The Prevalence and Predictors of an Abnormal Ankle-Brachial Index in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial

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OBJECTIVE—To examine ankle-brachial index (ABI) abnormalities in patients with type 2 diabetes and coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS—An ABI was obtained in 2,240 patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. ABIs were classified as: normal, 0.91–1.3; low, ≤0.9; high, >1.3; or noncompressible artery (NC). Baseline characteristics were examined according to ABI and by multivariate analysis.

RESULTS—ABI was normal in 66%, low in 19%, and high in 8% of patients, and 6% of patients had NC. Of the low ABI patients, 68% were asymptomatic. Using normal ABI as referent, low ABI was independently associated with smoking, female sex, black race, hypertension, age, C-reactive protein, diabetes duration, and lower BMI. High ABI was associated with male sex, nonblack race, and higher BMI; and NC artery was associated with diabetes duration, higher BMI, and hypertension.

CONCLUSIONS—ABI abnormalities are common and often asymptomatic in patients with type 2 diabetes and CAD.

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There is limited data on ankle-brachial index (ABI) abnormalities in patients with type 2 diabetes and coronary artery disease (CAD). Using the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial, our aim was to compare the prevalence and risk factors associated with normal, low, and high ABI and noncompressible artery (NC). We hypothesized that due to the different pathogenesis of obstructive peripheral artery disease (PAD) and arterial stiffness, the risk factors for these conditions would differ.

RESEARCH DESIGN AND METHODS

—Details of the BARI 2D Trial have been previously published (1,2). The local institutional review boards approved the protocols, and participants provided informed consent. The study population included 2,240 patients that had an ABI assessment at baseline.

ABI protocol

Central training was provided, and a standard protocol for obtaining ABIs was used. Patients were placed supine for at least 5 min. The systolic blood pressure of the brachial artery of both arms and the posterior tibial artery of both ankles were measured using a blood pressure cuff and a Parks Model 841-A pocket Doppler probe (Parks Medical Electronics, Aloha, OR). The highest arm pressure was used to calculate ABI. The ratio of ankle to arm systolic blood pressure was calculated for each leg, and the lowest ratio was recorded as the ABI. ABIs were classified as: low ≤0.9, normal 0.91–1.3, and high >1.3 or NC when the operator was unable to occlude the ankle artery with maximum cuff inflation. Asymptomatic PAD was defined as a low ABI in the absence of physician-reported claudication.

Statistical analysis

We compared clinical characteristics between ABI groups using the normal ABI group as referent. We used χ^2 tests for categorical variables and Student *t* tests for continuous variables. Associations between clinical variables and presence of low ABI, high ABI, or NC artery were assessed with logistic regression using predictor variables that had biological plausibility for being causally related to the outcome variable. We present odds ratios (ORs) (95% CIs) for this model. A value of $P \leq 0.05$ was considered statistically significant. SAS version 9 for Windows was used for all analyses (version 9.2; SAS Institute).

RESULTS

Baseline characteristics according to ABI

The distribution of ABI was approximately symmetrical, with a mean value of 1.05. A normal ABI was found in 66% (n = 1,489), low ABI in 19% (n = 430), high ABI in 8% (n = 182), and NC artery in 6% (n = 139) of patients. The baseline

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Table 1—*Baseline characteristics and clinical predictors of an abnormal ABI*

		Low ABI		High ABI		NC artery	
	Normal ABI (ref. *n* = 1,489)	*n* = 430	Adjusted OR (95% CI)	*n* = 182	Adjusted OR (95% CI)	*n* = 139	Adjusted OR (95% CI)
Variables hypothesized to be causally related to ABI							
Age (years)	61.9 (8.8)	63.4 (8.9)*	1.29 (1.13–1.48)	61.9 (8.5)	0.99 (0.82–1.19)	64.2 (9.7)*	1.20 (0.97–1.49)
Sex (% female)	28.3	38.8†	1.41 (1.10–1.79)	17.6*	0.53 (0.35–0.80)	30.2	0.81 (0.54–1.22)
Black race vs. all others (%)	15.2	27.4†	1.89 (1.44–2.48)	4.9†	0.30 (0.15–0.60)	17.3	
Diabetes duration (years)	9.7 (8.1)	11.4 (9.0)†	1.18 (1.03–1.34)	10.2 (9.1)		15.1 (10.0)†	1.84 (1.52–2.22)
Insulin treatment (%)	25.9	32.3*		25.3		40.3†	
HbA_{1c} (%)	7.6 (1.6)	7.8 (1.6)		7.6 (1.8)		7.8 (1.6)	
BMI	31.5 (5.7)	31.0 (5.7)	0.88 (0.79–0.97)	33.7 (5.9)†	1.44 (1.26–1.65)	32.8 (6.7)*	1.23 (1.06–1.43)
Hypertension (%)	87.8	92.3*	1.56 (1.04–2.33)	87.4		95.7*	2.95 (1.27–6.89)
Hypercholesterolemia (%)	81.6	82.1		76.9		74.8	0.67 (0.44–1.02)
Current cigarette smoker (%)	11.6	20.7†	2.40 (1.76–3.26)	3.8*	0.30 (0.14–0.66)	7.3	
Chronic renal dysfunction (%)	2.5	4.4*		2.7		6.6*	
CRP log (μg/ml)	0.85 (1.25)	1.06 (1.22)*	1.12 (1.01–1.23)	0.83 (1.19)		1.13 (1.42)*	
Additional baseline variables							
White race vs. all others (%)	65.1	58.1*		83†		67.6	
Hispanic vs. all others (%)	13.9	10.5		8.2*		15.1	
Other (vs. white/black/Hispanic) (%)	5.8	4		3.8		0*	
Cardiac disease							
Number of disease regions (%)							
0	4.3	2.3*		2.7		4.3	
1	30.9	25.8		33		28.1	
2	35.8	35.8		35.7		30.9	
3	28.9	36		28.6		36.7	
MJI	43.7 (24.4)	46.8 (24.2)*		41.4 (22.0)		47.5 (25.1)	
ACR >30 mg/g (%)	28.7	40.5†		27.6		53.7†	
Former cigarette smoker (%)	54.2	54.9		56.6		55.5	
Erectile dysfunction (%)	53.4	63.2*		62		64	
Peripheral neuropathy (%)	32.6	36.7		38.3		66†	
Carotid artery disease (%)	6.3	14.9†		3.3		9.4	
Intermittent claudication (%)	13.7	31.9†		12.1		23.7*	
Peripheral vascular surgery (%)	1.5	5.4†		3.8*		5.8†	

Data are means (SD) unless otherwise indicated. ACR, urine albumin-to-creatinine ratio; MJI, myocardial jeopardy index. **P* value for comparison with normal ABI <0.05, †*P* value for comparison with normal ABI <0.001.

characteristics according to ABI are presented (Table 1).

ABI and lower extremity symptoms

With respect to symptoms status, 68% of patients with a low ABI did not have claudication. Compared with low-ABI patients with claudication, aymptomatic subjects had higher mean ABI values (0.75 vs. 0.66, $P < 0.0001$), were less likely to have peripheral neuropathy (28 vs. 55%, $P < 0.0001$), carotid artery disease (8 vs. 29%, $P < 0.0001$), and chronic renal dysfunction (3 vs. 8%, $P = 0.047$), and were less likely to be current smokers (16 vs. 31%, $P = 0.0003$), suggesting that the severity of atherosclerotic disease may play a role.

Abnormal ABI risk factors

After adjustment, with normal ABI as referent, low ABI was independently associated with older age, female sex, black race, diabetes duration, lower mean BMI, hypertension, current smoking, and higher C-reactive protein (CRP). Using similar methodology, a high ABI was associated with male sex, nonblack race, nonsmoking status, and higher mean BMI; an NC artery was associated with diabetes duration, higher mean BMI, and hypertension (Table 1).

CONCLUSIONS—In this large study of patients with type 2 diabetes and CAD, we found a high prevalence of obstructive PAD and arterial stiffness and identified risk factors for an abnormal ABI. A longer duration of type 2 diabetes and hypertension were independently associated with a low ABI and NC artery. Certain factors, however, were associated only with a low ABI, such as older age, female sex, black race, current smoking, and higher CRP level. A higher prevalence of PAD among women and blacks has been observed and does not appear to be due to known atherosclerosis risk factors (3,4). Our study extends these findings to patients with type 2 diabetes and CAD. The higher prevalence of PAD in women and blacks may be due to biologic or social differences, as well as slightly lower normal ABI values in these populations (5). Older age, smoking, and CRP, similar to our study, are associated with the presence or progression of PAD in patients with diabetes (6,7).

Similar to a low ABI, a high ABI or NC artery is associated with an increased risk of mortality, cardiovascular events, and amputation (8–10). We observed a high prevalence of arterial stiffness, similar to that seen in older individuals, American Indians, and dialysis patients (9,10). As observed in our study, diabetes duration has been identified as a risk factor for obstructive PAD and arterial stiffness (11,12). Unlike PAD outcomes, which are not known to improve with glycemic control, intensive treatment of diabetes can reduce peripheral arterial calcification and therefore may prevent development of NC arteries (13). The association between higher mean BMI and a high ABI or NC artery in our population may be related directly to adiposity or differences in physical activity levels.

This is a large study of well-characterized patients that includes a large number of women and minority ethnic groups. Limitations include the cross-sectional study design, which limits any conclusions about causality, the fact that ABI measurement may not detect all obstructive PAD, and the fact that an NC artery can mask obstructive PAD.

In summary, we have shown that both an abnormally low or high ABI are common in patients with established type 2 diabetes and CAD and that associated factors can be identified and deserve further study of causality. Prior studies have shown that PAD is frequently overlooked in high-risk patients and that the absence of symptoms does not modify the risk of cardiovascular events (14). The high prevalence of asymptomatic patients in our study supports the recommendations for a more aggressive approach to PAD detection. Whether early identification of PAD and implementation of aggressive medical measures can influence the progression of lower-extremity vascular disease or associated cardiovascular mortality in type 2 diabetes is unknown.

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References

1. Brooks MM, Frye RL, Genuth S, et al; Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial Investigators. Hypotheses, design, and methods for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. Am J Cardiol 2006;97(12A): 9G–19G
2. Angioplasty Revascularization Investigation B; Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. Am Heart J 2008;156:528–536
3. Kullo IJ, Bailey KR, Kardia SLR, Mosley TH Jr, Boerwinkle E, Turner ST. Ethnic differences in peripheral arterial disease in the NHLBI Genetic Epidemiology Network of Arteriopathy (GENOA) study. Vasc Med 2003;8:237–242
4. Zheng Z-J, Rosamond WD, Chambless LE, et al; ARIC Investigators. Lower extremity arterial disease assessed by ankle-brachial index in a middle-aged population of African Americans and whites: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Prev Med 2005;29(Suppl. 1): 42–49
5. Aboyans V, Criqui MH, McClelland RL, et al. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA). J Vasc Surg 2007;45: 319–327

6. Palumbo PJ, O'Fallon WM, Osmundson PJ, Zimmerman BR, Langworthy AL, Kazmier FJ. Progression of peripheral occlusive arterial disease in diabetes mellitus. What factors are predictive? Arch Intern Med 1991;151:717–721
7. Selvin E, Wattanakit K, Steffes MW, Coresh J, Sharrett AR. HbA1c and peripheral arterial disease in diabetes: the Atherosclerosis Risk in Communities study. Diabetes Care 2006;29:877–882
8. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006; 113:388–393
9. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation 2004;109:733–739
10. Sutton-Tyrrell K, Venkitachalam L, Kanaya AM, et al. Relationship of ankle blood pressures to cardiovascular events in older adults. Stroke 2008;39:863–869
11. Chen Y, Huang Y, Li X, et al. Association of arterial stiffness with HbA1c in 1,000 type 2 diabetic patients with or without hypertension. Endocrine 2009;36:262–267
12. Kallio M, Forsblom C, Groop P-H, Groop L, Lepäntalo M. Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. Diabetes Care 2003;26:1241–1245
13. Carter RE, Lackland DT, Cleary PA, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive treatment of diabetes is associated with a reduced rate of peripheral arterial calcification in the diabetes control and complications trial. Diabetes Care 2007;30:2646–2648
14. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–1324