The Association of Pericardial Fat with Coronary Artery Plaque Index at MR Imaging: The Multi-Ethnic Study of Atherosclerosis (MESA)¹

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Purpose:

To determine the relationship of pericardial fat, which secretes proinflammatory markers that have been implicated in coronary atherosclerosis, with atherosclerotic plaque in an asymptomatic population-based cohort.

Materials and Methods:

In this institutional review board–approved study, all participants supplied written informed consent. One hundred eighty-three participants (89 women, 94 men; mean age, 61 years $\pm$ 9 [standard deviation]) from the community-based Multi-Ethnic Study of Atherosclerosis (MESA) were included. The coronary artery eccentricity (ratio of maximal to minimal coronary artery wall thickness) was determined by using magnetic resonance (MR) imaging and served as an index of plaque burden. The pericardial fat volume was determined by using computed tomography. Linear regression coefficient analysis was used to correlate pericardial fat volume with coronary artery wall thickness and plaque eccentricity.

Results:

Pericardial fat volume correlated significantly with degree of plaque eccentricity ($P < .05$) in both men and women. After adjustments for body mass index (BMI) and waist circumference, traditional risk factors, C-reactive protein level, and coronary artery calcium content, the relationship between pericardial fat and plaque eccentricity remained significant in men ($P < .01$) but not in women. BMI and waist circumference correlated with degree of plaque eccentricity in the univariate model ($P < .05$) but not after adjustment for pericardial fat volume or traditional risk factors.

Conclusion:

Pericardial fat volume, rather than BMI and waist circumference, was more strongly related to plaque eccentricity as a measure of coronary atherosclerotic plaque burden. The results support the proposed role of pericardial fat in association with atherosclerosis.

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Pericardial fat is an adipose tissue depot surrounding the heart, with anatomic proximity to the epicardial coronary arteries. Similar to visceral adipose tissue, pericardial fat secretes proinflammatory chemokines and cytokines (1,2) that may be implicated in early-stage coronary artery atherosclerosis (3,4). Results of population-based studies have demonstrated that pericardial fat is positively correlated with coronary artery calcification measured by using nonenhanced computed tomography (CT) (5,6). Catheter- and CT-based angiography correlations have shown greater pericardial fat in association with noncalcified coronary plaques (7–10), but similar amounts of fat have been present in patients with coronary calcified plaques and in those with noncalcified plaques (7,8). Information about noncalcified plaque and pericardial fat in asymptomatic individuals is lacking owing to the absence of routine noninvasive methods to assess coronary artery plaque burden.

Black-blood coronary artery wall magnetic resonance (MR) imaging enables the detection of atherosclerotic plaque in patients with conventional angiography-documented disease (11–14). This method can enable the detection of increased coronary artery wall thickness, including the identification of positive remodeling of the vascular lumen (15), even in asymptomatic individuals with or without coronary calcium (15,16). The purpose of this study was to deter-

mine the relationship of pericardial fat with atherosclerotic plaque in an asymptomatic population-based cohort.

Materials and Methods

Study Participants

Study subjects were recruited from the cohort of participants in the Baltimore and Chicago field centers of the Multi-Ethnic Study of Atherosclerosis (MESA). The study design of MESA was previously described (17). In brief, participants of four ethnic origins (White, African American, Hispanic, and Chinese) from six U.S. field centers (Baltimore, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; Northern Manhattan, NY; and St Paul, Minn) who were aged 45–84 years and free of clinically determined cardiovascular disease were enrolled. Individuals with known clinical cardiovascular disease at baseline were excluded. All participants underwent standard-protocol chest CT for assessment of coronary artery calcification at baseline.

From October 2005 to February 2008, 225 participants from the parent MESA were enrolled in the MESA Coronary Artery Wall Study and completed the imaging protocol. We excluded participants who had a heart rate above 85 beats per minute (because of the technical limitations of MR imaging), claustrophobia, and/or contraindications to MR imaging and who did not have a sinus cardiac rhythm. Demographic, smoking history, and medical history information was collected, and measurements of the covariates, including plasma lipid levels, fasting glucose level, and resting blood pressure, were obtained according to the MESA study design and methods (17). The study was approved by the institutional review boards of the participating centers. All

participants provided written informed consent.

Coronary Artery Wall MR Imaging

All participants were imaged with use of a 1.5-T whole-body MR unit (Avanto; Siemens, Erlangen, Germany) with a gradient strength of 45 mT/m, a slew rate of 200 (T · m⁻¹)/sec, and 12-channel receive coils (six anterior, six posterior) while in a supine position, as previously described (15). Briefly, a whole-heart coronary MR angiogram was acquired by using the navigator technique during free breathing. The three-dimensional multiplanar reformations were reformatted to localize the left main, proximal left anterior descending, and right coronary arteries. Cross-sectional coronary wall MR imaging was performed by using a double-inversion-recovery motion-adapted navigator-gated T2-weighted turbo spin-echo sequence (spatial resolution, 0.8 × 0.8 × 5 mm) at 5-mm intervals from the origins of the left main artery (one image) and the proximal portions of the left anterior descending and right coronary arteries (three images for each artery at 5-mm intervals) (Fig 1). The examination time was limited to 60 minutes or less.

Advances in Knowledge

- In individuals free of clinically determined coronary artery disease (CAD), pericardial fat volume is associated with MR imaging-measured atherosclerotic plaque.
- Pericardial fat appears to be more strongly related to atherosclerotic plaque burden than to body mass index or waist circumference.
- Coronary wall MR imaging and pericardial fat assessment may be useful in risk assessment for CAD burden.

Implications for Patient Care

- Coronary artery wall MR imaging enables noninvasive assessment of CAD burden.
- Increased pericardial fat may be an indication of greater CAD.

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Abbreviation:

MESA = Multi-Ethnic Study of Atherosclerosis

Author contributions:

Guarantors of integrity of entire study, C.M., D.A.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, C.M., S.C., R.M., J.V., J.A.C.L., D.A.B.; clinical studies, C.M., J.D., R.M., D.A.B.; statistical analysis, S.C., K.L., S.L.; and manuscript editing, C.M., S.C., J.D., K.L., D.L., R.M., J.V., J.A.C.L., D.A.B.

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Figure 1: Coronary artery MR images in 70-year-old man. **(a)** Coronary MR angiogram shows normal right coronary artery (RCA), smaller left main artery (LM), and left descending coronary artery (LAD) without significant stenosis. **(b–d)** Cross-sectional coronary artery wall MR images show irregular wall thickness in left anterior descending artery (arrow in **b**), right coronary artery (arrow in **c**), and left main artery (arrow in **d**), with average eccentricity index of 5.7. Insets in bottom right corner show magnified views of vessels.

Two physicians (R.M., C.M., 5 and 6 years cardiovascular MR imaging experience, respectively) graded the coronary artery wall MR images on a three-point scale: Grade 1 indicated non-visualization; grade 2, adequate visualization; and grade 3, good visualization. Images with a grade of 2 or 3 were analyzed by a blinded observer by using VesselMASS software (Division of Image Processing, Radiology Department, Leiden University Medical Center, Leiden, the Netherlands). The outer and inner boundaries of the coronary wall were traced manually, and maximal, minimal, and mean coronary artery wall thickness measurements were obtained from a report generated by the software for each coronary wall MR imaging examination. Values of interobserver variability regarding mean wall thickness, outer contour area, and vessel wall area

were 7.2%, 10.2%, and 11.2%, respectively (13). Coronary plaque index was defined as plaque eccentricity, which was calculated as the ratio of maximal to minimal wall thickness (18).

Pericardial Fat Measurement

Pericardial fat volumes were measured on the cardiac CT scans that were used to assess coronary calcification. CT scanning was performed at the Chicago field center by using an electrocardiographically triggered (at 80% of the R-R interval) electron-beam scanner (Imatron C-150; GE Imatron, Milwaukee, Wis) or at the Baltimore field center with prospectively electrocardiographically triggered scan acquisition at 50% of the R-R interval by using a four-detector row CT system (LightSpeed; GE Medical Systems, Milwaukee, Wis), with which four simultaneous 2.5-mm

sections were obtained for each cardiac cycle in an axial scanning mode (19). Pericardial fat was defined, according to previously described methods, as epicardial fat within the visceral pericardium plus paracardial (ie, mediastinal) fat (20). The epicardial fat, whose origin differs from the origin of the pericardial fat, secretes proinflammatory chemokines and cytokines that are associated with coronary atherosclerosis. Investigators in a previous study (20) measured pericardial and epicardial fat volumes in a random sample of 159 MESA participants. The Spearman correlation coefficient for the correlation between pericardial fat and epicardial fat was 0.92 ($P < .0001$) (20). The pericardial fat volume was measured on sections from the region of the heart within 15 mm above and 30 mm below the superior extent of the left main coronary artery, as previously described (5). This selected region includes the pericardial fat around the left main artery and the proximal portions of the left anterior descending and right coronary arteries. The anterior border of the volume was defined by the chest wall, and the posterior border was defined by the aorta and the bronchus. The pericardial fat volume (in cubic centimeters) was measured by using Volume Analysis software (GE Healthcare, Waukesha, Wis), with an attenuation threshold of -190 to -30 HU used to identify fat-containing voxels. The final volume was the sum of all voxels containing pericardial fat.

Statistical Analysis

The statistical analysis was performed with SAS, version 9.2, software (SAS Institute, Cary, NC). Continuous variables were cited as means with standard deviations. The calcium score was determined by using the Agatston method (21). Categorical variables were expressed as numbers and percentages. Plaque eccentricity was calculated on the basis of findings on an image of the coronary wall. When multiple measurements of a single coronary artery were available, they were averaged to yield a single data point. The measurements for a participant were calculated by averaging the measurements from the

different coronary arteries. To express the strength of the association between pericardial fat volume and plaque burden, standard deviations were used as the increments for fat measurement. The unpaired *t* test was used to compare group mean values. The Satterthwaite *t* test was used to compare coronary calcium scores between the men and women, with the assumption of unequal variance between the groups. The Fisher exact test was used to compare the categorical variables. Relationships of pericardial fat volume with mean coronary wall thickness, maximal wall thickness, and plaque eccentricity were evaluated by using a linear regression analysis stratified according to sex. *P* < .05 was considered to indicate statistical significance.

Results

Participant Characteristics

Two hundred twenty-five participants who met the enrollment criteria completed coronary artery wall MR imaging examinations. One hundred ninety-two (85%) of these participants (98 men, 94 women; mean age, 61 years $\pm$ 9 [standard deviation]) had coronary wall MR images with a quality score of 2 or 3. Pericardial fat volume could be determined in 183 of these 192 subjects (94 men, 89 women; mean age, 61 years $\pm$ 9 [standard deviation]) (Table 1).

Significantly more men than women had dyslipidemia (*P* < .05) and a non-zero coronary artery calcium score (*P* < .001). In addition, compared with the women, the men had higher pericardial fat volumes (mean, 88.8 cm³ $\pm$ 53.8 vs 58.7 cm³ $\pm$ 30.6), waist circumferences (mean, 99.7 cm $\pm$ 10.8 vs 90.9 cm $\pm$ 14.2), blood glucose levels (mean, 105.1 mg/dL $\pm$ 35.8 vs 93.7 mg/dL $\pm$ 19.5), diastolic blood pressure (mean, 73.7 mm Hg $\pm$ 9.1 versus 68.4 mm Hg $\pm$ 9.4), Agatston calcium scores (mean, 150.6 $\pm$ 368.4 vs 48.0 $\pm$ 142.1), carotid intima-to-media thicknesses (mean, 0.87 mm $\pm$ 0.18 vs 0.82 mm $\pm$ 0.14) (*P* < .05 for all measure comparisons), and lower high-density lipoprotein levels (mean, 45.6 mg/dL $\pm$ 10.1 vs 65.2 mg/dL $\pm$ 19.4). The women had sig-

Table 1

Participant Characteristics

Parameter*	Men (n = 94) [†]	Women (n = 89) [†]	P Value
Age (y)	60.6 $\pm$ 9.5	61.0 $\pm$ 8.5	.75
White [‡]	60 (64)	57 (64)	...
African American [‡]	34 (36)	32 (36)	...
Diabetes [‡]	12 (13)	5 (6)	.13
Dyslipidemia [‡]	52 (55)	34 (38)	.02
Hypertension [‡]	40 (43)	36 (40)	.77
Ever smoked [‡]	54 (57)	39 (44)	.06
Pericardial fat volume (cm ³)	88.8 $\pm$ 53.8	58.7 $\pm$ 30.6	<.0001
Waist circumference (cm)	99.7 $\pm$ 10.8	90.9 $\pm$ 14.2	<.0001
Body mass index (kg/m ²)	28.0 $\pm$ 4.3	27.4 $\pm$ 5.5	.41
Triglycerides level (mg/dL)	107.8 $\pm$ 53.5	105.3 $\pm$ 46.7	.73
Total cholesterol level (mg/dL)	183.8 $\pm$ 33.3	201.3 $\pm$ 34.3	.0004
Low-density lipoprotein level (mg/dL)	116.6 $\pm$ 31.1	115.4 $\pm$ 34.5	.79
High-density lipoprotein level (mg/dL)	45.6 $\pm$ 10.1	65.2 $\pm$ 19.4	<.0001
Glucose level (mg/dL)	105.1 $\pm$ 35.8	93.7 $\pm$ 19.5	.006
C-reactive protein level (mg/L)	2.6 $\pm$ 3.3	4.5 $\pm$ 5.8	.009
Systolic blood pressure (mm Hg)	123.3 $\pm$ 17.1	122.5 $\pm$ 21.3	.75
Diastolic blood pressure (mm Hg)	73.7 $\pm$ 9.1	68.4 $\pm$ 9.4	.0001
Carotid intima-to-media thickness (mm)	0.87 $\pm$ 0.18	0.82 $\pm$ 0.14	.02
Agatston calcium score > 0 [‡]	55 (58)	30 (34)	.0005
Agatston calcium score	150.6 $\pm$ 368.4	48.0 $\pm$ 142.1	.01
Maximal wall thickness (mm)	2.8 $\pm$ 0.5	2.7 $\pm$ 0.5	.04
Minimal wall thickness (mm)	1.21 $\pm$ 0.28	1.26 $\pm$ 0.30	.22
Mean wall thickness (mm)	2.0 $\pm$ 0.3	1.9 $\pm$ 0.3	.03
Coronary plaque eccentricity	2.4 $\pm$ 0.9	2.3 $\pm$ 0.7	.84

* Dyslipidemia was defined as total cholesterol higher than 200 mg/dL, high-density lipoprotein level lower than 40 mg/dL, triglyceride level higher than 150 mg/dL, and/or use of lipid-lowering medications. Coronary plaque eccentricity refers to ratio of maximal to minimal wall thickness.

[†] Unless otherwise noted, values are means $\pm$ standard deviations.

[‡] Data are numbers of subjects, with percentages in parentheses.

nificantly higher total cholesterol (mean, 201.3 mg/dL $\pm$ 34.3 vs 183.8 mg/dL $\pm$ 33.3) and serum C-reactive protein (mean, 4.5 mg/L $\pm$ 5.8 versus 2.6 mg/L $\pm$ 3.3) levels.

Coronary Artery Wall Assessment

A total of 387 coronary artery wall images (203 in men, 184 in women) with an image quality grade of 2 or 3 were evaluated. Compared with the women, the men had a significantly greater mean coronary artery wall thickness (2.0 mm $\pm$ 0.3 vs 1.9 mm $\pm$ 0.3, *P* < .05) and mean maximal wall thickness (2.8 mm $\pm$ 0.5 vs 2.7 mm $\pm$ 0.5, *P* < .05). No significant difference in mean minimal coronary artery wall thickness or mean coronary plaque eccentricity was observed between the men and women (*P* > .05). There were no significant differences

in mean wall thickness, mean maximal wall thickness, or mean plaque eccentricity between the left main, left anterior descending, and right coronary arteries (*P* > .05).

Relationships of Pericardial Fat Volume with Coronary Artery Wall Plaque

In the men, pericardial fat volume was positively correlated with MR imaging-determined plaque eccentricity (*r* = 0.34, *P* < .001) (Fig 2). An increment of 1 standard deviation in pericardial fat volume was associated with a 0.3 increase in plaque eccentricity. In the univariate model, pericardial fat volume (*P* < .001), body mass index (*P* < .01), and waist circumference (*P* < .01) were positively correlated with coronary plaque eccentricity (Table 2). After adjustment for body mass index and waist

Figure 2: (a) Axial cardiac CT image in 68-year-old man shows minimal pericardial fat; pericardial fat volume is 26.8 cm³. (b) Cross-sectional right coronary artery wall MR image in same patient shows minimal plaque eccentricity, with average eccentricity index of 1.5. (c) Axial cardiac CT image in 70-year-old man shows large amount of pericardial fat (*); pericardial fat volume is 248.6 cm³. (d) Cross-sectional right coronary artery wall MR image in same patient shows high degree of plaque eccentricity, with average eccentricity index of 9.8. Arrow = right coronary artery. Insets in bottom right corner show magnified views of vessels.

circumference, pericardial fat volume continued to correlate with plaque eccentricity ($P < .05$). Of note, neither body mass index nor waist circumference was related to plaque eccentricity after adjustment for pericardial fat volume ($P > .05$). The significant relationship of pericardial fat with plaque eccentricity remained after further adjustments for traditional risk factors and C-reactive protein level ($P < .01$) and coronary artery calcification ($P < .01$) (Table 2).

In women, pericardial fat volume was positively correlated with plaque eccentricity in the univariate model ($P < .05$) (Table 2). After adjustment for body mass index and waist circumference, the relationship was attenuated ($P = .05$). The relationship was not significant after further adjustment for traditional cardiovascular risk factors.

In men, pericardial fat volume was positively correlated with maximal wall

thickness in the univariate model only ($P < .05$), but this relationship was not significant in women. Pericardial fat volume was not significantly related to mean wall thickness in men or women.

Discussion

To our knowledge, pericardial fat has not been previously studied in relation to a direct assessment of coronary artery plaque in asymptomatic individuals. In this study, we used MR imaging to noninvasively assess plaque eccentricity as a measure of early-stage atherosclerosis. Our results demonstrated that pericardial fat is positively associated with eccentricity of the coronary artery plaque in an asymptomatic study population without clinically defined cardiovascular disease. Our results in these asymptomatic individuals are consistent with findings in patients with advanced

atherosclerotic disease—namely, that a large amount of pericardial fat is significantly associated with measures of atherosclerotic disease (7–10).

Coronary plaques are usually eccentric in the early stage of atherosclerosis (22). Plaque with higher eccentricity represents a greater disease extent of a focal atherosclerotic lesion. Plaque eccentricity is associated with plaque vulnerability and instability (23,24). In prior studies of coronary plaque eccentricity, intravascular ultrasonography (US) was used to assess eccentricity. To our knowledge, coronary plaque eccentricity has not been previously assessed in an asymptomatic cohort because of the invasive nature of intravascular US.

Pericardial Fat and Atherosclerosis

Investigators in a prior study (8) used dual-source CT angiography to determine the pericardial adipose tissue volume and detect coronary atherosclerotic lesions. In that study, pericardial adipose tissue volume was significantly higher in patients with any type of coronary plaques than in those without plaque (mean volume, 226 cm³ $\pm$ 97 vs 134 cm³ $\pm$ 56; $P < .01$), and pericardial fat volume correlated with a larger number of coronary plaques ($r = 0.44$, $P < .0001$). The investigators found no significant difference in pericardial adipose tissue volume between patients with noncalcified plaque, patients with calcified plaque, and those with a mixture of all plaque types, although the patients with solely noncalcified plaque were younger and had a significantly lower plaque burden. The pericardial fat volume has been reported to be larger in patients with any coronary plaques than in those without plaques ($P < .0001$) (7). The same report indicated that pericardial fat volume was not significantly different between patients with noncalcified plaque, patients with mixed plaque types, and those with calcified plaque. However, the results from recent studies (9,10) indicate that the amount of epicardial fat is associated strongly with the presence of plaque overall and primarily with the presence of noncalcified plaque. In these studies, the predominant method used to assess coronary atherosclerosis

Table 2

Correlations of Pericardial Fat Measures with Coronary Artery Plaque Eccentricity

Model*	Men		Women	
	Regression Coefficient†	P Value	Regression Coefficient†	P Value
Univariate model				
Pericardial fat volume (per SD increment)	0.31 (0.13, 0.48)	.0007‡	0.14 (0.004, 0.27)	.04‡
Body mass index (per SD increment)	0.27 (0.10, 0.44)	.002‡	−0.023 (−0.12, 0.17)	.76
Waist circumference (per SD increment)	0.26 (0.09, 0.43)	.003‡	−0.045 (−0.10, 0.19)	.55
Multivariate model				
Model 1				
Pericardial fat volume (per SD increment)	0.24 (0.01, 0.48)	.04‡	0.16 (0.003, 0.31)	.05‡
Body mass index (per SD increment)	−0.21 (−0.22, 0.65)	.33	−0.027 (−0.28, 0.23)	.84
Waist circumference (per SD increment)	−0.09 (−0.55, 0.37)	.70	−0.058 (−0.32, 0.21)	.67
Model 2: pericardial fat volume (per SD increment)	0.42 (0.15, 0.68)	.002‡	−0.14 (−0.036, 0.32)	.11
Model 3: pericardial fat volume (per SD increment)	0.40 (0.14, 0.66)	.003‡	−0.17 (−0.04, 0.33)	.12

* Model 1 included pericardial fat, body mass index, and waist circumference. Model 2 included model 1 parameters and additionally adjusted for age, smoking status, diabetes, hypertension, dyslipidemia, low- and high-density lipoprotein cholesterol levels, triglyceride levels, and C-reactive protein levels. Model 3 included model 2 parameters plus carotid intima-to-media thickness and coronary artery calcification. SD = standard deviation.

† Numbers in parentheses are 95% confidence intervals.

‡ Significant correlation between given parameter and coronary plaque eccentricity.

was conventional or CT angiography. The differences in associations between the various investigators may have been due to selection bias, since invasive methods and/or ionizing radiation was used in these studies.

The studies just described support the concept that visceral adipose tissue is related to growth factors (25) and endothelial dysfunction, a marker of early atherosclerosis (26,27). Adipose tissue-derived proatherogenic factors may be responsible for early endothelial dysfunction and the predisposition for atherosclerosis. Lear et al (28) found that abdominal visceral fat accumulation was more strongly associated with carotid intima thickness than with the extent of atherosclerotic lesions. In the population-based MESA, Ding et al (5) found that pericardial fat volume was associated with increased odds of calcified coronary plaque as measured with CT (odds ratio, 1.92; 95% confidence interval: 1.27, 2.90), independent of cardiovascular risk factors. Another population-based study involving postmenopausal women showed a graded association between the amount of epicardial adipose tissue and the amount of coronary artery calcification (6). In the current study, associations between pericardial

fat and coronary plaque eccentricity were stronger in men than in women. This finding is consistent with the more advanced atherosclerotic disease in men than in women of the same age range in this study.

Limitations

The results of this cross-sectional study do not provide information regarding the origin of the correlation between pericardial fat and plaque burden. We do not know whether the stronger relationships between pericardial fat and coronary plaque in men, as compared with women, were due to technical limitations (ie, limited spatial resolution and coverage) or represented real differences between these groups. However, the atherosclerosis burden, as defined according to multiple parameters, including MR imaging findings, coronary artery calcification score, carotid intima-to-media thickness, and clinical cardiovascular risk factors, was substantially lower in women than in men, limiting the power of the study in the detection of these changes in women. Male sex and increased coronary artery calcium score have been reported to be associated with higher coronary MR image quality score (29).

In conclusion, pericardial fat volume was positively related to coronary atherosclerotic plaque burden in asymptomatic individuals. This relationship was stronger in men than in women—possibly because of the greater atherosclerotic disease burden in men. In men in particular, pericardial fat accumulation may be an indication of greater risk for increased plaque burden.

Disclosures of Potential Conflicts of Interest:

C.M. No potential conflicts of interest to disclose. **S.C.** No potential conflicts of interest to disclose. **J.D.** No potential conflicts of interest to disclose. **K.L.** No potential conflicts of interest to disclose. **D.L.** No potential conflicts of interest to disclose. **R.M.** No potential conflicts of interest to disclose. **S.L.** No potential conflicts of interest to disclose. **J.V.** No potential conflicts of interest to disclose. **E.R.B.** No potential conflicts of interest to disclose. **J.A.C.L.** No potential conflicts of interest to disclose. **D.A.B.** No potential conflicts of interest to disclose.

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