From the Western Vascular Society

Risk factors for premature peripheral vascular disease: Results for the National Health and Nutritional Survey, 1999-2002

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Purpose: Premature peripheral vascular disease (PVD), occurring <60 years of age, is associated with significant cardiovascular morbidity, limb loss, and death. We hypothesized that different risk factors predict the development of PVD in patients <60 years than in patients ≥60 years.

Methods: To address this question, we conducted a population-based observational study using the National Health and Nutritional Survey (NHANES) data set, which represents the noninstitutionalized civilian population in the United States. From 1999 to 2002, 5083 participants were analyzed as part of the NHANES survey. PVD status was defined by an ankle-brachial index (ABI) of <0.9. Putative risk factors for the development of PVD were collected by physical examination, interview, and laboratory testing. Univariate and multivariate logistic regression analyses were used to evaluate interactions between age strata and the development of PVD.

Results: Premature PVD was found in 2.1% ± 0.2% of the population <60 years, and PVD was found in 12.0% ± 0.8% of the population ≥60 years. This corresponds to approximately 1.44 million people with premature PVD. Multivariate analysis determined coronary artery disease (odds ratio [OR] 2.90 vs 1.26, P = .083) and elevated serum fibrinogen (OR 1.07 vs 1.03, P = .034) were stronger predictors of PVD in subjects <60 years than in older subjects. Chronic renal insufficiency (OR 1.02 vs 1.16, P = .006) was more highly predictive of PVD in subjects >60 years. Other significant predictors, irrespective of age, in the multivariate model included hypertension (OR 1.99, P < .001), smoking (OR 2.22, P < .001), and serum homocysteine (OR 1.27, P = .067).

Conclusions: Clinicians should be aware of the high risk of developing premature PVD in patients <60 years with coexisting coronary artery disease or elevated plasma fibrinogen. Routine screening by ABI measurements in high-risk patients would enhance the detection of subclinical premature PVD and allow for secondary intervention. (J Vasc Surg 2006;44:319-25.)

Premature peripheral vascular disease (PVD) <60 years of age is associated with an extremely poor prognosis.[1] Affected patients have high rates of cardiovascular morbidity, limb loss, and death.[2-4] This early onset of PVD presumably represents an accelerated development of atherosclerosis in these patients. Etiologic factors responsible for the development of atherosclerosis may be more readily identified in this younger patient population.

Previous studies have underscored the progressive nature of PVD in younger patients. Among young, white men (≤45 years) referred to a Veterans Administration vascular surgery service, 40% of patients required multiple surgical interventions or amputation to treat their PVD.[2] Additionally, 30% of patients had progression of their coronary artery disease (CAD), and 17% died ≤5 years of follow-up. In a related study, an incredibly high prevalence of asymptomatic CAD (71%) was detected by coronary angiography or noninvasive testing.[5] Presumably, the development of

atherosclerotic disease in this population affected both the coronary and peripheral vascular beds at an accelerated rate.

These same investigators also attempted to identify putative risk factors associated with premature peripheral vascular disease. They found a strong association with smoking and family history[6] and a serologic association with elevated serum lipoprotein (a).[7] These studies are compelling, but they suffer from their small sample size and lack generalizability owing to their highly selected patient populations.

We have conducted a population-based study to examine risk factors for the development of premature PVD. For the purpose of this study, we defined premature PVD as occurring in the population <60 years of age. We hypothesized that different risk factors identify premature PVD in patients <60 years of age than in older patients. Data from the National Health and Nutritional Examination Survey for years 1999-2002 (NHANES 2000) was used to determine the prevalence of premature PVD in the US population. In addition, presumptive risk factors were used as covariates to model the occurrence of PVD. Interactions between these risk factors and age (<60 years vs ≥60 years) were used to identify strong predictors of premature PVD.

METHODS

Data sources. NHANES conducts national, cross-sectional surveys of the noninstitutionalized US popula-

tion. Sampling is performed using a complex, stratified, multistage probability-cluster design. Data collected using this method are representative of the overall US population, allowing a population-based study design.

NHANES incorporates data collected from interview and examination as well as laboratory data. Beginning in 1999, NHANES has provided a detailed lower extremity examination, including the measurement of ankle-brachial indices (ABI), a noninvasive measurement of lower extremity atherosclerosis. The prevalence of PVD is determined using the ABI measurement and is correlated with other collected variables on the sampled population.

Data for this study included the years 1999-2000 and 2001-2002 (NHANES 2000). Files were obtained from the NHANES Website (http://www.cdc.gov/nchs/nhanes.htm) and were merged to create a single data set.

ABI measurements. Details of the ABI measurement procedure can be found on the NHANES Website. All study participants ≥40 years were invited to participate in the lower extremity examination. Exclusion criteria included people weighing ≥400 pounds or with bilateral amputation. Other reasons for nonparticipation in the lower extremity exam included (1) casts, ulcers, dressings or other conditions of the participant interfered with the testing, (2) participant could not understand the test instructions, (3) participant became ill and the test could not be performed, (4) an equipment failure occurred, (5) the participant refused, (6) the participant came late or left early from the mobile examination center (MEC) and the lower extremity disease (LED) exam could not be performed, or (7) some other reason.

Supine systolic pressure was measured two times in the arm (brachial artery) and both ankles (posterior tibial arteries). The ABI was calculated by dividing the systolic blood pressure at the ankle by the mean systolic blood pressure in the arm. The higher of the two measurements was used as the ABI measurement in this study. Peripheral vascular disease (PVD) was then defined as an ABI <0.9. This definition conforms to accepted standards of reporting for peripheral vascular disease.[8]

Risk factors. Premature atherosclerotic lesions have been observed in children and young adults.[9] The presence of premature atherosclerosis may be differentially associated with established PVD risk factors. The established PVD risk factors we considered included current smoking, body mass index, history of CAD, self-reported diabetes, hypertension, cholesterol, C-reactive protein, homocysteine, and kidney function. All models controlled for race/ethnicity as a five-level categoric variable, conforming to revised National Institutes of Health reporting standards. For the purpose of reporting, race was defined as non-Hispanic black vs all other. Hypertension status was defined as history of hypertension by self-report or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg on physical examination. CAD status was defined as self-reported history of CAD, angina, or stroke. Respondents not asked these questions in 1999-2000 were kept as a separate category. The Cockroft-Gault formula was used

to calculate creatinine clearance standardized to body surface area. Subjects were considered to have renal insufficiency if their creatinine clearance was <60 mL/(min · 1.73 m²).

Statistical analysis. All statistical analyses used the *svy* functions in STATA 8.2 (StataCorp, College Station, Texas). These functions incorporate NHANES survey weights, which reflect differential probability of selection resulting from over-sampling of certain subgroups and are adjusted for nonresponse. In addition, the *svy* functions account for the stratification and clustering of observations resulting from the complex NHANES sampling design, ensuring correct estimation of standard errors, confidence intervals, and *P* values.

In preliminary analysis, we compared PVD risk factors by age category (<60 vs ≥60), using F tests for categoric variables, and *svy* linear regression models for continuous measures. Both methods take account of weighting, stratification, and clustering.

Differential associations between risk factors and prevalent PVD by age category were first explored by using a Wald test for interaction between the risk factor and age category in unadjusted logistic regression models. If the interaction was significant at $P < .1$, separate indicators for this risk factor were incorporated into the multivariate model for both the older and younger age categories. Risk factors in which no interaction with age was seen in the unadjusted model were assumed to have comparable effects in both age strata and were included in the multivariate model in their simplified form.

In the multivariate analysis, an initial regression model was estimated including age, race/ethnicity, all risk factors identified a priori, and the interactions identified in unadjusted analysis. Backwards selection was then used to eliminate predictors and interactions with age with $P > .1$ after adjustment.

In model checking, the linearity of the associations between continuous predictors and PVD were examined using piecewise linear splines. No departures from linearity significant at $P < .1$ were found. We also assessed heterogeneity of risk factor effects by gender, and by age and gender jointly, and no important additional interactions were found.

RESULTS

Demographics. Results of the population characteristics of the United States are summarized in Table I. Comparisons are made between members of the population aged <60 years and ≥60 years. The younger population had a higher percentage of men and blacks. Obesity, as measured by BMI, was roughly equivalent in the two age categories.

Premature PVD was found in 2.1% ± 0.3% of the population <60 years, and PVD was found in 12.0% ± 0.8% of the population ≥60 years. This corresponds to approximately 1.44 million people with premature PVD. On average, people <60 years were less likely to have major comorbid conditions, including hypertension, CAD, dia-

Table I. Population characteristics by age <60 or ≥60 years from NHANES, 1999-2002

Characteristic	Age <60 (n = 2498)	Age ≥60 (n = 2585)	P
Mean age, y	48.6 ± 0.2	70.3 ± 0.2	<0.001
Female (%)	50.3 ± 1.0	55.0 ± 0.8	0.002
Black (%)	9.9 ± 1.2	7.6 ± 1.2	0.007
Body mass index	28.2 ± 0.2	28.0 ± 0.1	0.050
Comorbid conditions (%)			
Peripheral vascular disease	2.1 ± 0.2	12.0 ± 0.8	<0.001
Hypertension	29.8 ± 1.4	65.1 ± 1.1	<0.001
Coronary artery disease	5.1 ± 0.7	17.9 ± 1.2	<0.001
Smoking	24.7 ± 1.3	12.7 ± 0.9	<0.001
Diabetes	6.3 ± 0.6	13.5 ± 0.6.	<0.001
Chronic renal insufficiency	10.2 ± 0.9	25.3 ± 1.1	<0.001
Laboratory values (mg/dL)			
Cholesterol	211.5 ± 1.5	212.8 ± 1.0	0.369
Homocysteine	8.4 ± 0.1	10.0 ± 0.1	<0.001
Fibrinogen	351.5 ± 3.4	386.8 ± 3.1	<0.001
Creatinine	0.82 ± 0.01	0.91 ± .01	<0.001
C-reactive protein	0.41 ± 0.02	0.51 ± .02	0.002

NHANES, National Health and Nutritional Survey; *n,* sample number of NHANES participants.

Data are mean or percent ± SE.

P values are χ^2 test for categoric variables and t test for continuous variables. All values were calculated with the examination weight variable (WTMEC4YR).

Table II. Bivariate logistic regression analyses adjusted for age (ABI <0.9)

Risk factor/predictor	OR of PVD	CI	P
Smoking	2.60	1.98-3.41	<.001
Hypertension	2.01	1.51-2.68	<.001
Diabetes	1.79	1.20-2.69	.006
CAD	1.53	.91-2.58	.106
Creatinine	1.34	1.14-1.58	.001
C-reactive protein	1.21	1.11-1.34	<.001
Cholesterol*	1.06	1.03-1.09	.001
Homocysteine	1.06	1.02-1.09	.001
Fibrinogen*	1.05	1.04-1.07	<.001
Creatinine clearance†	0.99	.98-.99	.025
BMI	0.99	.96-1.03	.785

ABI, Ankle-brachial index; *OR,* odds ratio; *PVD,* peripheral vascular disease; *CI,* confidence interval; *CAD,* coronary artery disease; *BMI,* body mass index.

*Reported as a 10-mg/dL change in laboratory value.

†Reported as a 10-unit change in creatinine clearance (mL/[min · 1.73m^2]).

betes, and chronic renal insufficiency. Younger patients were more likely to be smokers, however.

Serologic risk factors for PVD, including serum concentrations of homocysteine, fibrinogen, creatinine, and C-reactive protein, were all numerically higher in older patients. Cholesterol levels were equivalent in the two groups.

Bivariate analysis. Results of the bivariate analyses are summarized in Tables II and III. In bivariate analyses, adjusted only for age, all risk factors are predictive of PVD with the exception of CAD, creatinine clearance, and BMI (Table II). The strongest positive associations with PVD were found with hypertension, smoking, and serum creatinine concentration.

Stratified bivariate analyses were then performed to determine interaction between age (<60 vs ≥60 years) and each risk factor (Table III). These reveal significant interactions for CAD, creatinine, creatinine clearance, homocysteine, and fibrinogen ($P < .10$). For CAD, creatinine clearance, and fibrinogen, the odds of PVD were increased in the younger age category. In contrast, increased serum homocysteine and creatinine clearance afforded higher odds of PVD in the older age category. The most profound interaction was seen with CAD, which was highly predictive of PVD in the younger age group (OR, 3.60; $P = .008$) but

was only weakly associated with PVD in the older age group (OR, 1.26; $P = .367$).

Multivariate analysis. After fitting the initial model, a backward selection process eliminated both cholesterol ($P = .33$) and C-reactive protein ($P = .70$). In addition, the previously observed interaction between age and homocysteine had been attenuated, and homocysteine was retained in the model as an unstratified predictor. The final multiple logistic model is reported in Table IV. The strong interaction seen with CAD remained in the final model, with CAD conveying higher odds of PVD in the younger age group (OR, 2.90 vs 1.26). Serum fibrinogen levels also were more predictive of PVD in the younger age group. A 10-mg/dL increase in fibrinogen was associated with a 7% increased odds in subjects <60 years compared with a 4% increase in patients ≥60 years. In contrast, a decrease creatinine clearance was more strongly associated with PVD in the older age group, with a 10-unit decrease affording a 16% increased odds of PVD. The association of creatinine clearance with PVD was not significant in the younger age group (OR, 1.02, $P = .712$).

Other significant predictors of PVD included hypertension (OR, 1.99; $P = .001$), smoking (OR, 2.22; $P < .001$), and serum homocysteine (OR, 1.27; $P = .067$). Diabetes (OR, 1.53, $P = .104$) was not independently predictive of PVD but was retained in the model for face validity. Interestingly, increased BMI (OR, 0.96; $P = .003$) was associated with a mild protective effect from PVD. However, this may represent residual negative confounding after adjusting for other factors such as hypertension.

DISCUSSION

We have found that premature PVD, defined as an ABI <0.9, affects only about 2% of the US population <60 years; however, this represents about 1.44 million Americans at risk. Clearly, identification of these individuals

Table III. Bivariate logistic regression analyses Stratified by Age <60 years (ABI<0.9)

Risk factor/predictor	OR	CI	P	P (heterogeneity)
Significant **interactions**				
Coronary artery disease				
Age <60	3.60	1.43-9.03	.008	.026
Age ≥60	1.26	.75-2.10	.367	
Creatinine clearance[†]				
Age <60	1.00	.99-1.00	.725	.009
Age ≥60	0.99	.98-.99	.008	
Creatinine				
Age <60	1.00	.63-1.59	.986	.099
Age ≥60	1.46	1.12-1.91	.007	
Homocysteine				
Age <60	0.87	.44-1.72	.684	.011
Age ≥60	2.52	1.63-3.91	<.001	
Fibrinogen*				
Age <60	1.08	1.05-1.10	<.001	.060
Age ≥60	1.04	1.03-1.06	<.001	
Other predictors				
BMI				
Age <60	1.00	.94-1.07	.974	.809
Age ≥60	0.99	.96-1.03	.654	
Cholesterol*				
Age <60	1.00	.93-1.08	.969	.702
Age ≥60	1.02	.96-1.07	.610	
Hypertension				
Age <60	2.01	1.15-3.51	.016	.989
Age ≥60	2.01	1.53-2.65	<.001	
Smoking				
Age <60	2.72	1.63-4.55	<.001	.828
Age ≥60	2.52	1.74-3.67	<.001	
Diabetes				
Age <60	1.56	.44-5.55	.477	.790
Age ≥60	1.86	1.25-2.77	.004	
C-reactive protein				
Age <60	11.52	1.61-82.59	.017	.560
Age ≥60	5.79	2.00-16.76	.002	

ABI, Ankle-brachial index; *OR,* odds ratio; *CI,* confidence interval.
*Reported as a 10-mg/dL change in laboratory value.
[†]Reported as a 10-unit change in creatine clearance (mL/[min · 1.73m²])

Table IV. Multivariate logistic regression analyses for peripheral vascular disease (ABI <0.9)

Risk factor	OR	CI	P	P (heterogeneity)
Significant **interactions**				
Coronary artery disease				
Age<60	2.90	.86-9.80	0.084	.083
Age≥60	1.26	.75-2.10	0.367	
Fibrinogen*				
Age<60	1.07	1.04-1.10	<0.001	.034
Age≥60	1.03	1.01-1.05	0.001	
Creatinine clearance[†]				
Age<60	1.02	.93-1.12	0.712	.006
Age≥60	1.16	1.08-1.25	<0.001	
Other significant **predictors:**				
Male gender	2.04	1.40-2.96	0.001	
Hypertension	1.99	1.40-2.85	<0.001	
Smoking	2.22	1.47-3.37	<0.001	
BMI	0.96	.93-.98	0.003	
Diabetes	1.53	.91-2.58	0.104	
Homocysteine*	.27	.98-1.65	0.067	

ABI, Ankle-brachial index; *OR,* odds ratio; *CI,* confidence interval; *BMI,* body mass index.
Significant predictors determined at *P* < .05
Significant interaction determined at *P* < .10.
Diabetes retained in the model for face validity.
*Reported as a 10-mg/dL change in laboratory value.
[†]Reported as a 10-unit change in creatinine clearance (mL/[min · 1.73m²]).

and homocysteine, have been used to identify high-risk individuals.[14] Increasing evidence supports the use of these factors in screening and disease prevention; however, previous studies have failed to meet consensus on which factors to include for optimal detection of premature PVD.

To answer this question, we used data from the NHANES 2000 survey. The strengths of this study design include the use of a population-based data set. Survey weights can be used to make estimates about the prevalence of PVD in the United States. The associations observed between risk factors and premature PVD can be generalized to the national population. The large sample size of this survey allows for the detection of relatively small effect sizes, which may uncover associations not appreciated in smaller studies. Finally, the large number of covariates collected by NHANES allows for the simultaneous consideration of multiple variables.

One major finding of this study is that a history of CAD is predictive of premature PVD in the US population <60 years of age. It is not surprising that atherosclerotic disease in the peripheral vascular bed is found concomitantly with disease in the coronary vascular bed; however, the strength of the interaction between younger and older patients deserves emphasis. In multivariate analysis, PVD is associated with other cardiovascular conditions in the younger age group, but an association is lacking in the older population (*P* heterogeneity = .83). The premature develop-

within our population is of public health importance. A low ABI is associated with an increased risk of stroke, myocardial infarction, cardiovascular death, and reduced functional status.[1-5] Additionally, previous studies have shown that the development of PVD at an early age leads to a particularly virulent course of disease, culminating in cardiovascular morbidity, limb loss, and death.[10] The aim of this study was to consider the risk factors that are associated with premature PVD in the US population.

Cardiovascular risk factors have traditionally been targeted as the major determinants of atherosclerosis.[11] These factors include smoking, hypertension, diabetes, hypercholesterolemia, and hyperlipidemia. Other prevalent diseases, such as CAD[12] and chronic renal insufficiency,[13] have also been used to effectively identify those at risk for premature PVD. More recently, a number of novel serologic markers, including C-reactive protein, lipoprotein A, fibrinogen,

ment of atherosclerosis in the peripheral beds may herald a severe systemic involvement of the coronary and cerebral vascular circulations. Because these patients are at high risk for cardiovascular death, this provides an opportunity to target young patients with a low ABI for screening and secondary prevention efforts. Measurement of ABI in young patients may improve the cardiac risk assessment when added to information gained from the medical history.

In addition, we found interaction between the development of premature PVD and elevated fibrinogen levels; however, the magnitude of this association was modest. A 10-mg/dL increase in fibrinogen was associated with a 7% increased odds in subjects <60 years compared with a 3% increase in patients ≥60 years. This statistical finding may be a result of our large sample size and does not argue for wide-scale screening for high fibrinogen levels to detect PVD. Among those with diagnosed PVD, however, the detection of elevated fibrinogen levels may also lead to secondary intervention.

Fibrates and niacin can lower fibrinogen levels.[15] However, a recent randomized controlled trial examining the effect of bezafibrate in patients with established PVD showed no effect on incident coronary events or stroke despite a 13% reduction in fibrinogen.[16] This study did not provide subgroup analysis of the fibrate effect in younger and older patients.

In contrast, we found a decrease in creatinine clearance is more predictive of PVD in the population ≥60 years of age. A recent analysis using the NHANES data set[13] found the unadjusted odds of developing PVD in patients with renal insufficiency was 9.7, with an odds ratio of 2.5 after adjustment for age and other comorbidities. The higher unadjusted association likely reflects more comorbidities, such as diabetes and hypertension, among those with renal insufficiency as well as a >20-year difference in mean age. Our result supports the effect of renal insufficiency increasing with age. One possibility is that prolonged renal insufficiency may cause vascular injury and predispose to the development of PVD. This may be mediated by alterations in metabolic pathways (calcium-phosphorus, homocysteine, lipoprotein) or alterations in inflammatory or coagulation cascades.[17]

Finally, we identified other strong risk factors that are independently associated with PVD, regardless of age category. These include smoking and hypertension, which are well-established risk factors for the development of atherosclerotic disease. A weaker positive association was also seen with plasma homocysteine ($P =$ .067). Errors in homocysteine metabolism have been associated with the development of atherosclerotic vascular disease.[18] A common mutation in the MTHFR gene (5,10-methylenetetrahydrofolate reductase) leads to moderate elevations of plasma homocysteine (about 25%), particularly in the low-folate state.[19] Meta-analyses have shown only weak evidence of the association between homocysteine and atherosclerotic vascular disease in the general population.[20] This weak association is

supported in our population-based study. The effect of high-dose folate supplementation in the prevention of cardiovascular disease is currently under investigation in multiple randomized trials.

The use of the NHANES data set has allowed us to overcome the problem of selection bias found in smaller studies by identifying risk factors for the development of PVD representative in the national population. The nature of this cross-sectional data set has limitations, however. The data collected by NHANES is itself subject to selection bias because not all the participants who were selected had the lower extremity examination. Furthermore, the ABI examination is subject to measurement bias owing to operator error or incompressibility of the lower extremity arteries. Because the data are observational, causality between risk factor and the development of PVD cannot be determined. In addition, the data set is not longitudinal, so no estimation of disease incidence is possible. Furthermore, associations can only be made on variables collected in the NHANES database. Potentially important predictors of PVD, such as lipoprotein (a),[7] are not presently collected by NHANES.

CONCLUSIONS

Despite these limitations, our findings have important clinical implications. The association between PVD and prevalent CAD has previously been recognized.[5] In fact, a decreased ABI has been shown to be one of the strongest predictors of cardiovascular morbidity and all-cause mortality.[21] With noninvasive screening for PVD using ABI measurement, subclinical cardiovascular disease can be inferred and secondary intervention performed. Screening for elevated levels of fibrinogen or homocysteine may also aid in the detection of premature PVD. A screening study from a high-risk cardiology clinic identified these factors as being independently predictive of mortality after adjustment for traditional (Framingham) risk factors.[21] Screening among such a highly selected population may help identify those that would most benefit from secondary intervention.

Clinicians should be aware of the high risk of developing premature PVD in patients <60 years with coexisting CAD or elevated fibrinogen. Screening by ABI measurements in these patients would enhance the detection of subclinical premature PVD and CAD and allow for secondary intervention.[22]

AUTHOR CONTRIBUTIONS

Conception and design: JL, EV, KL, JH, LM
Analysis and interpretation: JL, EV
Data collection: JL, EV
Writing the article: JL, EV, KL, JH, LM
Critical revision of the article: JL, EV, KL, JH, LM
Final approval of the article: JL, EV, KL, JH, LM
Statistical analysis: EV
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Overall responsibility: JL

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DISCUSSION

Audience (unidentified speaker). Just one question. Why did you pick age 60 as a definition for premature atherosclerosis? I think in Valentine's work it is age 50, and I know other authors who have actually called it age 40, so it seems like the definition of premature keeps getting older and older. Any answers about why you did that?

Dr John Lane. Thank you for the question. Yes, as you are familiar with the literature, Dr Valentine's group actually a lot of times would define this as age 45. One of the reasons we defined it as age 60 is that some authors have used this in the past. It is kind of a moving target of how and when you define premature peripheral vascular disease, and one of the reasons I did allow for a roughly equal sample size in both the older and younger age groups. We did look at different cut points, and it didn't really significantly change our findings by using a cutoff at age 45.

Dr Charles Andersen (Tacoma, Wash). I rise to suggest that it may be time for a terminology change in our field. We talk about peripheral vascular disease as if it were something separate, a separate area of atherosclerosis. I would throw out a suggestion that screening with ABIs is not about the legs at all. It is about early detection of atherosclerotic vascular disease and then an aggressive approach to a systemic disease. My question is if you pick up an early abnormal ABI, what do you do from there?

Dr Lane. Thank you for the question and your observation. I do think this is incredibly important. In fact, there was a recent article in the *Annals of Internal Medicine* out of UCSF that showed now ABI screening is also important in predicting early renal failure, so it seems that ABIs are becoming an incredibly powerful marker, and you are right, it is not just for detecting peripheral vascular disease, but finding for vascular disease in the entire body.

To your question, I think when you find a patient with an abnormal ABI, this is your opportunity to afford early secondary intervention. How this can be done is by altering risk factors, including the treatment of hypertension, cholesterol, and diabetes, and the new serologic risk factors that we were analyzing in the study. I think we also have some evidence that there is medical treatment for them. So I think this is a way that we can prevent patients from coming to the operating table and trying to treat these risk factors early when you identify them with an early abnormal ABI.

Audience (unidentified speaker). Very nice presentation. If you ask a practicing vascular surgeon what the greatest risk factors are for the younger patients, it seems to me the no-brainers would be patients who have type 1 or insulin-dependent diabetes and patients on dialysis, chronic renal failure. I may have missed it in your methodology, but were those patients excluded, or could you explain how the data would be assessed that those patients would not fall out in your analysis, because to me, those are the no-brainers. These are the subtle risk factors that we don't always measure, but I would think that the highest risk would be in that group of patients, and that is what our clinical experience is.

Dr Lane. Thank you. Yes, diabetes and dialysis are certainly very important risk factors. Diabetes was included; however, we did not—the data in NHANES was not stratified to type 1 versus

type 2 diabetes—so, unfortunately, I can't give you which type of diabetes. Dialysis patients were not excluded from sampling in NHANES. I did not present nor did I analyze the dialysis group independently. One of the reasons was because even with the sampling, there were 5000 patients in the sample. The occurrence was only 2% in the younger age category and 12% in the older. If you start breaking it down all the way to the number actually on dialysis, the number of outcomes is going to be small in the age category, and it might not have been powerful in the analysis so that wasn't performed, but, yes, we all know that is incredibly important in developing premature disease.

Dr Christian Devirgilio (Los Angeles, Calif). I enjoyed your presentation. Very nice work. I had sort of a practical question for the family practitioner who might be looking to screen. Given that hypertension and smoking were important risk factors in both old and young, if they were to simply use smoking and hypertension as a guide to getting the simple ABI, how many patients would be missed if you did not use, say, the fibrinogen? In other words, is it practical to be telling the family practitioner that they should be screening fibrinogen when a simple ABI could be done just based on smoking and hypertension?

Dr Lane. Thank you, Dr Devirgilio. Yes, very insightful. When you are talking about screening a general population, certainly the strongest risk factors are the ones that are most important such as smoking and hypertension as well as diabetes. Whether these serologic risk factors are really important in the general population, it may not be clear, and certainly our data do not bear that out. When you are talking about screening for those things, I think it is more important in a high-risk population. There was a paper out of The Cleveland Clinic that looked at screening for these more subtle risk factors in patients that are extremely high risk, such as referrals to a high-risk cardiology clinic, and in our instance, maybe a referral to a vascular clinic. In those, the novel risk factors did add something to the prediction, and again, it offers an opportunity for treatment. So in a general population such as a US population, which I am talking about here, I don't think our data support that this makes sense. I think you should concentrate on the big risk factors such as smoking, hypertension, and diabetes, but when you are looking at a referral population or a high-risk population, I think in that case it makes sense and I think this should be considered more closely in our peripheral vascular patients in a future study.

Dr Thomas Rehring (Denver, Colo). I have one comment and then a question for you. To Dr Andersen's question, I mean those patients who you identify with a diagnosis of PAD should instantly be started on all secondary prevention strategies you initiate in somebody with coronary artery disease, which would include β-blockade, ACE inhibitors, antiplatelet therapy, and probably a statin to target an LDL of less than 100. I think it is

within our purview and should be our recommendation, if we don't initiate therapy ourselves, that you should have a strong letter back to that referring physician.

My question for you is this: we know that as many as two thirds of patients in the elderly population that have a diagnosis of peripheral arterial disease would be asymptomatic, that is, they can be identified with a low ABI but may not have symptoms. It is my impression that the younger population presents more commonly with symptoms. Did they have data from this survey at all about how many of these patients had symptoms?

Dr Lane. Yes. Thank you for your question. I certainly agree with aggressive medical therapy for all people that have evidence of vascular disease in any of the peripheral or coronary beds.

The lower extremity examination did have a symptom index, or at least they ask if people are having claudication. Again, it wasn't very detailed and again, when you are talking about younger patients with symptoms, when you are getting down to that small of numbers, the analysis is not very powerful, so I did not include that in the analysis; but, yes, the NHANES data set in the lower extremity does ask if you have leg pain with walking and that is something that could be analyzed in a future study.

Dr Preston Flanagin (Orange, Calif). Regarding the ankle-brachial index being the best way to screen for peripheral vascular disease in terms of having early intervention, I think that it is actually a late manifestation if your ankle-brachial index is abnormal. Most active patients that have an abnormal ankle-brachial index are going to be symptomatic. If you have an abnormal ankle-brachial index, you already have a critical stenosis somewhere in your lower extremity vasculature. I have always been intrigued with the use of that and I suspect it is mostly for cost reasons, but it seems to me that duplex scanning, as we do for the carotids and as we do for screening for abdominal aortic aneurysms, would be a lot more effective in finding earlier peripheral vascular disease and therefore allow for earlier and hopefully more effective intervention.

Dr Lane. Thank you for your comment. We did use a very somewhat high cut point. Most of us would not consider treating a patient with an ABI of 0.9 unless they are very symptomatic from that, which is hard to imagine, but certainly when you are talking about ABIs in the lower category certainly they do also—say if you use a cutoff of 0.5—they all have very profound peripheral and possibly atherosclerotic disease in other vascular beds. Certainly, this study does not look at duplex scanning as a sensitive marker. People have tried to do this looking in the carotid circulation and measuring intimal-to-medial thickness as trying to be an early marker. Certainly, that is something important. People have tried to use this as a predictive tool; however, we did not use this in the study, and I don't have any data to present that for the group.