Utility of Nontraditional Risk Markers in Individuals Ineligible for Statin Therapy According to the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines

Joseph Yeboah, MD, MS; Tamar S. Polonsky, MD; Rebekah Young, PhD; Robyn L. McClelland, PhD; Joseph C. Delaney, PhD; Farah Dawood, MD, MS; Michael J. Blaha, MD, MPH; Michael D. Miedema, MD; Christopher T. Sibley, MD; J. Jeffrey Carr, MD, MSc; Gregory L. Burke, MD, MS; David C. Goff, Jr, MD, PhD; Bruce M. Psaty, MD, PhD; Philip Greenland, MD; David M. Herrington, MD, MHS

Background—In the general population, the majority of cardiovascular events occur in people at the low to moderate end of population risk distribution. The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol recommends consideration of statin therapy for adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk ≥7.5% based on traditional risk factors. Whether use of nontraditional risk markers can improve risk assessment in those below this threshold for statin therapy is unclear.

Methods and Results—Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population sample free of clinical CVD at baseline, we calibrated the Pooled Cohort Equations (cPCE). ASCVD was defined as myocardial infarction, coronary heart disease death, or fatal or nonfatal stroke. Adults with an initial cPCE <7.5% and elevated levels of additional risk markers (abnormal test) whose new calculated risk was ≥7.5% were considered statin eligible: low-density lipoprotein cholesterol ≥160 mg/dL; family history of ASCVD; high-sensitivity C-reactive protein ≥2 mg/dL; coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; and ankle-brachial index <0.9. We compared the absolute and relative ASCVD risks among those with versus without elevated posttest estimated risk. We calculated the number needed to screen to identify 1 person with abnormal test for each risk marker, defined as the number of participants with baseline cPCE risk <7.5% divided by the number with an abnormal test reclassified as statin eligible. Of 5185 participants not taking statins with complete data (age, 45–84 years), 4185 had a cPCE risk <7.5%. During 10 years of follow-up, 57% of the ASCVD events (183 of 320) occurred among adults with a cPCE risk <7.5%. When people with diabetes mellitus were excluded, the coronary artery calcium criterion reclassified 6.8% upward, with an event rate of 13.3%, absolute risk of 10%, relative risk of 4.0 (95% confidence interval [CI], 2.8–5.7), and number needed to screen of 14.7. The corresponding numbers for family history of ASCVD were 4.6%, 15.1%, 12%, 4.3 (95% CI, 3.0–6.4), and 21.8; for high-sensitivity C-reactive protein criteria, 2.6%, 10%, 6%, 2.6 (95% CI, 1.4–4.8), and 39.2; for ankle-brachial index criteria, 0.6%, 9%, 5%, 2.3 (95% CI, 0.6–8.6), and 176.5; and for low-density lipoprotein cholesterol criteria, 0.5%, 5%, 1%, 1.2 (95% CI, 0.2–8.4), and 193.3, respectively. Of the 3882 with <7.5% cPCE risk, 431 (11.1%) were reclassified to ≥7.5% (statin eligible) by at least 1 of the additional risk marker criteria.

Conclusions—In this generally low-risk population sample, a large proportion of ASCVD events occurred among adults with a 10-year cPCE risk <7.5%. We found that the coronary artery calcium score, high-sensitivity C-reactive protein, family history of ASCVD, and ankle-brachial index recommendations by the American College of Cardiology/American Heart Association cholesterol guidelines (Class IIB) identify small subgroups of asymptomatic population with a 10-year cPCE risk <7.5% but with observed ASCVD event rates >7.5% who may warrant statin therapy considerations.

Key Words: cholesterol ■ coronary artery calcium ■ epidemiology ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ primary prevention


Key Words: cholesterol ■ coronary artery calcium ■ epidemiology ■ hydroxymethylglutaryl-CoA reductase inhibitors ■ primary prevention

Received April 3, 2015; accepted June 22, 2015.

From Heart and Vascular Center of Excellence, Wake Forest Baptist Health, Winston Salem, NC (J.Y., F.D., D.M.H.); Section of Cardiology, Department of Internal Medicine, University of Chicago, IL (T.S.P.); Department of Biostatistics (R.Y., R.L.M., J.C.D.) and Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services (B.M.P.), University of Washington, Seattle; Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins University School of Medicine, Baltimore, MD (M.J.B.); Minneapolis Heart Institute and Minneapolis Heart Institute Foundation, MN (M.D.M.); Radiology, Oregon Health and Science University, Portland (C.T.S.); Radiology, Vanderbilt University School of Medicine, Nashville, TN (J.J.C.); Public Health, Wake Forest University School of Medicine, Winston Salem, NC (G.L.B.); Public Health, University of Colorado School of Public Health, Aurora (D.C.G.); Group Health Research Institute, Group Health Cooperative, Seattle, WA (B.M.P.); and Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (P.G.).

Correspondence to Joseph Yeboah, MD, MS, Heart and Vascular Center of Excellence, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157. E-mail jyeboah@wakehealth.edu

© 2015 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.115.016846

916
In the recently published guidelines on the assessment of cardiovascular risk and treatment of blood cholesterol to reduce atherosclerotic risk in adults,1,2 the American College of Cardiology (ACC) and American Heart Association (AHA) introduced a new approach to decision making for statin therapy. Specifically, the guidelines recommended that "In selected individuals who are not in 1 of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional markers may be considered to inform treatment decision making (Class II)."1 The markers mentioned included low-density lipoprotein (LDL) cholesterol (LDL-C) ≥160 mg/dL, other genetic hyperlipidemias, family history of premature atherosclerotic cardiovascular disease (ASCVD), high-sensitivity C-reactive protein (hs-CRP), coronary artery calcium (CAC), lifetime ASCVD risk, and ankle-brachial index (ABI). If these additional markers could be used to identify subsets of lower-risk people (<7.5% 10-year ASCVD risk) who are actually at higher risk on the basis of additional risk marker testing, this could be extremely important because on a population level the greatest number of cardiovascular events occur, somewhat paradoxically, in those traditionally assessed as being at low to moderate risk.3–5

Methods

Study Population and Data Collection

The design for the MESA study has been published elsewhere.6 In brief, MESA is a prospective, population-based cohort study to investigate the prevalence, correlates, and progression of subclinical CVD in persons without known CVD at baseline. The full cohort includes 6814 women and men 45 to 84 years of age who were recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, NY; and St. Paul, MN). MESA included 38% white, 28% black, 22% Hispanic, and 12% Chinese adults. Demographics, medical history, and anthropometric and laboratory data for the present study were taken from the first examination (July 2000–August 2002). The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

For the present analysis, we excluded participants who had missing data related to traditional or additional risk factors or missing follow-up and those who were using statins at baseline.

Conventional Risk Factors

As part of the baseline examination, clinical teams collected information on traditional and additional putative cardiovascular risk factors. Current smoking was defined as having smoked a cigarette in the last 30 days. Use of medications was based on medication inventory. Diabetes mellitus was defined as self-reported history of diabetes mellitus, diabetes medication use, or fasting glucose ≥126 mg/dL. Resting blood pressure was measured 3 times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or use of antihypertensive medication. Body mass index was calculated as weight in kilograms divided by height in meters squared. Total cholesterol and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-hour fast. LDL-C was estimated by the Friedewald equation.7

Additional Risk Markers Recommended in the Guidelines

The presence of genetic hyperlipidemias as recommended in the guidelines8 was not assessed in the present analysis because it was not collected in MESA. Lifetime ASCVD risk was also not assessed in the present study because it can be calculated only in adults 20 to 59 years of age and many MESA participants are >59 years old. In addition, to create the lifetime risk calculator, only cohorts with >15 years of follow-up were included, which is beyond the duration of follow-up in MESA.

Primary LDL-C ≥160 mg/dL

Measurement of baseline LDL-C is as reported above. Individuals without type 2 diabetes mellitus, with LDL-C <190 mg/dL but a 10-year ASCVD risk of <7.5%, and with LDL-C ≥160 mg/dL were classified as having primary LDL-C ≥160 mg/dL.

Family History of ASCVD

In MESA, we did not specifically define family history of ASCVD as premature (ie, <55 year of age for men and <65 years of age for women). Family history of ASCVD was obtained by asking participants whether any member in their immediate family (first-degree relatives; parents, siblings, and children) experienced fatal or nonfatal myocardial infarction or stroke. Age at onset of the event was not specified, so it is not known whether the events were premature.

hs-CRP ≥2 mg/dL

hs-CRP was measured with the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington). Analytic intra-assay coefficients of variation ranged from 2.3% to 4.4%, and interassay coefficients of variation ranged from 2.1% to 5.7% with a detection level of 0.18 mg/L.

CAC Score ≥300 Agatston Units or ≥75th Percentile for Age, Sex, and Ethnicity

Details of the MESA computed tomography (CT) scanning and interpretation methods have been reported by Carr et al.9 Scanning centers assessed CAC by chest CT with either a cardiac-gated electron-beam CT scanner (field centers in Chicago, IL; Los Angeles, CA; and New York, NY) or a multidetector CT system (field centers in Baltimore, MD; Forsyth County, North Carolina; and St Paul, MN). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA, Torrance, CA). We used the mean Agatston score for the 2 scans in all analyses.9 Intraradiologist and interobserver agreement was excellent (κ=0.93 and κ=0.90, respectively).

ABI <0.9

Details of the MESA ABI measurement protocol have been published by Criqui et al.10 Briefly, systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position with a hand-held Doppler instrument with a 5-MHz probe. To avoid potential bias from subclavian stenosis, the higher of the brachial artery pressures was used as the denominator. For each lower extremity, the ABI numerator used was the highest pressure (dorsalis pedis or posterior tibial) from that leg. Reproducibility of the ABI was evaluated with measurements of 43
participants by 2 technicians. The interreader and intrareader correlation coefficients were 0.845 and 0.937, respectively, with intrareader and interreader coefficients of variation of 5.14% and 3.27%, respectively. Participants with an ABI >1.4 were excluded.

Event Ascertainment
A detailed description of the event ascertainment procedures and the adjudication process in MESA has been published. Briefly, every 9 to 12 months since the baseline examination, MESA participants or their proxies when necessary are contacted to inquire about hospital admissions, CVD diagnosis, and death that may have occurred. Hospital and other documents of possible cardiovascular events and deaths are subsequently obtained. These documents are sent to at least 2 MESA morbidity and mortality committee members for adjudication using a standard protocol. The MESA morbidity committee includes cardiologists, physician epidemiologists, and neurologists. All possible events with disagreements after adjudication by at least 2 MESA morbidity and mortality members are discussed and voted on by the committee during the monthly meetings. For the purposes of this study, we define incident ASCVD as adjudicated myocardial infarction, coronary heart disease death, and fatal and nonfatal stroke as described by the MESA protocol (http://www.mesa-nhlbi.org).

Statistical Analysis
Baseline characteristics are presented as mean±SD for continuous variables and percentages for categorical variables. To avoid overestimating the contribution of the additional risk markers to the PCE risk estimates and to account for estimated baseline survival and censoring, the PCE was calibrated using MESA data. Calibration was accomplished by including the PCE in a Cox model predicting ASCVD events. These calibrated PCEs (cPCEs) were used in all subsequent analyses. Analyses were performed to address 2 specific questions.

1. What proportion of ASCVD events occurred in participants with 10-year cPCE risk <7.5%? This was obtained by dividing the number of adjudicated ASCVD events that occurred in participants with an initial cPCE <7.5% by the total number of ASCVD events that occurred in the whole cohort (n=5185).

2. Among MESA participants with initial 10-year ASCVD risk <7.5% estimated with the new cPCE, what proportion will become statin eligible on the basis of each abnormal test?

Participants with levels of each additional marker that were above the predefined thresholds outlined in the ACC/AHA guidelines (CAC ≥300 Agatston units or ≥75th percentile for age, sex, and race; hs-CRP ≥2 g/dL; ABI <0.9; LDL >160 mg/dL; positive family history in any first-degree relative) whose new calculated 10-year risk for ASCVD events that occurred in participants with an initial cPCE <7.5% was higher than that of the <7.5% subgroup (13.8% versus 4.7%).

Results
Of the 6814 MESA participants, 1629 (23.9%) were on statins, had an ABI ≥1.4, or had incomplete data and were therefore eliminated from this analysis. Baseline characteristics are described in Table 1 for the remaining 5185 participants. The mean age of the participants included in this analysis was 61.2 years; 53.1% were female; 38% were white; 12.1% were Chinese; 27% were black; and 22.9% were Hispanic. After a median of 10.2 years (25th percentile, 9.6 years; 75th percentile, 10.7 years) of follow-up, 320 ASCVD events (6.2%) occurred: 139 (43.4%) were myocardial infarctions, 132 (41.3%) were fatal or nonfatal strokes, and 49 (15.3%) were coronary heart disease deaths.

Before recalibration of the PCE, 1791 of 2456 participants (72.9%) with initial 10-year risk <7.5% had at least 1 abnormal test. Fifty-three of the 320 adjudicated ASCVD events (16%) occurred in those classified by PCE (not calibrated) as <7.5% 10-year risk at baseline. However, 3157 of 4185 participants (75.4%) with initial <7.5% cPCE risk had at least 1 abnormal test after recalibration of the PCE. Table 1 shows the demographic characteristic, risk factors, and proportion of the subcohorts (<7.5% and ≥7.5% cPCE) with abnormal tests for each additional marker.

Discussion
The present study shows that among the additional risk markers enumerated in the new cholesterol guidelines, 1...
Yeboah et al  Utility of Nontraditional Risk Markers 919

CAC, family history of ASCVD, and hs-CRP each identified a small subgroup among those with baseline cPCE risk <7.5% who in fact had a 10-year ASCVD event rate significantly higher than 7.5%. With the use of the risk threshold for statin therapy advocated in the guidelines (7.5% 10-year ASCVD risk), these people would be potentially eligible for statin therapy. Among the risk markers studied, the NNSI was lowest for CAC (14.7). Family history and hs-CRP also have promising yields for identifying higher-risk people. Ultimately, the decision to use these additional risk markers as screening tests for statin therapy will depend on many additional factors, including the risks and costs of the specific tests (nominal for family history of ASCVD, more so for CAC) and the efficacy of statin therapy in the subgroups they identify. Nevertheless, these data emphasize the potential (albeit small) for further refinement of risk assessment.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the MESA Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age (mean±SD), y</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Cholesterol (mean±SD), mg/dL</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>LDL*</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>BMI (mean±SD), kg/m²</td>
</tr>
<tr>
<td>Blood pressure (mean±SD), mm Hg</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Former</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Antihypertensive medication use, n (%)</td>
</tr>
<tr>
<td>CAC ≥300 Agatston units or ≥75th percentile</td>
</tr>
<tr>
<td>hs-CRP ≥ 2 mg/dL</td>
</tr>
<tr>
<td>ABI &lt;0.9</td>
</tr>
<tr>
<td>LDL-C ≥160 mg/dL</td>
</tr>
<tr>
<td>Family history</td>
</tr>
</tbody>
</table>

ABI indicates ankle brachial index; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium score; cPCE, calibrated Pooled Cohort Equation; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; and MI, myocardial infarction.

*LDL sample size=5123 (because of missing values).
through targeted application of additional risk markers such as those considered in this study.

The present study sits at the nexus between the Geoffrey Rose Prevention Paradox and more recently advocated goals of precision medicine. More than 20 years ago, Rose described the fundamental epidemiological observation that, although conventional risk factors identify patients with high relative risk for cardiovascular events, they still miss the much larger number of apparently low-risk people who go on to experience CVD. This observation continues to justify a 2-tiered strategy for CVD prevention: targeted interventions (plus therapeutic lifestyle changes) for those at highest risk and population-based (untargeted) therapeutic lifestyle changes for the rest of the population.

However, for the last 30 years, the proper boundary between targeted therapy and therapeutic lifestyle changes has been vigorously debated and frequently revised, as evidenced most recently by the newest iteration of the AHA/ACC primary prevention guidelines. It is not surprising that the proper definition of this boundary has been so vigorously debated. Achieving the proper balance between CVD reduction and the risks and costs of achieving those reductions has enormous implications for both public health and public healthcare expenditures.

The 2 essential elements required to define the boundary between targeted and untargeted interventions are the risk threshold for targeted therapy and the tests used to estimate the risk for each individual under consideration. The first issue has received tremendous attention since the publication of the new guidelines and is not the subject of the present analysis. This report is focused on the second question of whether additional tests are useful to more precisely identify
individuals classified as low risk by current risk tools who should still be considered for targeted intervention.

The additional risk markers recommended in the new guidelines and evaluated here have been extensively studied previously. However, these studies have generally focused on the incremental information of these markers in intermediate-risk people defined by the Framingham Risk Score. Now that the risk threshold and the method of estimating that risk have changed, it is important to reconsider the utility of these markers for identifying additional higher-risk individuals, especially because the utility of any screening test is determined in part by the prior probability of events in the population to be screened. Understanding which, if any, additional screening tests should be used among the roughly 70 million Americans adults who would otherwise be considered ineligible for statins (but will produce the majority of cardiovascular events) has major implications for the optimization of screening and treatment for the primary prevention of ASCVD.

The present study has limitations. Even though we excluded participants who were taking statins during the baseline MESA examination from this analysis, some of the participants included in this analysis were prescribed statins (28%) during the follow-up. This may have affected the observed event rates and therefore the results described here. However, participants with an abnormal test (based on the additional risk markers) were ≈3 times as likely to be prescribed statins as those with a normal test in this MESA cohort. Hence, the AR associated with an abnormal test (based on the additional risk markers) in the present study is most likely underestimated, further strengthening our findings and conclusions. Finally, MESA included participants from 4 race/ethnic groups without baseline clinical CVD who were 45 to 84 years of age at baseline. Our result was also not stratified by sex or race, given the relatively few ASCVD events that occurred in this low-risk cohort. The findings of this study may not apply to dissimilar populations.

Conclusions
In this study of a well-characterized multiethnic cohort followed up for 10 years, we found that the majority of ASCVD events occurred in individuals with <7.5% 10-year cPCE risk. We also found that the CAC, hs-CRP, family history of ASCVD, and ABI recommendations by the ACC/AHA cholesterol guidelines (Class IIb) identify small subgroups of asymptomatic populations with <7.5% 10-year cPCE risk but with observed ASCVD event rates >7.5% who may warrant statin therapy considerations. Replication of our findings in other race/ethnic groups and other cohorts is needed.

Acknowledgments
We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding
This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-RR-025005 from National Center for Research Resources Diversity Supplement to R01HL098445 (principal investigator, Dr Carr).

Disclosures
None.

References
14. Lenzer J. Majority of panelists on controversial new cholesterol guideline have current or recent ties to drug manufacturers. BMJ. 2013; 347:f6989. doi: 10.1136/bmj.f6989.


**CLINICAL PERSPECTIVE**

The 2013 American College of Cardiology/American Heart Association cholesterol guidelines recommended using additional risk markers at specific thresholds to help with clinical decision making in selected individuals who are not in 1 of the 4 statin-benefit groups and for whom a decision to initiate statin therapy is otherwise unclear (Class II). The markers mentioned included low-density lipoprotein cholesterol ≥160 mg/dL; other genetic hyperlipidemias; family history of premature atherosclerotic cardiovascular disease (ASCVD); high-sensitivity C-reactive protein ≥2 mg/dL; coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; lifetime ASCVD risk; and ankle-brachial index <0.9. Prospective data from participants of the Multi-Ethnic Study of Atherosclerosis and 10-year adjudicated ASCVD events were used to assess the yield of this recommendation in those with <7.5% 10-year risk. Using a calibrated Pooled Cohort Equation, we showed that majority (57%) of the ASCVD events occurred in those who were not statin eligible (10-year calibrated Pooled Cohort Equation–estimated risk <7.5% at baseline), emphasizing the need for further ASCVD risk stratification in this subgroup in the population. This was not the case when the actual Pooled Cohort Equation (not calibrated) was used (only 16% ASCVD events occurred). Abnormal results of coronary artery calcium, high-sensitivity C-reactive protein, and family history of ASCVD (above the recommended thresholds) resulted in revised higher risk estimates in small subcohorts of the group with <7.5% risk estimated by the calibrated Pooled Cohort Equation. The yield of genetic hyperlipidemia and lifetime ASCVD risk was not evaluated in this analysis.
Utility of Nontraditional Risk Markers in Individuals Ineligible for Statin Therapy According to the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines
Joseph Yeboah, Tamar S. Polonsky, Rebekah Young, Robyn L. McClelland, Joseph C. Delaney, Farah Dawood, Michael J. Blaha, Michael D. Miedema, Christopher T. Sibley, J. Jeffrey Carr, Gregory L. Burke, David C. Goff, Jr, Bruce M. Psaty, Philip Greenland and David M. Herrington

_Circulation_. 2015;132:916-922; originally published online July 29, 2015; doi: 10.1161/CIRCULATIONAHA.115.016846

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/132/10/916

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/