Socioeconomic Inequality and Peripheral Artery Disease Prevalence in US Adults

Reena L. Pande, MD, MSc; Mark A. Creager, MD

Background—Lower socioeconomic status is associated with cardiovascular disease. We sought to determine whether there is a higher prevalence of peripheral artery disease (PAD) in individuals with lower socioeconomic status.

Methods and Results—We analyzed data from the National Health and Nutrition Examination Survey 1999 to 2004. PAD was defined based on an ankle–brachial index ≤0.90. Measures of socioeconomic status included poverty–income ratio, a ratio of self-reported income relative to the poverty line, and attained education level. Of 6791 eligible participants, overall weighted prevalence of PAD was 5.8% (SE, 0.3). PAD prevalence was significantly higher in individuals with low income and lower education. Individuals in the lowest of the 6 poverty–income ratio categories had more than a 2-fold increased odds of PAD compared with those in the highest poverty–income ratio category (odds ratio, 2.69; 95% confidence interval, 1.80–4.03; P<0.0001). This association remained significant even after multivariable adjustment (odds ratio, 1.64; 95% confidence interval, 1.04–2.6; P=0.034). Lower attained education level also associated with higher PAD prevalence (odds ratio, 2.8; 95% confidence interval, 1.96–4.0; P<0.0001) but was no longer significant after multivariable adjustment.

Conclusions—Low income and lower attained education level are associated with PAD in US adults. These data suggest that individuals of lower socioeconomic status remain at high risk and highlight the need for education and advocacy efforts focused on these at-risk populations. (Circ Cardiovasc Qual Outcomes. 2014;7:532-539.)

Key Words: epidemiology ■ peripheral arterial disease ■ social class

Despite marked improvements in cardiovascular care during the past several decades, substantial disparities persist in the management and outcomes of patients with cardiac and vascular diseases. Socioeconomic status (SES), reflecting education, income, occupation, and social status, continues to be an important contributor to overall health. Low SES has been linked with higher prevalence of coronary heart disease, coronary heart disease mortality, and with higher rate of risk factors for coronary heart disease, such as diabetes mellitus, hypertension, smoking, and physical inactivity. Moreover, the substantial improvements in cardiovascular disease (CVD) care have not been experienced equally by all socioeconomic segments of the population.

Although the association between SES and heart disease is well established, few studies have examined the relationship between SES and peripheral artery disease (PAD). Existing studies of the association between SES and PAD have been inconsistent. Furthermore, although it has been shown that racial disparities, sex, and cardiovascular risk factors affect the prevalence of PAD, the factors that account for the association of low SES with vascular disease are not well understood. We hypothesized that there would be a significantly higher prevalence of PAD in individuals with lower SES and sought to understand the factors that might account for an association between SES and PAD. We used nationally representative data from the National Health and Nutrition Examination Survey (NHANES) to explore the association of SES and PAD in the US population.

Methods

NHANES is a series of surveys conducted by the National Center for Health Statistics to assess the health and nutritional status of the civilian US population. By using a complex, stratified, multistage survey design with oversampling of traditionally under-represented individuals, NHANES is a nationally representative data set. NHANES has been reviewed and approved by the Institutional Review Board at the National Center for Health Statistics.

Definition of PAD and Ankle–Brachial Index

Methodology in NHANES

Ankle–brachial index (ABI) measurements were obtained as part of the NHANES lower extremity examination in adults aged ≥40 years during the survey years 1999 to 2004. According to NHANES protocol, blood pressure measurements were obtained with subjects in the supine position. Systolic blood pressure was measured in the right arm only and in the posterior tibial arteries at both ankles using an 8-MHz Doppler probe. We calculated the ABI for each leg by dividing the ankle pressure by the arm pressure. A diagnosis of PAD was assigned if either leg had an ABI ≤0.90. An ABI value >1.40 was considered to reflect noncompressible vessels secondary to vascular calcification.
WHAT IS KNOWN

• Socioeconomic inequalities have a significant impact on cardiovascular disease, resulting in higher prevalence and poorer outcomes in patients with coronary disease. Few studies have explored the impact of socioeconomic status on the prevalence of peripheral artery disease, a manifestation of systemic atherosclerosis with significant morbidity and mortality.

WHAT THE STUDY ADDS

• Lower income and lower attained education level, measures of socioeconomic status, are associated with higher prevalence of peripheral artery disease in the United States.
• This research highlights the need to focus on education and advocacy efforts for these at-risk populations in lower socioeconomic strata.

Definitions of Socioeconomic Variables

The poverty–income ratio (PIR) was used as a measure of household income. The PIR is a ratio of self-reported household income relative to a family’s poverty threshold based on family size and composition, year (allowing annual updates to account for inflation), and state of residence. Household income was self-reported as an absolute value. In the small number of individuals who chose not to provide exact income, income was reported as above or below $20000. PIR could not be calculated for these respondents. A PIR value <1.0 indicates family income below the poverty threshold. PIR was categorized as <1.0, 1.0 to 1.99, 2.0 to 2.99, 3.0 to 3.99, 4.0 to 4.99, and ≥5.0 given that the PIR variable in NHANES was top coded at 5.0. PIR data were available for 6791 individuals in our sample population.

Participants provided their highest attained grade or level of education by self-report. Responses were categorized as less than 9th grade education, 9th to 11th grade, completed high school or equivalent, some college education, and college graduate or higher. We further categorized education as less than high school, high school or some college, and college graduate or above. Education data were available on 7441 individuals in our sample population. Health insurance coverage was self-reported. Subjects also reported whether coverage was private insurance, Medicare, or Medicaid.

Definitions of Covariates

Age, sex, race/ethnicity, and smoking status were based on self-report as previously reported. A diagnosis of hypertension was assigned if systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90, based on prior physician diagnosis or if subjects reported taking a prescription medication for hypertension. Hyperlipidemia was considered present if subjects reported a physician diagnosis of elevated cholesterol or had a total cholesterol level ≥240 mg/dL (6.21 mmol/L). Subjects were considered to have diabetes mellitus if they reported a physician diagnosis of diabetes mellitus, were taking prescription medications for diabetes mellitus (either insulin or oral agents), or had nonfasting glucose values ≥200 mg/dL (11.1 mmol/L) or fasting glucose values ≥126 mg/dL (7 mmol/L). Diagnosis of CVD was based on an affirmative response to the question, “Has a doctor or other health professional ever told you that you had [coronary heart disease, angina (also called angina pectoris), heart attack (also called myocardial infarction), or stroke]?” The Modification of Diet in Renal Disease (MDRD) study equation was used to estimate glomerular filtration rate, and estimated glomerular filtration rate <60 mL·min⁻¹·m² indicated chronic kidney disease (CKD).

Medication use was self-reported, although interviewers examined all prescription medication containers when available to confirm medication use. We included statin therapy, aspirin and any antiplatelet therapy (including aspirin, clopidogrel, dipyridamole, ticlopidine, or combinations of these medications), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and β-blocker use.

Statistical Methods

Analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC) using survey-specific methods with use of appropriate sample weights, stratum, and primary sampling unit variables to account for NHANES’ complex sample design. Descriptive statistics are reported as weighted mean and SE for continuous variables or weighted proportion (or percentage) and SE for categorical variables. Categorical variables were compared using the χ² test. Comparisons of mean values across groups and correlations between continuous variables were achieved by linear regression. The association of PAD and socioeconomic variables was estimated by logistic regression with data presented as odds ratios (ORs) and 95% confidence intervals (CIs). Multivariable logistic regression models were crafted to account for demographic variables (age, sex, race/ethnicity), atherosclerotic risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking status), existing CVD, CKD, and the inflammatory biomarker C-reactive protein (CRP). Additional analyses accounted for the other available measures of SES (education for income analyses and income for education analyses) and health insurance status. A 2-sided P value of <0.05 was considered to be statistically significant for all analyses.

Results

During the years 1999 to 2004, 7571 NHANES participants aged ≥40 years underwent ABI measurement. We excluded 113 subjects who had ABI ≥1.4 indicating vascular calcification artifact. After exclusion of 667 individuals without available socioeconomic data, the study population comprised 6791 NHANES participants. There were 586 cases of PAD for an overall weighted prevalence of 5.8% (SE, 0.3).

Baseline characteristics and baseline socioeconomic variables are shown in Table 1. Participants with PAD were older and were more likely to be current or former smokers. Prevalence of diabetes mellitus, hypertension, hyperlipidemia, CKD, and other CVD was higher in subjects with PAD. Body mass index was not significantly different between the 2 groups. Subjects with PAD who were insured were more likely to have Medicare (reflecting the higher average age in this group) and Medicaid coverage. Fewer subjects with PAD had a college degree or higher.

We examined the baseline characteristics of patients who were excluded on the basis of missing socioeconomic data. Of the 667 patients excluded, there were 61 cases of PAD. There was no significant difference in the weighted prevalence of PAD in this group (7.3% [SE, 1.2] compared with those included in the final analysis [5.8% [SE, 0.3]; P=0.18]. There were also no significant differences in the baseline characteristics of the individuals excluded from the analysis (data not shown).

Characteristics of all participants according to SES (PIR category) are shown in Table 2. Individuals in the lowest income categories were more likely to be of nonwhite race/ethnicity and had higher prevalence of cardiovascular risk factors, including smoking, diabetes mellitus, hypertension, and hyperlipidemia. History of existing CVD was also more common in the lower PIR categories. Use of statin therapy, any

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lipid-lowering agent, aspirin or antiplatelet therapy, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and β-blocker use was lowest in the lower PIR categories, although the trend across categories was not consistent (Table 2).

### PAD and Income

PAD prevalence was significantly higher in individuals in lower income categories (Figure 1). Accordingly, when compared with individuals in the highest PIR category (≥5), the odds of PAD was significantly higher for individuals with PIR <1.0 (OR, 2.67; 95% CI, 1.7–4.3; P<0.0001; Table 3). The odds of PAD were not significantly different for those in higher PIR categories compared with the highest category (OR, 1.08; 95% CI, 0.6–1.9 for PIR 3.0–3.99 and OR, 1.1; 95% CI, 0.7–1.9 for PIR 4.0–4.99). The association remained statistically significant for the lowest 3 PIR categories even after adjustment for age, sex, and race/ethnicity (Table 3). After additional multivariable adjustment including atherosclerotic risk factors, existing CVD, CKD, CRP, education, and insurance status, the odds of PAD remains significantly higher in the lowest PIR category (OR, 1.64; 95% CI, 1.04–2.6; P=0.034).

Based on the prevalence data suggesting a threshold of increased PAD prevalence in the lower 3 PIR categories <1.0,
Table 2. Baseline Characteristics by Poverty–Income Ratio Category

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Poverty–Income Ratio (and n Per Category)</th>
<th>&gt;5.0 (1418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>&lt;1.0 (1036)</td>
<td>&lt;1.0–1.99 (1751)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>57 (1.9)</td>
<td>51.5 (2.0)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white (%)</td>
<td>53.1 (4.1)</td>
<td>68.9 (3.0)</td>
</tr>
<tr>
<td>Non-Hispanic black (%)</td>
<td>17.7 (2.9)</td>
<td>12.2 (1.5)</td>
</tr>
<tr>
<td>Mexican American (%)</td>
<td>10.2 (2.5)</td>
<td>7.6 (1.4)</td>
</tr>
<tr>
<td>Other (including multiracial) (%)</td>
<td>18.9 (3.9)</td>
<td>11.2 (1.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>130.2 (1.0)</td>
<td>132.0 (0.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.8 (0.6)</td>
<td>71.6 (0.5)</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; and GFR, glomerular filtration rate.

1.0 to 1.99, and 2.0 to 2.99 (Figure 1), we dichotomized PIR in 2 categories (<3.0 or ≥3.0). Individuals with PIR <3.0 had a nearly 3-fold increased odds of PAD compared with those in the higher PIR categories (OR, 2.75; 95% CI, 2.2–3.5; P <0.0001). This relationship remained statistically significant even after multivariable adjustment for demographics (OR, 1.81; 95% CI, 1.4–2.4; P <0.0001), as well as atherosclerotic risk factors, CVD, CKD, CRP, education, and insurance status with individuals of lower income having a 50% increased odds of PAD compared with those in higher income categories (OR, 1.50; 95% CI, 1.13–1.98; P =0.0045). There was no significant difference in the findings even after adjusting for differences in use of cardiovascular risk-modifying medications, such as antiplatelet therapy, statins, β-blockers, and...
angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

**PAD and Education Level**

Compared with individuals without PAD (Table 1), participants with PAD had lower education levels with more PAD subjects having less than high school level of education (30.4±2.5% versus 18.8±0.9%) and fewer having completed college (16.4±2.1% versus 26.5±1.3%). When considering the prevalence of PAD according to education level, there was significantly greater PAD prevalence in individuals with lower levels of achieved education (Figure 2). The highest prevalence of PAD was noted in individuals with less than high school education (9.0±0.7%) and the lowest prevalence was in those with a college education or greater (3.7±0.5%). This resulted in an unadjusted odds of PAD of 2.8 (95% CI, 1.96–4.0; \( P = 0.0001 \)) among those with less than high school education level and 1.69 (95% CI, 1.2–2.4; \( P < 0.0001 \)) among those with high school education or some college compared with those with a college education or greater (Table 4). These findings remained significant after adjustment for demographics, but were no longer significant in a fully adjusted model (OR, 1.02; 95% CI, 0.7–1.5; \( P = 0.9 \)) compared with those with less than high school education; Table 4). Findings were similar for those with high school education or some college (OR, 1.005; 95% CI, 0.7–1.4; \( P = 0.9 \)) compared with the highest level of education. These findings remained unchanged after additionally accounting for differences in medication use (including antiplatelet therapy, statins, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers).

**Discussion**

In this nationally representative sample of adults in the United States, we observed a strong relationship between indicators of lower SES, such as income or education level, and higher prevalence of PAD. The relationship between PAD and low income persisted even after multivariable adjustment, including adjustment for other socioeconomic variables, such as education and insurance status. As might be expected, however, the association was attenuated by demographic factors and disparities in the prevalence of recognized cardiovascular risk factors. These data demonstrate that income has a significant impact on the prevalence of vascular disease and that some of this effect may be attributable to factors not accounted for in traditional demographics and cardiovascular risk factors. In contrast, the association between education and PAD was largely accounted for by demographics and by the prevalence of traditional cardiovascular risk factors.

That socioeconomic factors and CVD are linked is well established. However, the relationship of socioeconomic factors to peripheral vascular disease in particular has been less rigorously studied and prior studies were inconsistent. Data from the Atherosclerosis Risk in Communities (ARIC) Study did not demonstrate an association between an individual’s cumulative SES across the life course with prevalence of PAD. In contrast, a prospective cohort study from Germany demonstrated greater prevalence of PAD and lower ABI measurements with lower education and income levels; however, the findings were no longer significant after multivariable adjustment. Prior studies have also shown that lower SES in patients with PAD may also be linked to worse vascular outcomes. One study showed a 65% greater rate of PAD-related amputations in individuals of lower SES. Our data are unique and novel in that they provide nationally representative and generalizable data from the United States using NHANES. These data also for the first time suggest a strong

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**Table 3. Association of Income (Poverty–Income Ratio) and Peripheral Artery Disease**

<table>
<thead>
<tr>
<th>Poverty–Income Ratio Category</th>
<th>&lt;1.0</th>
<th>1.0–1.99</th>
<th>2.0–2.99</th>
<th>3.0–3.99</th>
<th>4.0–4.99</th>
<th>≥5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.69 (1.8–4.0)</td>
<td>3.14 (2.2–4.4)</td>
<td>2.67 (1.7–4.3)</td>
<td>1.08 (0.6–1.9)</td>
<td>1.1 (0.7–1.9)</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 1 (unadjusted model-age, sex, race/ethnicity)</td>
<td>2.11 (1.4–3.3)</td>
<td>1.70 (1.2–2.4)</td>
<td>1.73 (1.02–2.9)</td>
<td>0.93 (0.5–1.6)</td>
<td>1.03 (0.63–1.7)</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 2 (model 1+DM, HTN, hyperlipidemia, smoking)</td>
<td>1.69 (1.1–2.6)</td>
<td>1.40 (0.98–2.0)</td>
<td>1.50 (0.87–2.6)</td>
<td>0.83 (0.48–1.5)</td>
<td>0.97 (0.58–1.6)</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 3 (model 2+CVD, CKD, CHF, and CRP)</td>
<td>1.67 (1.1–2.5)</td>
<td>1.29 (0.92–1.8)</td>
<td>1.48 (0.86–2.5)</td>
<td>0.82 (0.47–1.5)</td>
<td>0.97 (0.58–1.6)</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 4 (model 3+income and insurance status)</td>
<td>1.64 (1.04–2.6)</td>
<td>1.26 (0.86–1.9)</td>
<td>1.46 (0.83–2.6)</td>
<td>0.82 (0.45–1.5)</td>
<td>0.97 (0.57–1.6)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; and HTN, hypertension.
and persistent association between lower SES, particularly income, and prevalence of PAD.

The present study also helps broaden the understanding of the factors that may contribute to the association between PAD and SES. Although demographic factors, including race/ethnicity, and traditional atherosclerotic risk factors, such as diabetes mellitus, hypertension, and smoking, contribute, they only partially account for these findings. The impact of racial disparities on the association between PAD and SES is underscored by prior studies showing that black patients with PAD are more likely to undergo amputation and less likely to undergo revascularization or wound debridement before amputation. However, our data also show that the association between income and PAD remains significant even after adjusting for race and ethnicity, traditional cardiovascular risk factors, comorbid cardiac conditions, and even other socioeconomic variables, including education and health insurance status. In addition, despite recent work from Subherwal et al demonstrating disparities in the use of cardiovascular medications among patients with PAD, we did not find that medication use affected the relationship between SES and prevalence of PAD.

Inflammatory markers, strongly linked to vascular disease, are higher in individuals of lower income and education, suggesting that they might serve as mediators of the link between SES and PAD. For example, in Women’s Health Study, the association of low SES and incident cardiovascular events was explained partially by novel cardiovascular risk factors including CRP, intercellular adhesion molecule-1, and fibrinogen. In the present data set, only CRP was available for inclusion in multivariable model, but we found that the relationship between income and PAD remained significant even after addition of this inflammatory marker into the model.

Several other unmeasured factors may serve as mediators of the SES and PAD association. Chronic psychosocial stress is known to have a major impact on CVD. Impaired lower extremity function can have an adverse impact on health-related quality of life, and perceived stress may further impair quality of life in patients with PAD. However, whether stress may have a causal effect on PAD prevalence remains unclear.

It is important to note that education and income are only 2 of many potential measures of SES, and although both are measures of SES, they may have distinct effects on overall health. Our data set does not allow assessment of other measures of SES, including total wealth (which may be a better measure of an individual’s ability to withstand financial or social stressors), familial and friend networks, material goods, and power and prestige. Also difficult to capture in SES is the reflection of overall access to resources and opportunities that may impact health outcomes.

The disparities in PAD prevalence highlighted here indicate that we need dedicated approaches to PAD awareness efforts, research endeavors, and treatment strategies that focus on those individuals of low socioeconomic strata who may be most likely to be affected by PAD. A telephone survey to assess PAD awareness showed that knowledge gaps around PAD were more notable in less educated and lower income respondents. Accordingly, PAD awareness efforts need to be targeted to subpopulations of lower SES that have the greatest gaps in awareness and at the same time are at higher risk of developing PAD. Similarly, in the evaluation and implementation of new therapies or treatment strategies, we need to consider not only that differences in outcomes may arise from socioeconomic differences, but also that we need to improve strategies to allow beneficial treatments to reach all segments of the population equally.

The limitations of these data are important to acknowledge. First, there are inherent and recognized limitations in the income and education variables used to reflect SES. Income, although theoretically easy to measure, can be limited by a respondent’s lack of willingness to reveal it.

Table 4. Association of Attained Education Level and Peripheral Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>Less Than HS</th>
<th></th>
<th>HS/Some College</th>
<th></th>
<th>College or Greater</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.8 (1.96–4.02)</td>
<td>&lt;0.0001</td>
<td>1.69 (1.2–2.36)</td>
<td>&lt;0.0001</td>
<td>Ref</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Model 1 (unadjusted model+age, sex, race/ethnicity)</td>
<td>1.87 (1.26–2.78)</td>
<td>0.0019</td>
<td>1.43 (1.02–2.02)</td>
<td>0.038</td>
<td>Ref</td>
<td>0.0017</td>
</tr>
<tr>
<td>Model 2 (model 1+DM, HTN, hyperlipidemia, smoking)</td>
<td>1.44 (0.98–2.1)</td>
<td>0.06</td>
<td>1.19 (0.84–1.68)</td>
<td>0.3</td>
<td>Ref</td>
<td>0.055</td>
</tr>
<tr>
<td>Model 3 (model 2+CVD, CKD, CHF, and CRP)</td>
<td>1.38 (0.93–2.1)</td>
<td>0.11</td>
<td>1.18 (0.82–1.7)</td>
<td>0.4</td>
<td>Ref</td>
<td>0.1</td>
</tr>
<tr>
<td>Model 4 (model 3+income and insurance status)</td>
<td>1.04 (0.7–1.6)</td>
<td>0.9</td>
<td>1.005 (0.7–1.4)</td>
<td>0.9</td>
<td>Ref</td>
<td>0.8</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; HS, high school; HTN, hypertension; and OR, odds ratio.
However, studies examining the reliability of self-reported income suggest that when compared with true wage and salary information (e.g., tax records), there is generally low bias and error. In some cases, and perhaps more so in lower socioeconomic strata, income can vary over a short period of time and can vary over one’s lifetime. In addition, the impact of income differs based on family size. We have accounted for this limitation by using the PIR instead of raw income. Income is also not a surrogate for wealth, and wealth, which includes not only income but also other existing resources such as real estate and stock ownership, may be a better measure of an individual’s ability to withstand financial stress. Although an excellent measure of SES, income is the Simon C. Fireman Scholar in Cardiovascular Medicine at Brigham and Women’s Hospital. is the recipient of a Scientist Development Grant Award (K12 HL083786) from the National Heart, Lung, Blood Institute and is the recipient of a Scientist Development Grant (K12 HL083786) from the National Heart, Lung, Blood Institute. Dr. Pande has received support from a Research Career Development Award (K07 HL083786), a grant from the National Heart, Lung, Blood Institute, and a grant from the National Heart, Lung, Blood Institute.}

None.

**Sources of Funding**

Dr Pande has received support from a Research Career Development Award (K12 HL083786) from the National, Heart, Lung Blood Institute and is the recipient of a Scientist Development Grant (K12 HL083786) from the National Heart, Lung, Blood Institute. Dr Creager is the simon C. Fireman Scholar in Cardiovascular Medicine at Brigham and Women’s Hospital.

**References**


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Circ Cardiovasc Qual Outcomes. 2014;7:532-539; originally published online July 1, 2014;
doi: 10.1161/CIRCOUTCOMES.113.000618
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circoutcomes.ahajournals.org/content/7/4/532

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