 4 myocardial infarctions, and 5 deaths (one patient had a myocardial infarction and a TIA on the same day and is counted as an myocardial infarction). These vascular events were identified during 6-monthly phone follow-up visits and verified by reviewing medical records. Only one case was lost to follow-up and not included in the analysis. Among the 76 patients who did not exhibit asymptomatic PAD, 12 (16%) had composite vascular events, including 5 strokes, 3 TIAs, 3 myocardial infarctions, and one death, over the same period of follow-up. Among the 26 patients who did exhibit asymptomatic PAD, 13 (50%) had composite vascular events, including 8 strokes, no TIA, one myocardial infarction, and 4 deaths, over the same period of follow-up. There was a significant difference in cumulative composite event-free survival between the asymptomatic PAD group (mean survival, 1.6 years; 95% CI, 1.2 to 1.9 years) and no-PAD group (mean survival, 2.3 years; 95% CI, 2.1 to 2.5 years). The two distributions were significantly different according to log rank testing ($P = 0.0001$) and are depicted in the Kaplan–Meier survival curve (Figure 1). There was also a significant difference in cumulative stroke-free survival between the asymptomatic PAD group (mean survival, 1.9 years; 95% CI, 1.5 to 2.2 years) and no-PAD group (mean survival, 2.5 years; 95% CI, 2.4 to 2.6 years). The distributions were significantly different according to log rank testing ($P = 0.0002$) and are depicted in the Kaplan–Meier survival curve (Figure 2).

Covariates assessed for confounding included clinical characteristics listed in Table 1, selected laboratory parameters (Table 2) known to be associated with stroke risk (total leukocyte count, high-sensitivity C-reactive protein, fasting lipid profile, and plasma homocysteine levels). Of these, black race, smoking, coronary artery disease, carotid stenosis, hypercholesterolemia, and log-transformed serum triglycerides were noted to change the association between asymptomatic PAD and composite vascular event (HR) by $\geq 5$%. These covariates were used to generate the propensity score in Model 1 for composite vascular events. Multivariable Cox

| Table 2. Baseline Laboratory Characteristics of Patients With Stroke or TIA With Asymptomatic PAD (ABI <0.90) and No PAD (ABI ≥0.90) |
|-----------------|-----------------|-----------------|
| Laboratory Parameters | No PAD (N=76) | Asymptomatic PAD (N=26) | P Value |
| Hemoglobin, g/dL | 13.7±1.8 | 13.5±2.3 | 0.64 |
| Hematocrit, % | 39.6±4.7 | 39.4±6.0 | 0.85 |
| Total white blood cell count, 10^9/L | 9.5±3.9 | 8.4±3.3 | 0.20 |
| Neutrophil count, 10^9/L | 5.9±2.4 | 5.7±2.2 | 0.73 |
| Lymphocyte count, 10^9/L | 1.9±0.8 | 1.7±1.0 | 0.48 |
| Monocyte count, 10^9/L | 0.4±0.24 | 0.4±0.15 | 0.70 |
| Eosinophil count, 10^9/L | 0.2±0.12 | 0.2±0.17 | 0.21 |
| Basophil count, 10^9/L | 0.05±0.05 | 0.05±0.05 | 0.73 |
| Platelet count, 10^9/L | 252±85 | 255±69 | 0.87 |
| Total cholesterol, mg/dL | 183±41 | 185±51 | 0.87 |
| Low-density lipoprotein cholesterol, mg/dL | 106±30 | 104±45 | 0.82 |
| High-density lipoprotein cholesterol, mg/dL | 50±13 | 50±15 | 0.99 |
| Triglycerides, mg/dL* | 118 (73, 197) | 137 (83, 200) | 0.20 |
| High-sensitivity C-reactive protein, mg/L* | 4.6 (1.25, 13.5) | 8.6 (4.0, 12.8) | 0.08 |
| Homocysteine, μg/mL* | 8.4 (6.7, 10.8) | 8.7 (7.3, 11.6) | 0.13 |

All data are depicted as mean±SD.

*Parameters not normally distributed, hence reported as median (interquartile range) and P value derived from t test performed on mean of log-transformed values.
regression showed that asymptomatic PAD was associated with composite vascular events (adjusted HR, 2.8; 95% CI, 1.1 to 7.2; \( P = 0.03 \)) after adjustment for propensity score (Table 3). Black race, hypertension, coronary artery disease, hypercholesterolemia, log-transformed serum triglycerides, and high-sensitivity C-reactive protein were noted to change the association between asymptomatic PAD and stroke (HR) by \( \geq 5\% \). These covariates were used to generate the propensity score in Model 1 for stroke. Multivariable Cox regression showed that asymptomatic PAD was associated with stroke (adjusted HR, 4.8; 95% CI, 1.5 to 15.3; \( P = 0.009 \)) after adjustment for propensity score (Table 3). In Model 2, confounders were selected based on covariates that had any potential association with PAD (\( P < 0.20 \); Tables 1 and 2). The confounders, thus selected, included age, black race, hypertension, smoker, coronary stenosis, hypercholesterolemia, serum homocysteine, and high-sensitivity C-reactive protein levels and were combined into a single propensity score. Multivariable Cox regression showed that asymptomatic PAD was associated with composite vascular events (adjusted HR, 3.4; 95% CI, 1.4 to 8.2; \( P = 0.006 \)) and stroke (adjusted HR, 5.2; 95% CI, 1.5 to 17.6; \( P = 0.008 \)) after adjustment for the propensity score (Table 3).

**Discussion**

Our findings indicate that among patients with stroke and those with TIA, 26% are found to have asymptomatic PAD as detected by ABI measurement. The prevalence noted was lower than prior studies that found abnormal ABI in 33.5% to 66.7% of patients with cerebrovascular disease. However, the earlier studies did not exclude patients with symptomatic PAD and hence provides estimates of PAD, both symptomatic and asymptomatic. 26, 27 In our study, including the 8 patients we excluded from enrollment because of symptoms, much higher than that noted in our study. 27 This may be attributed to selection of sicker patients with stroke presenting to the stroke units. Both studies have reported a high rate of recurrent vascular events in patients with abnormal ABI. Our study, although evaluating fewer patients presenting to a single center, has the advantage of a more comprehensive assessment of stroke risk factors such as cardiac stenosis, atrial fibrillation, and high-sensitivity C-reactive protein, which potentially could confound the PAD–vascular event

| Table 3. Relationships Between a Low ABI and Adjusted* Composite Vascular Events (Ischemic Stroke, TIA, Myocardial Infarction, and Death) and Adjusted† Ischemic Stroke Adjusted for Covariates (Models 1 and 2) |
|---------------------------------|---------------------------------|-----------------|
| Outcome                        | Composite Event† (Stroke, TIA, Myocardial Infarction, Death) | Stroke†          |
| Unadjusted                     | 4.21 (1.92–9.26)               | 6.49 (2.16–19.88) |
| Model 1                        | 2.82 (1.10–7.23)               | 4.75 (1.47–15.32) |
| Model 2                        | 3.43 (1.43–8.21)               | 5.20 (1.54–17.60) |

Results of univariate unadjusted Cox proportional hazards regression analysis for composite† of stroke, TIA, myocardial infarction, and death and stroke† are depicted in the first row. Model 1: Confounders selected based on covariates that were noted to change the HR by \( \geq 5\% \): results of multivariable Cox proportional hazards regression analysis for composite events† and stroke† were adjusted for age, black race, hypertension, smoker, coronary stenosis, hypercholesterolemia, serum homocysteine, and high-sensitivity C-reactive protein levels combined into a single propensity score.

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association. To our knowledge, this is one of the first studies to report an independent positive, adjusted association between asymptomatic PAD and composite vascular events, including stroke, TIA, myocardial infarction, and death among patients with stroke and those with TIA. The Kaplan–Meier plots (Figure 1) suggest significant separation of survival curves in the asymptomatic PAD and no-PAD groups according to ABI measurement. Observer bias is an unlikely explanation for the association, because the observers recording the vascular event were masked to the patients’ clinical information and/or outcome. The association between abnormal ABI and adverse outcome may be explained by an overall greater atherosclerotic burden, greater inflammation, inadequate management of risk factors, or all of these factors together.

Besides ABI, several new markers of primary and secondary cardiovascular risk exist or have recently been proposed.23 Among these, C-reactive protein seems to be the most interesting candidate for secondary risk stratification for adverse outcome in patients with coronary syndromes and cerebrovascular disease, although recent findings bring into question its role as a powerful predictor of risk.28,29 ABI and C-reactive protein are expressions of different processes in terms of pathophysiology, ABI being a marker of widespread atherosclerosis30 and C-reactive protein indicating plaque destabilization.30 The two markers could provide additional information when measured in the same patients.31 Hence, it is not unanticipated that ABI was found to improve the accuracy of cardiovascular risk prediction beyond the Framingham risk score.32 We found that ABI was associated with adverse outcome independent of C-reactive protein, homocysteine, and lipids. Because low ABI was a marker of recurrent vascular event, it could be potentially used to select patients with stroke with a higher risk of recurrence achieving the necessary number of end point events with smaller sample size or with a shorter follow-up period.

In Model 1, we used a liberal definition of confounders, that is, clinically relevant covariates that were noted to change the effect measure (HR) by ≥5%, and we identified several confounders (Table 3). In Model 2, we used a more conservative definition of confounders, covariates that showed even a marginally significant association with exposure variable \( P < 0.20 \). The difference in some of the confounders elected to generate propensity score in each of these models may be explained by the nature of the covariate definition. As an example, coronary artery disease (CAD) selected as a confounder in Model 1, but not Model 2, is defined as those with symptomatic CAD, meaning the asymptomatic CAD may be misclassified as no CAD. An association between asymptomatic CAD and PAD has been described.33 Similarly, those without PAD, although deemed to have lower triglyceride and high-sensitivity C-reactive protein levels, these levels are still higher than those recorded in healthy individuals without vascular disease. The similarity of a significant association of symptomatic PAD with recurrent vascular events and stroke, in both models, is an indication of the robustness of the associations.

Our study, like other observational studies, has some limitations such as the nonstandardized treatment of patients. However, it should be mentioned that, consistent with the current guidelines, all of the patients were using an antiplatelet agent, oral anticoagulation, one or more antihypertensive agents, and/or lipid-lowering agents at the time of the ABI measurement. The somewhat lower than expected incidence of fatal and nonfatal events in the entire group and the lack of difference in the markers (C-reactive protein, lipids, and homocysteine) between asymptomatic PAD and no-PAD groups (Table 2) could have been a consequence of these therapeutic approaches. Although the HRs are substantial and significant (Table 3), the CIs are wide and the relatively small sample size means that these results should be interpreted with some caution. However, the study also has strengths that merit mentioning. We included patients with stroke and those with TIA within a well-defined clinical setting of a standardized stroke workup. All the clinical events were independently adjudicated by a member of the study team who was unaware of the ABI results. Moreover, mortality accounted for a significant proportion of outcome events in the study.

In conclusion, our study showed that an abnormal ABI is prevalent in approximately one fourth of the patients with cerebrovascular disease and identifies a population at high risk of fatal and nonfatal cardiovascular events over a median of 2 years. ABI measurement may be appropriate for screening patients with stroke and those with TIA who may be at high risk for vascular events. Further studies are needed to determine if screened high-risk patients may benefit from aggressive monitoring, risk factor modifications as well as possibly selecting patients for a more effective clinical trial design.

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