Gender-Specific Risk Factors for Peripheral Artery Disease in a Voluntary Screening Population

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Background—Women have high rates of peripheral artery disease (PAD) despite fewer cardiovascular disease (CVD) risk factors, compared to men. We sought to determine the gender-specific prevalence of low ankle brachial index (ABI) and the relationship to C-reactive protein (CRP) levels and CVD risk factors in the Life Line Screening population.

Methods and Results—Between April 2005 and August 2011, 133 750 women and 71 996 men had ABI and CRP measured at a Life Line Screening Center. Women were slightly older than men, whereas men were more likely to be current smokers, have diabetes mellitus (DM), and coronary artery disease (CAD) ($P<0.001$ for each). Women were more likely to have ABI≤1.0, compared to men (26.6% versus 14.4%, respectively; $P<0.001$), as well as ABI≤0.9 (4.1% women versus 2.6% men; $P<0.001$). Women had higher median CRP levels (1.94 mg/L; interquartile range [IQR], 0.89, 4.44 mg/L), compared to men (1.35 mg/L; IQR, 0.73, 2.80 mg/L; $P<0.001$). Men and women shared similar risk factors for ABI≤0.9, including older age, black race, smoking, DM, hypertension, hypercholesterolemia, CAD, and elevated CRP levels. In an adjusted model, there were significant interactions between gender and age ($P<0.001$), CRP ($P<0.001$), CAD ($P=0.03$), and DM ($P=0.06$) with ABI as the outcome. The associations between age, CRP, CAD, and DM with ABI≤0.9 were stronger in men than in women.

Conclusions—Women participating in the Life Line Screening had higher CRP levels and a higher prevalence of PAD, compared to men. Neither higher CRP levels nor conventional CVD risk factors explained the excess prevalence of PAD in women. (***J Am Heart Assoc***. 2014;3:e000651 doi: 10.1161/JAHA.113.000651)

Key Words: C-reactive protein • gender differences • peripheral artery disease • risk factor

P eripheral artery disease (PAD) affects millions of people in the United States[1–4] and is now recognized as a global pandemic, affecting over 202 million people worldwide.[5] Not only is PAD a major cause of functional impairment and limb loss, but it is also strongly associated with an increased risk of myocardial infarction (MI), stroke, and death.[6–11] Although not widely recognized by the public or by clinicians, the prevalence and burden of PAD is equal, if not higher, in women compared to men.[2,5,12–14] In addition, women with PAD experience faster functional decline[15] and have poorer outcomes after lower extremity revascularization procedures,

compared to men.[16–18] Because women have a longer life expectancy than men, women will be even more disproportionately affected with PAD in the future as the population ages.

Traditional cardiovascular disease (CVD) risk factors are strongly associated with the development and progression of PAD, and the prevailing paradigm is that the risk factors for PAD are the same for men as they are for women. However, traditional CVD risk factors are more prevalent in men with PAD compared to women with PAD,[19–22] suggesting that alternative risk factors for PAD may affect women disproportionately. Inflammation is a strong risk factor for PAD,[23–26] and inflammatory profiles appear to be different in women and men. C-reactive protein (CRP) is an acute-phase protein that is elevated in individuals with PAD,[23,24] and higher CRP levels are associated with both risk and progression of PAD.[25–28] In addition, several population studies have demonstrated higher CRP levels in women compared to men.[29,30] It is not known whether gender differences in CRP levels explain observed differences in the prevalence of PAD in women compared to men.

Although women experience PAD and PAD-related consequences at rates that are at least as high as those observed in

men, PAD continues to be understudied in women. Women are under-represented in contemporary PAD studies,[31–50] contributing to significant gaps in knowledge about PAD risk factors in women. The Life Line Screening (Independence, OH) data set contains extensive records of participants who completed detailed medical questionnaires and had measurements of both ankle brachial index (ABI) and CRP levels. This population is also unique in that women are over-represented (approximately 2:1) compared to men. The aim of this study is to determine the prevalence of abnormal ABI levels in this voluntary screening population of women and men and to compare the gender-specific associations of CVD risk factors and CRP with ABI levels.

Methods

Life Line Screening Background

The Life Line Screening program began in 1993 and was designed to provide community-based screening services to help make people aware of unrecognized health problems.[51] The study cohort consists of self-referred individuals who paid for vascular screening tests, which were performed at over 20 000 sites across the United States. Each individual completed a detailed questionnaire before undergoing the screening procedure, which included information on demographics, smoking, CVD risk factors, and medical comorbidities. No information was collected on socioeconomic factors (such as education level or yearly income) or specific names of medications (ie, statin use for hypercholesterolemia). Life Line Screening utilizes laboratories that are certified by the Clinical Laboratory Improvement Amendments by the U.S. government's Division of Laboratory Services. All Life Line Screening sites across the United States utilize identical procedural protocols. Institutional Review Board approval was not required for this study because this research involved unidentifiable, coded data without access to a key to decipher the code.

Participants

Because the purpose of this study was to determine the gender-specific associations between CVD risk factors and CRP with ABI, only participants with measurement of both ABI and CRP, as well as complete information on 3 specific CVD risk factors (hypercholesterolemia, hypertension, and smoking) were included in this study. Between April 2005 and August 2011, 133 750 women and 71 996 men had measurement of ABI and CRP performed at a Life Line Screening center in the United States and had no missing information on age, gender, race, hypercholesterolemia, hypertension, and smoking, which was extracted from

detailed questionnaires completed at the time of their screening. For those who underwent multiple screenings, only the first screening during this time period was used. Any participant who reported a previous procedure to treat lower-extremity PAD was excluded from the analysis.

Ankle Brachial Index Measurement

Blood pressures were measured using standard blood pressure cuffs, an aneroid sphygmomanometer, and an 8-MHz Doppler ultrasound probe. Systolic pressures were measured in both arms (bilateral brachial arteries) and both ankles (bilateral posterior tibial [PT] and dorsalis pedis [DP] arteries). The left ABI was calculated by dividing the highest of the left PT or DP systolic pressure by the highest of the brachial pressures. Similarly, the right ABI was calculated by dividing the highest of the right PT or DP systolic pressure by the highest of the brachial pressures. The lower value between the 2 legs was used in the analysis. Participants who could not have the lower-extremity arteries occluded before 300 mm Hg were recorded as having noncompressible arteries and included in the ABI≥1.30 category.

Measurement of CRP, Glucose, and Lipids

CRP, glucose, total cholesterol, high-density lipoprotein (HDL), and triglycerides (TGs) were measured using the Cholestech LDX system (http://www.cholestech.com). CRP was measured using reflectance photometry, with a measurement range of 0.3 to 10 mg/L. Total cholesterol and HDL cholesterol were measured by enzymatic methods.[52,53] TGs were measured by an enzymatic method based on the hydrolysis of TGs by lipase to glycerol and free fatty acids. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (LDL-cholesterol=Total cholesterol−HDL cholesterol−TGs). Glucose was measured by an enzymatic method that uses glucose oxidase to catalyze the oxidation of glucose to gluconolactone and hydrogen peroxide. The measurement ranges (mg/dL) were: total cholesterol, 100 to 500; HDL cholesterol, 15 to 100; TGs, 45 to 650; and glucose, 50 to 500.

Medical Comorbidities

A diagnosis of hypertension was based on either a self-reported diagnosis of hypertension or the use of antihypertensive medications. Diabetes mellitus (DM) was defined as self-report of DM or use of DM medications. Hypercholesterolemia was defined as a self-report of hypercholesterolemia or use of lipid/cholesterol-lowering medications. Participants reported being never, former, or current smokers. A diagnosis of coronary artery disease (CAD) was based on the participant

answering yes to a wide range of questions, such as: "Have you ever had a heart attack?"; "Have you ever had angina, a heart attack, angioplasty, or bypass surgery?"; and "Do you have coronary artery disease?"

Statistical Analysis

Baseline characteristics of male and female participants were evaluated for statistical significance using a *t*-test, chi-square test, or Wilcoxon's signed-rank test, where appropriate. Demographic characteristics of male and female participants were also evaluated across different categories of ABI (≤0.9, 0.91 to 1.0, 1.01 to 1.29, and ≥1.3). We used a multinomial logistic regression to model the nominal outcome variable (ABI categories, where the referent category of the outcome included ABI values between 1.01 and 1.29). The log odds of the outcomes were modeled as a linear combination of the predictor variables. Gender interactions for risk factors and ABI were tested. Associations of ABI categories with risk

factors were evaluated separately for men and women in fully adjusted (age, race, hypertension, smoking, CRP, prevalent CAD, cholesterol/HDL ratio, and DM) models. All analyses were performed using S-Plus (release 8.0; Insightful Inc, Seattle, WA) and SPSS statistical software (release 16.0.1; SPSS, Inc., Chicago, IL).

Results

The majority of the participants were white (91%), and the women were slightly older than the men in this cohort (mean age, 62.1 versus 60.9 years, respectively; *P*<0.001). Men were more likely than women to have DM, higher glucose levels, a history of CAD, and to be current or former smokers (*P*<0.001 for each) (Table 1). Although men were more likely than women to have a history of hypercholesterolemia, women had higher total cholesterol levels (207±50 versus 192±46 mg/dL; *P*<0.001). Overall, women had a higher

Table 1. Demographic Characteristics of Life Line Cohort, by Gender

	Women	Men	P Value
N	133 750	71 996	
Age, y	62.1 (10.6)	60.9 (10.7)	<0.001
Race/ethnicity			
White	120 767 (90%)	65 780 (91%)	<0.001
Black	4646 (4%)	2157 (3%)	
Asian	1030 (1%)	746 (1%)	
Hispanic	3115 (2%)	1527 (2%)	
Native American	3177 (2%)	1336 (2%)	
Other	1015 (1%)	450 (1%)	
Hypertension	53 909 (40%)	29 271 (41%)	0.122
Hypercholesterolemia	61 960 (46%)	33 690 (47%)	0.042
Diabetes mellitus	9743/112 346 (9%)	5965/60 905 (10%)	<0.001
Smoking			
Never	87 529 (65%)	39 424 (55%)	<0.001
Former	20 493 (15%)	14 672 (20%)	
Current	25 728 (19%)	17 900 (25%)	
Coronary artery disease	5582/123 371 (5%)	5538/65 952 (8%)	<0.001
C-reactive protein*	1.94 (0.89, 4.44)	1.35 (0.73, 2.80)	<0.001
Glucose	94 (20)	100 (25)	<0.001
Total cholesterol	207 (50)	192 (46)	<0.001
High-density lipoprotein	57 (18)	43 (15)	<0.001
Low-density lipoprotein	124 (38)	122 (37)	<0.001
Triglycerides*	114 (80, 161)	120 (82, 175)	<0.001

*Median and interquartile range.

median CRP level (1.94 mg/L; interquartile range [IQR], 0.89, 4.44 mg/L), compared to men (1.35 mg/L; IQR, 0.73, 2.80 mg/L; $P<0.001$), and had higher CRP values within each subgroup of ABI categories.

Women had a lower mean ABI, compared to men (1.05 versus 1.10, respectively; $P<0.001$). Women were more likely to have an ABI≤1.0, compared to men (26.6% versus 14.4%, respectively), as well as ABI≤0.9 (4.1% women versus 2.6% men, $P<0.001$; Table 2). The excess prevalence of ABI≤0.9 in women was not driven by their older age in this cohort. When PAD prevalence was examined in 10-year increments across the spectrum of ages (30 to 90 years old), the prevalence of ABI≤0.9 was consistently 1% to 2% higher in women compared to men, in all of the 10-year age groups. Men were more likely to have an abnormally high ABI (ABI≥1.3), compared to women (3.4% versus 0.9%, respectively; $P<0.001$) (Table 2).

Men and women shared similar risk factors for ABI≤0.9 and ABI≤1.0, including older age, black race, current smoking, DM, CAD, hypertension, cholesterol/HDL ratio, and elevated CRP levels (Table 3). In a fully adjusted model, there were significant interactions between gender and age ($P<0.001$), CRP ($P<0.001$), CAD ($P=0.03$), and DM ($P=0.06$) with ABI≤0.9 as the outcome. The associations between age, CRP, CAD, and DM with ABI≤0.9 were stronger in men than in women (Table 3). In women, there were no significant associations between any of these risk factors and ABI≥1.3. In men, older age and diabetes were significantly associated with ABI≥1.3 (Table 3).

A secondary analysis was performed in a "healthy" subgroup, defined as those participants without hypertension, DM, CAD, hypercholesterolemia, not a current smoker, and with a CRP level <3 mg/L. This resulted in a subgroup of 20 508 (15.3%) women and 11 906 (16.5%) men. In this "healthy" subgroup, women still had a significantly lower mean ABI, compared to men ($P<0.001$), and a significantly higher prevalence of ABI≤0.9 and ABI≤1.0 ($P<0.001$; Table 4).

Table 2. Comparison of Ankle Brachial Index Values in Women and Men

	Women	Men	P Value
N	133 750	71 996	
Mean ankle brachial index (SD)	1.05 (0.10)	1.10 (0.11)	<0.001
Ankle brachial index categories			
≤0.90	5542 (4%)	1901 (3%)	<0.001
0.91 to 1.00	30 091 (23%)	8472 (12%)	
1.01 to 1.29	97 013 (73%)	59 195 (82%)	
≥1.30	1204 (1%)	2428 (3%)	

Discussion

Several population studies, including this study, have demonstrated higher rates and burden of PAD in women compared to men.[1,12–14,54–56] A recent global estimate found PAD prevalence to be the same in women and men in high-income countries, but more prevalent in women than men in low- or middle-income countries.[5] The reasons for the surprisingly high prevalence of PAD in women are unknown and understudied. In our study, we found traditional CVD risk factors to have similar or stronger associations with PAD in men compared to women. Although higher CRP levels were significantly associated with lower ABI levels in both men and women, the association was stronger in *men* compared to women.

Our study and others have shown that women have higher CRP levels compared to men. In both the Multi-Ethnic Study of Atherosclerosis (MESA)[29] and the Dallas Heart Study,[30] women had significantly higher CRP levels than men, despite adjustment for estrogen use, body mass index (BMI), and other variables. There is also evidence that inflammation may pose a more substantial cardiovascular risk in women compared to men. For instance, subgroup observations from both the Cardiovascular Health Study and the Rural Health Promotion Project demonstrated the cardiovascular risks associated with CRP to be greater for women than for men.[57] Similarly, in the Women's Health Study,[58] the adjusted relative risk for either MI or stroke in women with the highest quartile of CRP was 5.5, compared to 2.8 in men participating in the Physicians' Health Study.[59] In our study, elevated CRP levels were significantly associated with PAD; however, the higher CRP levels in women did not explain the excess prevalence of PAD in the women in our cohort.

Although CRP has been shown to be independently associated with multiple atherosclerotic outcomes, including PAD, it is certainly not the only measure of inflammation. For example, fibrinogen is an acute-phase reactant that affects platelet and red cell aggregation[60–63] and is associated with the development[64,65] and severity of PAD.[66,67] Fibrinogen levels also differ by gender and race and have been reported to be higher in women than men[68–73] and in blacks compared to whites.[68,69,73] Adiponectin is the most abundant circulating adipokine and has both antiatherogenic and -inflammatory effects.[74–76] Adiponectin levels are also significantly higher in women than in men,[77–81] even after adjusting for BMI.[82] Higher adiponectin levels have also been associated with a lower risk of incident PAD among initially healthy women.[83] Unfortunately, neither fibrinogen nor adiponectin was measured in this data set, and further investigation of these and other inflammatory biomarkers could provide better insights into the role of inflammation, PAD, and gender.

Table 3. Association of ABI With Risk Factors, Stratified by Gender

ABI (outcome)	Women				Men			
	≤0.90	0.91 to 1.00	1.01 to 1.29	≥1.30	≤0.90	0.91 to 1.00	1.01 to 1.29	≥1.30
N	5442	30 091	97 013	1204	1901	8472	59 195	2428
Unadjusted	OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)	OR (95% CI)		OR (95% CI)
Age (per 10-year increase)	1.69 (1.65, 1.74)	1.15 (1.14, 1.17)	1.00 (ref)	1.08 (1.02, 1.14)	2.07 (1.99, 2.17)	1.15 (1.12, 1.17)	1.00 (ref)	1.18 (1.13, 1.22)
Blacks (vs whites)	2.10 (1.87, 2.36)	1.31 (1.22, 1.40)	1.00 (ref)	1.07 (0.78, 1.48)	1.70 (1.37, 2.12)	1.55 (1.38, 1.74)	1.00 (ref)	0.62 (0.46, 0.84)
Smoking (current vs former/never)	1.95 (1.83, 2.07)	1.32 (1.28, 1.36)	1.00 (ref)	0.79 (0.67, 0.93)	2.53 (2.30, 2.77)	1.41 (1.34, 1.48)	1.00 (ref)	0.81 (0.73, 0.90)
CRP (per doubling)	1.21 (1.18, 1.23)	1.08 (1.07, 1.09)	1.00 (ref)	0.99 (0.95, 1.03)	1.38 (1.33, 1.43)	1.09 (1.07, 1.11)	1.00 (ref)	0.99 (0.96, 1.02)
Coronary artery disease	2.78 (2.52, 3.06)	1.27 (1.19, 1.36)	1.00 (ref)	1.23 (0.94, 1.62)	3.91 (3.49, 4.38)	1.47 (1.36, 1.59)	1.00 (ref)	1.15 (0.99, 1.34)
Cholesterol/HDL ratio	1.09 (1.08, 1.11)	1.03 (1.02, 1.04)	1.00 (ref)	0.97 (0.93, 1.01)	1.03 (1.01, 1.05)	1.02 (1.01, 1.03)	1.00 (ref)	0.96 (0.94, 0.99)
Diabetes mellitus	2.10 (1.93, 2.28)	1.20 (1.14, 1.26)	1.00 (ref)	1.20 (0.97, 1.48)	2.66 (2.36, 3.01)	1.29 (1.19, 1.39)	1.00 (ref)	1.33 (1.16, 1.52)
Hypertension	2.06 (1.95, 2.18)	1.25 (1.22, 1.28)	1.00 (ref)	1.03 (0.92, 1.16)	2.09 (1.91, 2.30)	1.20 (1.14, 1.25)	1.00 (ref)	1.07 (0.99, 1.16)
Adjusted*								
Age (per 10-year increase)	1.65 (1.60, 1.71)	1.15 (1.13, 1.17)	1.00 (ref)	1.05 (0.98, 1.13)	1.93 (1.82, 2.04)	1.13 (1.09, 1.16)	1.00 (ref)	1.14 (1.08, 1.20)
Blacks (vs whites)	2.02 (1.74, 2.34)	1.35 (1.24, 1.46)	1.00 (ref)	1.24 (0.86, 1.79)	1.95 (1.50, 2.54)	1.57 (1.36, 1.81)	1.00 (ref)	0.57 (0.39, 0.83)
Smoking (current vs former/never)	2.25 (2.08, 2.43)	1.34 (1.28, 1.39)	1.00 (ref)	0.84 (0.70, 1.02)	2.29 (2.04, 2.57)	1.36 (1.28, 1.44)	1.00 (ref)	0.79 (0.70, 0.89)
CRP (per doubling)	1.16 (1.13, 1.19)	1.06 (1.05, 1.07)	1.00 (ref)	0.99 (0.94, 1.04)	1.30 (1.24, 1.35)	1.08 (1.06, 1.10)	1.00 (ref)	1.00 (0.97, 1.04)
Coronary artery disease	1.90 (1.68, 2.14)	1.16 (1.08, 1.26)	1.00 (ref)	1.16 (0.82, 1.63)	2.22 (1.93, 2.56)	1.28 (1.16, 1.41)	1.00 (ref)	0.92 (0.76, 1.12)
Cholesterol/HDL ratio	1.08 (1.06, 1.10)	1.02 (1.01, 1.03)	1.00 (ref)	0.95 (0.90, 1.00)	1.06 (1.04, 1.09)	1.03 (1.01, 1.04)	1.00 (ref)	0.98 (0.95, 1.01)
Diabetes mellitus	1.45 (1.31, 1.51)	1.06 (1.00, 1.13)	1.00 (ref)	1.08 (0.82, 1.42)	1.71 (1.47, 1.98)	1.11 (1.01, 1.22)	1.00 (ref)	1.33 (1.13, 1.57)
Hypertension	1.40 (1.31, 1.51)	1.13 (1.09, 1.16)	1.00 (ref)	1.02 (0.87, 1.19)	1.30 (1.16, 1.47)	1.09 (1.02, 1.15)	1.00 (ref)	1.04 (0.93, 1.15)

ABI indicates ankle brachial index; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; OR, odds ratio.
*Adjusted for age, race, hypertension, smoking, CRP, coronary artery disease, cholesterol/HDL ratio, and diabetes mellitus.

Table 4. Comparison of Ankle Brachial Index Values in Healthy Subgroup* of Women and Men

	Women	Men	P Value
N	20 508	11 906	
Mean ankle brachial index (SD)	1.06 (0.09)	1.11 (0.10)	<0.001
Ankle brachial index categories			
≤0.90	438 (2%)	125 (1%)	<0.001
0.91 to 1.00	4015 (20%)	1183 (10%)	
1.01 to 1.29	15 836 (77%)	10 182 (86%)	
≥1.30	219 (1%)	416 (4%)	

*Healthy subgroup includes those participants without hypertension, diabetes mellitus, coronary artery disease, hypercholesterolemia, not a current smoker, and with C-reactive protein level <3 mg/L.

Our subgroup analysis of "healthy participants" demonstrated that women without CVD risk factors were still significantly more likely than men without CVD risk factors to have PAD. These results are similar to findings from other large studies and suggest that alternative risk factors may be more strongly associated with PAD in women compared to men. In a cohort of over 15 000 participants in the Atherosclerosis Risk in Communities Study, women who had never smoked were more likely to develop PAD, compared to male never-smokers, even after adjustment for age, LDL cholesterol, hypertension, and DM.[13] In a study of 1932 participants free of 4 traditional CVD risk factors (smoking, DM, hypertension, and dyslipidemia) in MESA, there was still a significant association between female gender and lower ABI.[84] This suggests that non-CVD risk factors might be driving the higher prevalence of PAD in women relative to men. In addition to inflammation, other PAD risk factors that disproportionately affect women, compared to men, may help to explain these findings, and further research studies are needed to identify these gender-specific PAD risk factors.

In our study, men had a significantly higher prevalence of abnormally high ABI levels (ABI≥1.3) compared to women. This finding is consistent with many previous studies,[9,10,85] but the reasons for this gender difference are not well understood. High ABI is believed to be the result of arterial wall stiffness secondary to medial arterial calcification, a common finding in diabetics. We found older age and diabetes to be significantly associated with ABI≥1.3 in men, but not in women. It is possible that the pathophysiology of diabetes and the effect of the disease on the various arterial beds are different in men compared to women, but this requires further study.

Because women with PAD experience higher rates of functional decline[15] and may have worse outcomes after invasive treatment for PAD compared to men,[17,18,86–96] it is imperative that we better understand gender-specific risk factors for this disease. In a longitudinal study of men and women with PAD, women were more likely to lose the ability to walk for 6 minutes continuously, had greater mobility loss, and faster decline in walking velocity at 4 years of follow-up.[15] Women with PAD also present for invasive treatment at later stages of disease,[97–99] are more likely to require emergent vascular procedures,[100,101] and may be more likely to require amputation as first-line treatment compared to men.[97] A better understanding of gender-specific risk factors for PAD could contribute to the development of lifestyle changes or therapies that could delay the development of advanced PAD, especially in women.

One might question whether this is an issue of misclassification, that perhaps there are different "normal" ABI levels in men, compared to women, and across ethnic groups. In a fully adjusted model of 1775 healthy participants in MESA, women had approximately 0.02 lower ABI values than men, and blacks had approximately 0.02 lower ABI levels than whites. Although women may have slightly lower ABI values, on average, compared to men,[102] this does not appear to be an issue of misclassification of risk for women, because an ABI≤1.0 carries considerable risk for adverse CVD events in both genders.[9,10,103] In the Health, Aging and Body Composition cohort, ABI≤1.0 was strongly associated with risk for CVD events in women, arguing against the idea that the higher prevalence of ABI≤1.0 simply reflects a lower "normal" ABI value in women.[104]

Our study has several limitations. This is a cross-sectional study without longitudinal data to evaluate the outcomes or progression of PAD. There is also the possibility of residual confounders. This is also a voluntary screening population of individuals who were willing to self-pay for diagnostic tests, which may not be generalizable to other populations. In addition, the majority of the participants were white, and our results may not be generalizable to a multiethnic population.

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Disclosures

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