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Low Ankle-Brachial Index Predicts Cardiovascular Risk After Acute Ischemic Stroke or Transient Ischemic Attack

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Background and Purpose—A low ankle-brachial blood pressure index (ABI) is an established risk marker for cardiovascular disease and mortality in the general population, but little is known about its prognostic value in individuals with acute ischemic stroke or transient ischemic attack (TIA).

Methods—An inception cohort of 204 patients with acute ischemic stroke or TIA was followed up for a mean of 2.3 years. At baseline, patients underwent ABI measurement and were assessed for risk factors, cardiovascular comorbidities, and cervical or intracranial artery stenosis. The association between low ABI (≤0.9) and the risk of the composite outcome of stroke, myocardial infarction, or death was examined by Kaplan–Meier and Cox regression analyses.

Results—A low ABI was found in 63 patients (31%) and was associated with older age, current smoking, hypertension, peripheral arterial disease, and cervical or intracranial stenosis. During a total of 453.0 person-years of follow-up, 37 patients experienced outcome events (8.2% per person-year), with a higher outcome rate per person-year in patients with low ABI (12.8% vs 6.3%, $P=0.03$). In survival analysis adjusted for age and stroke etiology, patients with a low ABI had a 2 times higher risk of stroke, myocardial infarction, or death than those with a normal ABI (hazard ratio=2.2; 95% CI, 1.1 to 4.5). Additional adjustment for risk factors and cardiovascular comorbidities did not attenuate the association.

Conclusions—A low ABI independently predicted subsequent cardiovascular risk and mortality in patients with acute stroke or TIA. ABI measurement may help to identify high-risk patients for targeted secondary stroke prevention. **(*Stroke*. 2009;40:3700-3705.)**

Key Words: ankle-brachial index ■ ischemic stroke ■ transient ischemic attack ■ cardiovascular risk ■ outcome

The ankle-brachial blood pressure index (ABI) is an established clinical test for the assessment of peripheral arterial disease (PAD) and an indicator of generalized atherosclerosis.[1–3] A low ABI is associated with increased mortality and risk of myocardial infarction (MI) and stroke in the general population, independent of conventional vascular risk factors and prevalent cardiovascular disease.[1,3,4] Recent evidence suggests that measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond traditional risk factors in the general population.[1]

In patients with ischemic stroke or transient ischemic attack (TIA), coexisting symptomatic PAD is a powerful predictor of long-term cardiovascular risk and mortality.[5,6] Yet the prognostic value of a low ABI, which is also a highly specific and sensitive test for asymptomatic PAD, has not been established in this population. Two studies recently reported high prevalences of low ABI among patients with acute ischemic stroke or TIA, ranging from 34%[7] to 51%,[8] but information regarding the role of the ABI in predicting subsequent cardiovascular risk was inconclusive. Moreover, it has not been studied whether a low ABI provides information on the future cardiovascular risk after stroke or TIA independently of other risk markers.

In this study, we examined the association between low ABI and the subsequent long-term risk of stroke, MI, or death in patients with acute ischemic stroke or TIA. We also examined whether this association was independent of age, vascular risk factors, cardiovascular comorbidities, and cervical or intracranial artery stenosis.

Patients and Methods

We recruited an inception cohort of 204 consecutive patients with acute ischemic stroke or TIA who were admitted to the Neurology Department of Charité Hospital in Berlin, Germany, between August 2002 and March 2003 (n=87) and between October 2003 and June 2004 (n=117). Diagnosis of ischemic stroke or TIA was verified by a stroke neurologist (F.M. or M.A.B.) on the basis of the clinical syndrome and results of diagnostic tests, including computed tomography and magnetic resonance imaging scans and cardiac and vascular tests. Patients who died or were comatose during the first week after the index event were excluded. The study was approved

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by the local research ethics committee, and all participants or their proxies gave written, informed consent.

ABI Measurement

Ankle and brachial systolic blood pressures were measured at baseline with an aneroid sphygmomanometer and a hand-held 8-MHz Doppler probe (ELCAT handydop, Wolfratshausen, Germany) with the subject in the supine position after a 5-minute rest. According to American Heart Association recommendations,[2] the ABI was calculated as the ratio of the higher of the systolic pressures in the posterior tibial or dorsalis pedis artery and the average of the right and left brachial artery pressures (in the case of a discrepancy ≥10 mm Hg between the arms, the higher reading was used). This method has been shown to result in the most accurate estimation of PAD prevalence in the general population.[9] ABI was calculated separately for each leg, and the lower of the 2 ABI values was used for analysis. In accordance with the Transatlantic Intersociety Consensus for the management of PAD[10] and previous studies in patients with stroke or TIA,[7,8] ABI values ≤0.9 were defined as low. Patients were assessed within the first week of admission by 2 trained examiners (J.-E.R. and K.L.).

Outcome Measures

The main outcome was the composite of stroke, MI, or death during follow-up. To screen for outcome events, patients and their family doctors were interviewed by telephone and were additionally asked to complete a postal questionnaire. Possible outcome events were investigated from hospital records, hospital discharge letters, and family doctor information. Only definite, ie, physician-diagnosed, events were included in the analysis. Recurrent stroke was diagnosed only if symptoms lasted for >24 hours or new lesions were demonstrated on computed tomography or magnetic resonance imaging brain scans. Complete mortality follow-up was achieved by identifying deaths from death records at the regional civil registration office. Cause of death was obtained from hospital records and death certificates and classified as vascular, nonvascular, and unknown. Last follow-up assessments were made in the summer of 2007.

Covariates

Demographic and clinical data at baseline were obtained from medical records and electronic hospital information systems with standardized data collection forms. Data on medical history, previous medications, and risk factors were confirmed by consultation with family doctors and patients or relatives.

The index event was classified as a TIA if neurologic symptoms resolved within 24 hours and as stroke if they persisted for >24 hours. Etiology of stroke or TIA was classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria as atherosclerotic (symptomatic cervical or intracranial artery stenosis ≥50%, other causes excluded), cardioembolic (cardiac source of embolism, other causes excluded), lacunar (clinical lacunar syndrome, brain infarct <1.5 cm, other causes excluded), other determined etiology, multiple possible etiologies (eg, concurrent atherosclerotic stenosis and cardiac source of embolism), and undetermined.[11] Because there were only a few patients in the last 3 categories and no difference in the prevalence between ABI groups was noted, these categories were combined for analysis.

Vascular risk factors assessed at baseline included hypertension (blood pressure >140/90 mm Hg, current antihypertensive therapy, or previous physician diagnosis), diabetes mellitus (fasting glucose >126 mg/dL, nonfasting glucose >200 mg/dL, current antidiabetic therapy, or previous physician diagnosis), hyperlipidemia (fasting total cholesterol >220 mg/dL, fasting triglycerides >150 mg/dL, or current therapy with lipid-lowering drugs), and smoking status (current, past, or never smoking).

Cardiovascular comorbidities included physician-confirmed history of stroke, MI, coronary heart disease (CHD: stable or unstable angina, MI, or coronary surgery or angioplasty), or atrial fibrillation as verified from medical records, discharge letters, or family doctors. History of PAD was defined as previous physician diagnosis of PAD, history of intermittent claudication caused by a confirmed stenosis of a leg artery, or history of peripheral arterial surgery, angioplasty, or amputation for PAD.

Cervical or intracranial artery stenosis ≥50% was diagnosed by routine vascular tests, with 96% of patients being examined by Doppler and duplex ultrasound and 43% being examined by computed tomography angiography, magnetic resonance angiography, or intra-arterial angiography. Symptomatic stenosis ≥50% was defined as stenosis of a cervical or intracranial artery that was considered likely to be responsible for the index event.

Statistical Analysis

We analyzed the survival time from the index event to the date of the first outcome event (stroke, MI, or death). Patients without outcome events were right-censored at their last follow-up date. We estimated outcome rates per person-years of follow-up and rate ratios comparing patients with low (≤0.9) and normal (>0.9) ABI for the main composite outcome and additionally for individual outcome events. All other analyses were done for the main composite outcome. Outcome-free survival was examined with Kaplan–Meier curves, with comparisons between ABI groups made with stratified survival curves. Cox regression analysis was used to estimate hazard ratios (HRs) and 95% CIs for the effects of low ABI and other baseline variables on outcome. Because age is associated with the prevalence of low ABI[3] and cardiovascular risk,[12] further analyses were adjusted for age by using chronological age as the time scale in survival analysis.[13,14]

Multivariable Cox regression analysis was used to examine whether the association between low ABI and outcome was confounded by age, sex, stroke etiology, risk factors, or cardiovascular comorbidities. To avoid overfitting, separate models were fitted that were adjusted for age and stroke etiology and included low ABI as the exposure of interest and 1 risk factor or comorbidity variable at a time. A final model included all variables that were associated with outcome to the $P<0.1$ significance level or were relevant confounders of the effect of low ABI; ie, their inclusion changed the HR associated with low ABI by >10%. Effect modification by sex and index event (stroke or TIA) was assessed in stratified analysis with Mantel-Cox methods and χ^2 tests for interaction. All statistical analyses were performed with STATA 9.2 (Stata Corp, College Station, Tex).

Results

The mean ABI at baseline among all 204 patients was 0.95 (SD=0.23; range, 0.21 to 1.5). An ABI ≤0.9 was found in 63 patients (31%), of whom 29% had a history of PAD, compared with 4% of 141 patients with a normal ABI ($P<0.001$). Baseline characteristics of participants are summarized in Table 1. Patients with a low ABI were, on average, 4.6 years older and more likely to be current smokers, to have hypertension, and to have any cervical or intracranial artery stenosis ≥50%.

Complete follow-up information was available for 197 patients (97%). Of the remaining, 2 could not be traced, 2 declined follow-up, and 3 were alive but no other information was available. Mean time to first outcome event or last follow-up was 2.3 years (SD=1.0; range, 0.2 to 3.9 years), with similar follow-up times in patients with low (mean±SD, 2.2±1.1 years) and normal (mean±SD, 2.4±0.9 years) ABI (Mann–Whitney U test, $P=0.3$).

During a total of 453.0 person-years of follow-up, 37 patients experienced outcome events (28 strokes [4 fatal] in 23 patients, 4 MIs [2 fatal], and 20 deaths), an unadjusted outcome rate of 8.2% (95% CI, 5.9 to 11.3) per person-year. Outcome rate was higher among patients with a low ABI (12.8% per year; 95% CI, 7.9 to 20.5) compared with those

Table 1. Baseline Characteristics

	All Patients (N=204)		ABI ≤0.9 (n=63)		ABI >0.9 (n=141)		
	n	(%)	n	(%)	n	(%)	P*
Female sex	91	(45)	32	(51)	59	(42)	0.2
Mean age (SD), y	63.9	(13.2)	67.1	(11.8)	62.5	(13.6)	0.02
Index event							
Stroke	154	(75)	52	(83)	102	(72)	0.1
TIA	50	(25)	11	(17)	39	(28)	
Etiologic subtype†							
Atherosclerotic	46	(23)	18	(29)	28	(20)	0.4
Cardioembolic	61	(30)	19	(30)	42	(30)	
Lacunar	57	(28)	15	(24)	42	(30)	
Other or undetermined	40	(19)	11	(17)	29	(20)	
Risk factors							
Hypertension	142	(70)	51	(81)	91	(65)	0.02
Diabetes	66	(32)	25	(40)	41	(29)	0.1
Hyperlipidemia	85	(42)	32	(51)	53	(38)	0.08
Current smoking	60	(29)	26	(41)	34	(24)	0.01
Cardiovascular comorbidities							
Previous stroke	45	(22)	19	(30)	26	(18)	0.06
Previous MI	25	(12)	9	(14)	16	(11)	0.6
Atrial fibrillation	36	(18)	14	(22)	22	(17)	0.3
History of CHD	37	(18)	14	(22)	23	(16)	0.3
History of PAD	24	(12)	18	(29)	6	(4)	0.0001
Cervical or intracranial stenosis							
Any stenosis ≥50%	85	(42)	34	(54)	51	(36)	0.02
Symptomatic stenosis	67	(33)	24	(38)	43	(31)	0.3

*P values for comparison of ABI groups were obtained from the Mann–Whitney U test for age and from the χ^2 test or Fisher exact test for other variables.

†Subtype according to TOAST classification (see text for details).

with a normal ABI (6.3% per year; 95% CI, 4.0 to 9.7), a rate ratio of 2.0 (95% CI, 1.1 to 3.9; $P=0.03$). With regard to individual outcome events, there was some evidence for an increased mortality in the low-ABI group (Table 2), whereas rates for stroke and MI were nonsignificantly higher. Among 20 deceased patients, the cause of death was vascular in 9 (45%), nonvascular in 9 (45%), and unknown in 2 (10%), with no difference between ABI groups (Fisher's exact test, $P=0.5$).

Kaplan–Meier curves (the Figure) show a lower probability of outcome-free survival among patients with a low ABI compared with those with a normal ABI (log-rank test, $P=0.02$). In univariate Cox regression analysis, patients with a low ABI had a 2 times higher risk of stroke, MI, or death (HR=2.0; 95% CI, 1.1 to 3.9; Table 3). Other factors associated with the composite outcome in univariate analysis were age, stroke etiology, and atrial fibrillation. After adjustment for age, the effect of low ABI on outcome was slightly increased (HR=2.2; 95% CI, 1.1 to 4.3). There was still some weak evidence for an association between stroke etiology and outcome, mainly owing to a better survival among patients with lacunar stroke (HR=0.2; 95% CI, 0.1 to 0.9), but no other baseline variable predicted outcome in age-adjusted analysis.

From the multivariable models adjusted for age, stroke etiology, and 1 risk factor or comorbidity variable at a time, there was no evidence that the effect of low ABI on outcome was confounded by any other baseline variable; ie, the HR associated with low ABI remained materially unchanged, ranging between 2.1 and 2.3 in all models. Also, none of the other baseline variables, including PAD, was associated with outcome in these multivariable models. In the final model adjusting for age and stroke etiology, the HR associated with low ABI was 2.2 (95% CI, 1.1 to 4.5). There was no evidence that the association between low ABI and outcome was modified by sex or index event (stroke or TIA) in stratified analyses (χ^2 tests for interaction, $P=0.9$ and $P=0.6$, respectively).

Discussion

In this inception cohort study of hospital-admitted patients with acute ischemic stroke or TIA, a low ABI was found in nearly a third of patients and independently predicted an increased long-term risk of subsequent cardiovascular events or death. These results suggest that measurement of the ABI may help to identify patients with stroke or TIA who are at increased cardiovascular risk beyond established risk markers and who could potentially benefit from a targeted, intensified, secondary prevention treatment.

Table 2. Outcome Rates per Person-Year According to ABI Category

	ABI ≤0.9 (n=61)			ABI >0.9 (n=136)				
	n*	Person-Years†	Rate	n*	Person-Years†	Rate	Rate Ratio (95% CI)	P
Composite outcome								
Stroke, MI, or death	17	133	12.8%	20	320	6.3%	2.0 (1.1–3.9)	0.03
Individual outcomes								
Stroke	9	133	6.8%	14	320	4.4%	1.5 (0.7–3.6)	0.3
MI	2	143	1.4%	2	333	0.6%	2.3 (0.3–16.0)	0.4
Death	10	143	7.0%	10	334	3.0%	2.3 (1.0–5.6)	0.05

*No. of patients with at least 1 outcome event. Note: n for composite outcome is smaller than the sum of individual outcomes owing to multiple outcome events in some patients.

†Person-years of follow-up until first outcome event or last follow-up.

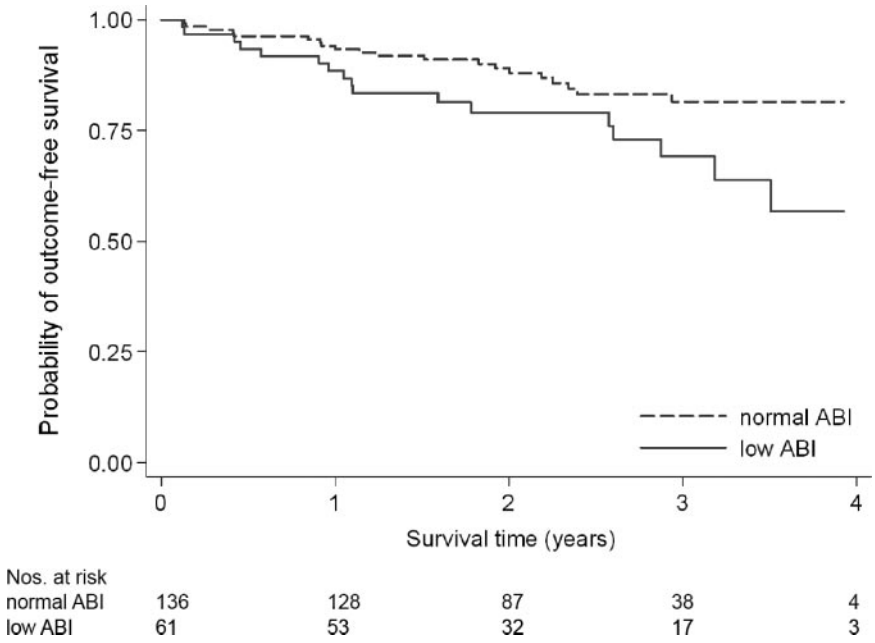

Figure. Kaplan–Meier estimates of the probability of survival free of stroke or MI, stratified by ABI category.

The high prevalence of a low ABI of 31% in this study indicates that nearly a third of patients with stroke or TIA had coexisting PAD. Although patients with a history of PAD were more likely to have low ABI values than those without, the vast majority of low ABI values (71%) were found in previously undiagnosed and asymptomatic patients.

Table 3. Associations Between Baseline Variables and Risk of Stroke, MI, or Death During Follow-Up (n=197)

	Univariate Analysis			Age-Adjusted Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Low ABI	2.0	1.1–3.9	0.03	2.2	1.1–4.3	0.02
Age >65 y	2.5	1.2–5.1	0.007			
Female sex	1.3	0.7–2.4	0.5	1.3	0.7–2.7	0.4
Etiologic subtype						
Atherosclerotic	1.0		0.008	1.0		0.06
Cardioembolic	1.5	0.7–3.2		0.9	0.4–2.3	
Lacunar	0.2	0.1–0.9		0.2	0.1–0.9	
Other or undetermined	0.9	0.4–2.4		0.8	0.3–2.0	
Risk factors						
Hypertension	1.9	0.8–4.4	0.1	1.6	0.6–3.9	0.3
Diabetes	1.8	0.9–3.4	0.1	1.5	0.8–3.1	0.2
Hyperlipidemia	0.6	0.3–1.3	0.2	0.7	0.3–1.4	0.3
Current smoking	0.6	0.3–1.4	0.3	1.0	0.4–2.3	0.9
Cardiovascular comorbidities						
Previous stroke	1.7	0.8–3.4	0.2	1.7	0.8–3.6	0.2
Previous MI	1.5	0.6–3.5	0.4	1.5	0.6–3.9	0.4
Atrial fibrillation	2.7	1.4–5.4	0.006	1.5	0.6–3.5	0.4
History of CHD	1.8	0.9–3.8	0.1	1.8	0.8–3.9	0.2
History of PAD	2.1	0.9–4.7	0.08	2.0	0.8–4.8	0.1
Cervical or intracranial stenosis						
Any stenosis ≥50%	1.4	0.7–2.6	0.3	1.7	0.8–3.3	0.2
Symptomatic stenosis	1.1	0.6–2.2	0.8	1.6	0.8–3.3	0.2

These results are comparable to the findings of 3 recent studies that reported ABI prevalence in patients with cerebrovascular disease.[7,15–17] In the German Epidemiological Trial on Ankle Brachial Index (getABI),[15,16] the prevalence of ABI <0.9 was 18.0% in the total sample of 6880 unselected primary care patients and 30.3% in 607 patients with a history of cerebrovascular disease. The Italian PATHOS study[7] examined 1758 patients admitted to 1 of 49 hospital departments for acute coronary syndromes (57%), acute ischemic stroke (29%), or TIA (14%); the prevalence of ABI ≤0.9 was 34% among 755 patients with stroke or TIA. In the SCALA study,[17] the prevalence of ABI ≤0.9 was higher, at 51% among 852 patients with stroke or TIA admitted to 85 stroke units across Germany. This higher prevalence may partly be explained by a higher mean age and a higher proportion of patients with atherosclerotic stroke in SCALA. As in our study, only a small minority of patients with a low ABI in these 3 studies had a history of PAD, ranging from 7% in PATHOS[7] to 20% in SCALA.[17]

There was a lower prevalence of low ABI (9%) among participants of the ARIC study with a history of stroke or TIA,[18] but the prevalence of PAD might have been underestimated because the ABI was measured in 1 leg only.[19] A Japanese study, which reported a prevalence of low ABI of 17%, had analyzed 58 retrospectively selected patients with ischemic stroke.[20]

Although low ABI has been consistently associated with the incidence of cardiovascular disease and mortality in the general population,[1,3] evidence on the role of the ABI as a predictor of recurrent cardiovascular events or death in individuals with prevalent cardiovascular disease is limited and less consistent. In the large population-based ARIC study, the association between low ABI and recurrence of CHD events or stroke in 766 individuals with prevalent CHD was weak and no longer significant after adjustment for

cardiovascular risk factors.[19] In a study of 165 patients with CHD referred for elective coronary angiography, low ABI predicted the risk of subsequent acute cardiovascular events after adjustment for age, cholesterol, and carotid atherosclerosis.[21] In a study of 1101 patients with acute coronary syndromes, low ABI was associated with higher in-hospital mortality and short-term recurrence of angina.[22] Among participants of the Italian PATHOS study with acute coronary syndromes, patients with a low ABI had a higher 1-year risk of MI, stroke, or death (odds ratio=2.35; 95% CI, 1.47 to 3.76), and this association remained significant after adjustment for risk factors and prognostic markers.[7]

The association between ABI and subsequent cardiovascular risk and mortality in patients with acute ischemic stroke or TIA has been explored in only 2 previous studies. The PATHOS study found an increased 1-year risk of stroke, MI, or death in patients with TIA but not in those with stroke and not when both groups were analyzed together.[7] The authors noted that these inconclusive results may partly be explained by the relatively short follow-up of 1 year, the exclusion of patients with cardioembolic stroke or TIA, and potentially by differences in treatment intensity. Also, the analysis of patients with stroke or TIA was not adjusted for age and risk factors. In the SCALA study, an increased risk of recurrent stroke or cardiovascular death during a mean follow-up of 17.5 months was found in patients with low ABI.[8] However, the analysis was not adjusted for potential confounders such as age, risk factors, or cardiovascular comorbidities, and it was not reported whether patients with low and normal ABI values differed in these important prognostic factors. Moreover, MI was not assessed as an outcome.

The main advantages of our study are the adjustment for relevant confounders in multivariable survival analysis and the longer follow-up times compared with those in previous studies. There are, however, several limitations to our study that merit discussion. Owing to the low number of outcome events, the analysis was not powered to identify significant associations between low ABI and individual outcomes, although rates for individual outcomes were higher in patients with ABI ≤0.9. For the same reason, we could not control for all covariates at the same time in the multivariable model, and a small effect of individual covariates on outcome may have been missed. We could not examine the influence of secondary prevention treatment, as data on medication adherence during follow-up was missing for 12% of patients. However, there was no evidence that adherence to antithrombotic medication influenced the outcome of patients with available information. The study was suspended from April to September 2003 because restructuring of local stroke services in combination with a shortage of study personnel meant that we could not guarantee complete ascertainment and assessment of all admitted patients with stroke or TIA during that time. However, there was no evidence for an effect of study period on baseline characteristics or study outcomes in univariate and multivariate analyses. Finally, our findings apply only to hospital-admitted patients with acute TIA or stroke. Larger population-based studies are needed to confirm the results, particularly with regard to individual outcomes such as stroke recurrence.

Conclusions

The results suggest that a low ABI independently predicts long-term cardiovascular risk and mortality in patients with acute stroke or TIA. Measurement of the ABI may help to identify high-risk patients for intensified secondary stroke prevention, including more aggressive treatment of hypertension, dyslipidemia, and diabetes. Moreover, ABI measurement may be used to facilitate risk education and increase risk awareness, thus potentially improving medication adherence and participation in smoking cessation and exercise programs. Before the value of a targeted approach to stroke prevention can be tested in intervention trials, further evaluation is required of the potential of incorporating ABI measurement in risk scores and risk stratification systems on which secondary prevention strategies are based.

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Disclosures

None.

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