Carotid Intima-Media Thickness Testing by Non-Sonographer Clinicians: The Office Practice Assessment of Carotid Atherosclerosis Study

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Background: The purpose of this study was to determine whether a non-sonographer clinician (NSC) could obtain ultrasound images of the carotid artery, measure carotid intima-media thickness (CIMT), and identify findings indicating increased cardiovascular risk in an office setting.

Methods: Eight NSCs from five sites were trained to use a handheld ultrasound device to screen the carotid arteries for plaques and to measure CIMT.

Results: NSCs scanned 150 subjects who provided 900 images, of which 873 (97%) were interpretable. Differences between NSCs and the core laboratory were small (0.002 $\pm$ 0.004 mm) and bioequivalent ($P_{TOST} < 0.05$) with a low coefficient of variation (3.9% $\pm$ 0.5%). There was $\geq$ 90% agreement on the presence of CIMT $\geq$ 75th percentile and $\geq$ 80% agreement on plaque presence.

Conclusions: This is the first multicenter study to show that NSCs can obtain images of the carotid arteries using a handheld ultrasound device, accurately measure CIMT, and identify findings indicating increased cardiovascular risk.

For many individuals, the first symptom of cardiovascular (CV) disease is myocardial infarction, sudden cardiac death, or stroke.[1] Improved prevention of these highly prevalent, morbid, and costly ischemic CV events underlies the increasing interest in identifying asymptomatic patients who, according to the assessment of traditional CV risk factors, may not be accurately risk-stratified. In this context, there are "low-risk" individuals who may not warrant intensive lipid-lowering therapy by current national guidelines; however, these guidelines have been challenged as not being evidence-based. It has been suggested that too many patients in primary prevention are being treated with lipid-lowering therapy.[2] Improved identification of increased CV risk would permit more targeted use of proven medical interventions, possibly reducing the number that require treatment.[3] An affordable and safe test that complements current CV risk assessment strategies and that can be used at the point-of-care (i.e., the office setting) would be clinically useful.

Increased carotid intima-media thickness (CIMT) and the presence of carotid plaques are markers of subclinical vascular disease that independently predict increased future CV risk.[3-8] Several recent guidelines and consensus statements recommend that measurement of CIMT can be used as a clinical test to assist with CV risk prediction.[2-4,9,10] Because assessment of CIMT requires accurate identification and measurement of subpixel echogenic structures, technical challenges have restricted its use to research settings where highly trained sonographers acquire data using complicated scanning protocols and standard ultrasound machines for subsequent measurement at a core laboratory. Translation of CIMT into a useful clinical tool will require more rapid data acquisition and analysis, while maintaining accuracy and image quality. This can be accomplished by training a non-sonographer clinician (NSC) to obtain ultrasound images of the carotid artery, measure CIMT, and identify findings indicating increased CV risk in an office setting. The purpose of this study was to determine whether an NSC can obtain ultrasound images of the carotid artery of sufficient quality to permit measurement of CIMT, accurately measure CIMT, and accurately identify findings indicating increased CV risk in an office setting using a small, portable, handheld ultrasound (HHU) system.

METHODS

Study Design

The institutional review board at the University of Wisconsin School of Medicine and Public Health and for each participating site approved this study. Each NSC and research subject provided informed

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consent. This multicenter study was performed at six clinical sites, and data were collected by 10 NSCs who completed a 2-day training program taught by the University of Wisconsin Atherosclerosis Imaging Research Program, the core laboratory and coordinating center for this study.

The training program included the didactic lectures covering carotid artery anatomy and pathology, rationale for use of carotid ultrasound as a clinical test, instrumentation, scanning protocol, CIMT measurement, and clinical interpretation of CIMT studies. Training also included hands-on, supervised practice scanning of at least two model patients and measurement of carotid ultrasound images using the study instruments and scanning protocol described below. After the training program, each NSC was required to scan at least three mock subjects in duplicate (six mock examinations total) and to submit images to the core laboratory to complete training and certification. The mock examinations were reviewed, and a summary letter with feedback and suggestions was returned to the NSC. Mock scans were graded on a qualitative, ordinal scale ranging from 1 to 3 (1 = good images, 2 = average image quality, some missing data, and 3 = limited data acquired, scan not suitable). Some NSCs needed extra training and practice scans to achieve certification.

The study was conducted in two phases. The objective of phase I was to determine whether NSCs could accurately measure CIMT. By using a previously validated semiautomated border detection program (SonoCalc 3.0, Sonosite, Inc., Bothell, WA),[11] each NSC independently measured CIMT from a set of 25 digital carotid ultrasound studies that had been acquired, stored, and read by a core laboratory sonographer (C.E.K.). Each study included a carotid plaque scan and images of the right and left common carotid arteries (CCAs), each from three different angles of interrogation. NSCs were required to identify the presence or absence of any carotid plaques and measure the mean far wall CIMT of the distal 1 cm of each from all views presented, for a total of 150 CIMT measurements per NSC. NSCs were blinded to the measurements of the other NSCs and the core laboratory. The traced images and values were submitted to the core laboratory for comparison. Batches of approximately five studies from a NSC were reviewed at the core laboratory at a time, and a summary letter with feedback and suggestions was returned to the NSC. Criteria used to request repeat readings included a comprehensive review of the CIMT tracings and editing of the detected borders, accurate choice of the measured segments, and consistency of results at each angle measured. Carotid plaque was defined as the presence of a discrete area of intimal-medial thickening $\geq$ 1.2 mm that encroached into the arterial lumen and was at least 50% thicker than the neighboring segment.[12-14]

The objectives of phase II were to determine whether (1) NSCs working in an office practice setting could perform carotid ultrasound studies for CIMT measurement and determination of plaque presence using a HHU, (2) CIMT measurements taken by NSCs could be reproduced in a core laboratory, and (3) NSCs could identify findings indicating increased CV risk. These findings included the presence of carotid plaque or increased CIMT, defined as right and/or left CIMT $\geq$ 75th percentile of the Atherosclerosis Risk in Communities Study, based on age, sex, and race.[15] In phase II, subjects who were 45 to 70 years old, who had no history of CV disease, and who were not receiving lipid-lowering therapy, but had at least one CV risk factor (e.g., current cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, or a family history of premature CV disease), were scanned by the NSCs. NSCs reviewed all studies for the presence or absence of carotid plaques and measured CIMT using the protocol described below. Their results were submitted to the core laboratory for comparison.

Finally, to evaluate interscanner reproducibility, five NSCs from three sites returned to a central location to scan six model subjects, who also were scanned by a sonographer with expertise in CIMT scanning and measurement (C.E.K.). These scans were performed in random order with each scanner blinded of each other's measurements. None of these five sonographers had previous CIMT scanning or reading experience before their participation in this study.

Ultrasound Scanning Protocol

HHU scans were performed using a MicroMaxx system with an L38e/10-5 MHz linear-array transducer (SonoSite, Inc.). An initial transverse scan from the proximal CCA through the internal carotid artery was performed, followed by a longitudinal circumferential scan to identify plaques in the common, bulb, and internal carotid arteries. Images for measuring CIMT of the distal 1 cm of the far walls of each CCA were obtained from three angles of interrogation on each side (anterior, middle, and posterior) with electrocardiogram gating to ensure that measurements were taken at end diastole. Images were stored digitally and measured offline.

Data Analysis

Descriptive data are presented as mean $\pm$ standard error. Differences between NSC and core laboratory CIMT values are described by mean $\pm$ standard error, the Pearson correlation coefficient, and calculation of the coefficient of variation. NSC CIMT measurements were compared with the core laboratory using Bland-Altman analysis[16] and the "two one-sided *t* test" (TOST) with and 1 digital pixel limits (0.055 and 0.110 mm, respectively).[17,18]

In phase I, between-reader differences in CVs were tested by the modified Levene test.[19] For phase II, aggregate sonographer deviation in CIMT readings was estimated using a multivariate hierarchical linear model with subjects as a repetition nested within each sonographer. The absolute deviation between the CIMT measurement for each sonographer and the core laboratory was the outcome variable. Predictor variables that were considered in the models included sonographer, subject age, CIMT, and body mass index. The accuracy of identification of findings indicating increased risk by NSCs was tested by calculating the percent agreement with the core laboratory. Components of scan quality were evaluated using a binary score (acceptable, not acceptable) including plaque screening technique, CIMT imaging technique, plaque detection, and editing of borders during CIMT measurement.

RESULTS

Phase I

The 10 NSCs participating in phase I had a wide range of medical backgrounds and included three physicians, one physician assistant, two registered nurses, two medical assistants, one emergency medical technician, and one nonmedical assistant. Two had previous carotid ultrasound scanning experience, one of whom also had CIMT reading experience. They were from two private community practices and four academic medical centers. The ages of the NSCs ranged from 31 to 50 years, and eight were women. Each NSC measured 150 images (six segments per case, 25 cases). The average number of cases that needed to be remeasured was 4.1 $\pm$ 1.9 (range 0-20). The single scanner who needed to repeat measurements in 20 cases had a dramatic improvement on the second set of measurements after education and feedback. This sonographer had sent in all 25 readings

Table 1 Comparison of carotid intima-media thickness measurements by each non-sonographer clinician with the core laboratory (N = 25 studies, 150 segments)

Mean difference with non-sonographer clinician	Mean difference with core laboratory (mm)	Correlation	Coefficient of variation (%)
1	−0.018 ± 0.007	0.96	5.7
2	0.010 ± 0.006	0.96	5.0
3	−0.001 ± 0.007	0.95	4.9
4	0.002 ± 0.009	0.92	4.8
5	0.014 ± 0.006	0.96	4.3
6	0.008 ± 0.005	0.98	5.5
7	0.000 ± 0.005	0.97	4.1
8	0.009 ± 0.004	0.98	3.3
9	0.001 ± 0.007	0.91	5.1
10	0.019 ± 0.006	0.96	4.1

simultaneously, rather than sending five studies at a time and waiting for feedback before proceeding. The most common reasons that NSCs needed to remeasure scans were selecting the wrong segment (too proximal), measuring too short a segment (<1 cm), and making errors in tracing CIMT (too thick or too thin). Other mistakes included measuring of the near instead of the far wall of the CCA, and in one instance, the jugular vein was measured rather than the CCA. A learning curve regarding the appropriate use of the software editing capabilities was evident.

The mean CIMT by the core laboratory was 0.720 ± 0.023 mm. CIMT differences between NSCs and the core laboratory were small (Table 1). The mean CIMT difference between the core laboratory and all NSCs was small (0.003 ± 0.003 mm). The coefficient of variation was 4.3% ± 0.2% without heterogeneity between readers ($p_{het} > 0.3$). With training and feedback, all 10 NSCs were able to measure CIMT at the predefined level of bioequivalence (0.11 mm, $p_{TOST} < 0.05$). A composite Bland-Altman plot for all readers is shown in Figure 1.

Phase II

Before initiation of phase II, NSCs were required to scan at least three model subjects (total: six mock examinations) in duplicate and to submit images to the core laboratory to complete training and certification. The average number of mock studies required for certification was 6.6 ± 1.0. The average score was 1.9 ± 0.1 (see above, 1 = good, 2 = average, 3 = not suitable). Common scanning errors included difficulty with plaque screening, which required significant manual transducer coordination to acquire high-quality carotid wall interfaces while acquiring transverse and longitudinal cine-loops from complementary angles. Another mistake frequently made during the certification process was to image and measure CCA intimal mean thickness from the middle rather than the distal 1 cm of the CCA. There was a qualitative learning curve for some NSCs to learn how to accurately recognize where the distal CCA transitions into the bulb and to discriminate between the internal and external carotid arteries without the assistance of Doppler imaging. These problems were resolved with individualized written and verbal feedback.

Each of the five sites then recruited 30 subjects (total study n = 150). Their average age was 56.8 ± 0.5 years, 75 were women, 118 were white, 25 were African-American, and 6 were Hispanic. Subjects included 31 (21%) current smokers, 15 (10%) with diabetes mellitus, 62 (41%) with hypertension, and 73 (49%) with a family history of CV disease. Their average body mass index was 28.2 ± 0.5 kg/m^2, and the average blood pressure was 132.4 ± 13.0/79.6 ± 10.7 mm Hg. Most subjects were enrolled during a routine office visit. The 150 subjects provided 900 images, of which 873 (97%) were interpretable. The average CIMT was 0.701 ± 0.013 mm. Carotid plaques were detected in 84 subjects (56%). The mean CIMT difference between the core laboratory and all NSCs was small (0.002 ± 0.004 mm) and bioequivalent ($p_{TOST} < 0.05$) with a low coefficient of variation (3.9% ± 0.5%) (Table 2). In multiple linear regression modeling, one NSC had a higher aggregate average deviation from the core laboratory than the other seven NSCs; however, after adjustment for subject age and body mass index, there were no statistically significant differences between NSCs. Increasing CIMT was the only predictor of increasing deviation from the core laboratory ($P = .032$). There was ≥ 90% agreement on the presence of increased CIMT percentile and ≥ 80% agreement on plaque presence. The most common scanning deficiency for NSCs was the performance of screening loops for plaque detection, which was observed in at least one scan plane on 21% of studies. Difficulties with imaging portions of the bulb and internal carotid arteries explained the disagreement on the presence or absence of plaque in most cases.

To evaluate interscanner variability, six models (age 50.6 ± 4.9, range 37-71 years old) were scanned by five NSCs and the core laboratory. Their average CIMT was 0.753 ± 0.040 mm, and three (50%) had plaques. The mean CIMT difference between the core laboratory and the NSCs was 0.008 ± 0.015 mm (Fig. 2). The coefficient of variation was 5.9% ± 0.6% (range 4.3%-7.3%). There was 100% agreement on the presence or absence of increased CIMT. There was 83% agreement on the presence or absence of plaque. Compared with the core laboratory, one NSC overcalled one plaque and two NSCs missed the plaques (in the same subject).

DISCUSSION

This study demonstrates that NSCs with a wide range of medical backgrounds, who practice in community and academic medical settings, could be trained to achieve a high level of proficiency at each of the steps necessary to perform CIMT studies with an HHU system in a clinical setting. After a 2-day didactic and hands-on training program followed by mock patient scanning and feedback, NSCs were able to measure CIMT using a semiautomated border detection program with a degree of proficiency similar to that of an expert CIMT reader in a core laboratory. Each NSC also was able to use a scanning protocol that permitted accurate and reproducible measurement of CIMT, as well as identification of carotid plaques. Finally, they were able to correctly identify patients with increased CIMT and carotid plaques, findings that indicate increased CV risk.[3-9] These are the key steps required for this diagnostic test to be translated into a clinical practice setting.

The application of carotid artery ultrasound to measure CIMT and identify nonocclusive plaques is a straightforward, evidence-based strategy to identify subclinical vascular disease, a marker of increased CV risk. Indeed, measurement of CIMT has been recommended as a screening tool to help refine CV risk assessment and therefore target risk-reducing interventions toward patients at the highest CV risk.[3,4,9,10] The evaluation of CIMT has been limited to individuals enrolled in research studies performed at selected tertiary care insti-

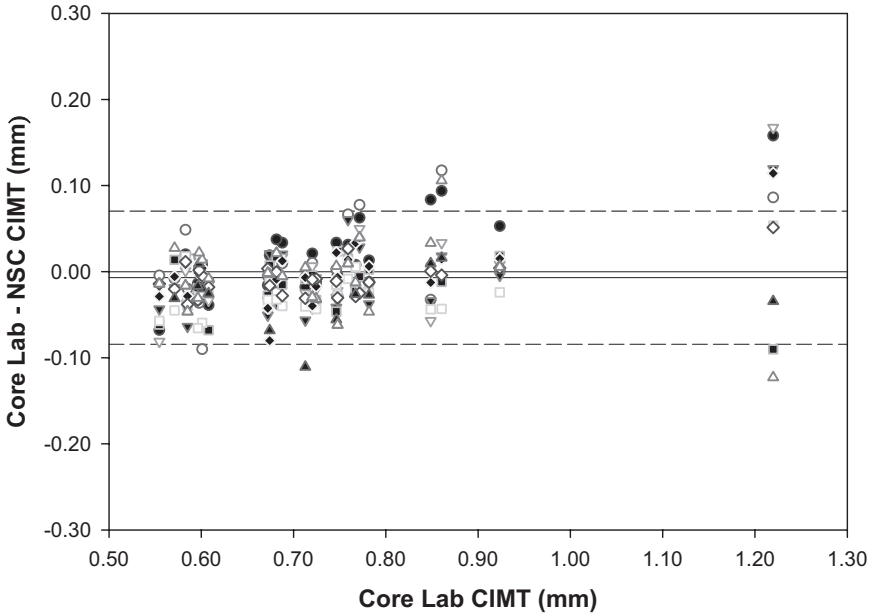

Figure 1 Composite Bland-Altman Plot comparing the results of 25 CIMT readings by 10 NSCs with core laboratory measurements. *NSC*, Non-sonographer clinician; *CIMT*, carotid intima-media thickness.

Table 2 Comparison of carotid intima-media thickness measurements by each site with the core laboratory (n = 30 subjects per site)

	CIMT comparison with core laboratory			% clinical agreement	
Site	Mean difference with core laboratory (mm)	Correlation	Coefficient of variation (%)	Increased CIMT	Plaque presence
01	−0.005 ± 0.006	0.89	4.9	97	80
02	0.004 ± 0.004	0.95	3.4	93	80
03	0.008 ± 0.008	0.93	5.2	93	90
04	0.001 ± 0.004	0.97	2.6	97	90
05	−0.016 ± 0.018	0.90	3.5	90	77

CIMT, Carotid intima-media thickness.

tutions. Barriers to transfer of this technique into clinical practice include the expense and size of standard ultrasound systems that make them less feasible for use in an office practice; technical challenges associated with complicated image acquisition protocols that have traditionally required highly trained sonographers, the need for CIMT measurement to be performed in a core laboratory, and the absence of an evidence-based schema for integrating CIMT measurements with existing CV risk prediction paradigms. Recent advances have made it possible to detect subclinical vascular disease more efficiently using HHU systems and to measure CIMT using a semiautomated border detection program. This study used a simplified CIMT scanning protocol that can be performed by non-sonographers who have completed a standardized training program.

In epidemiologic studies and clinical trials of lipid-lowering therapy, small changes in CIMT of approximately 1 digital pixel (0.11 mm) were associated with clinically significant increments in CV risk.[6-8,20,21] Accordingly, adherence to CIMT scanning protocols must be rigorous, images must be of high quality, and measurement must be accurate and reproducible. Assessment of CIMT is operator-dependent; however, the standardized training program used in this study led to accurate and reproducible imaging sufficient to identify findings of clinical significance, such as increased CIMT and the presence of carotid plaques. Indeed, the absence of standardized training programs also has been a barrier to implementation of CIMT testing in clinical practice.

This study used an abbreviated CIMT scanning protocol that focused on the far wall of the distal CCA because it is relatively superficial and easy to locate, therefore allowing its interrogation in a relatively short time. Its straight geometry also lends itself to the use of border detection programs. In eight studies that each had more than 1000 participants, far wall CCA measurements were related to future CV events, even after adjustment for CV risk factors.[6-8,13,22-25] Measurement of CIMT from the near wall and other segments has been performed in other studies; however, obtaining and measuring these images is time-consuming and more technically challenging, and these values have not been shown to improve risk prediction.[9] Because evaluating only CCA CIMT may miss increased carotid wall thickness in the bulb or internal carotid artery, it should be supplemented by scanning for plaques, the presence of which are independently associated with increased CV risk and composite CIMT obtained from multiple segments.[5,9,12] In a recent study of patients referred for clinical CIMT scanning, measurement of far wall CCA CIMT and plaque screening identified all patients with increased CIMT determined by a comprehensive scanning protocol that incor-

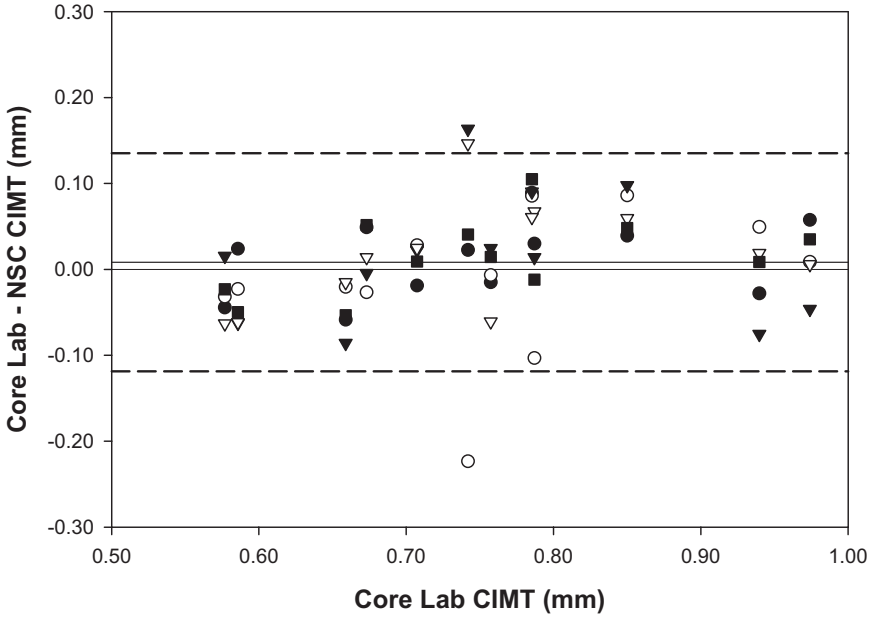

Figure 2 Composite Bland-Altman Plot comparing the CIMT measurement results of six model subjects scanned by five NSCs with the those by the core laboratory sonographer. NSC, Non-sonographer clinician; *CIMT,* carotid intima-media thickness.

porated CIMT measurements of multiple carotid arterial segments, indicating that this abbreviated strategy is effective.[26]

Limitations

Imaging the carotid arteries and measuring CIMT require adequate training. The high degree of accuracy and reproducibility achieved by the NSCs in this study were the result of intensive training and feedback on a case-by-case and image-by-image basis from an experienced core ultrasound laboratory that is experienced at performing and teaching CIMT scanning and measurement. There was a clear learning curve, and some NSCs were more technically proficient than others. This study was not designed to identify predictors of the ease of learning the skills to perform carotid ultrasound studies. However, in this study, all NSCs, regardless of their background, eventually achieved proficiency. To date, there is not a standard training or certification process for performing and interpreting CIMT studies; however, the methods and results of this study and of prior clinical and epidemiologic studies can inform the development of a more accessible CIMT training process.[27] Well-designed ultrasound-based training programs have been used successfully to create a standard of excellence that defines quality sonography for noninvasive vascular laboratories and usually is linked to sonographer and laboratory accreditation. However, these training programs have not focused on quantitative CIMT measurement or plaque detection for the purpose of CV risk assessment. For CIMT scanning to become a widely used clinical tool, such training and performance standards will need to be developed and implemented.

The most commonly observed scanning difficulties for NSCs included misidentification of plaques during screening and difficulty discriminating between the internal and external carotid artery. By site, plaque agreement ranged from 77% to 90%, whereas agreement on the presence of increased CIMT was more than 90%. Instruction on basic spectral and color Doppler imaging techniques may help the NSC overcome these problems but adds complexity and time to the protocol. During training, more emphasis on plaque scanning, especially of the distal carotid arterial segments, may be helpful.

This study was designed to evaluate the feasibility of CIMT measurements by NSCs. It did not evaluate whether measurement of CIMT and identification of carotid plaques can improve patient outcomes. Other studies have shown that the results of carotid ultrasound studies can lead to changes in patient behaviors that would be expected to reduce CV events, such as increased compliance with smoking cessation and other lifestyle interventions.[28,29] Also, a pilot study recently demonstrated that identification of carotid plaques in an office practice setting led physicians to prescribe aspirin and lipid-lowering therapy to patients who otherwise would not have received these therapies (Rachael A. Wyman, MD and James H. Stein, MD, Personal Communication, December 2006). The large number of plaques identified in this study underscores the potential clinical importance of this screening tool. Published reports from clinical CIMT scanning programs have shown that CIMT measurements can help reclassify patients at intermediate risk.[30-32] Phase III of the Office Practice Assessment of Carotid Atherosclerosis study is investigating whether the scanning protocol used in this study can alter physician treatment plans and patient motivation in an office setting.

CONCLUSIONS

This is the first multicenter study to show that NSCs can obtain images of the carotid arteries by using an HHU, use the images to accurately measure CIMT, and identify findings indicating increased CV risk in an office setting. These data demonstrate that CIMT can be used in an office setting as a practical tool to assist with CV risk assessment.

The core laboratory and coordinating center for this study was the University of Wisconsin Atherosclerosis Imaging Research Program, University of Wisconsin School of Medicine and Public Health,

Madison, WI (James H. Stein, MD (Principal Investigator, PI); Claudia E. Korcarz, DVM, RDCS). The following individuals and institutions participated in this study: Heart Prevention Clinic of Idaho, Boise, ID (Bryan Pogue, MD (site PI), Kelli Sizemore, Amy Webb), Mayo Clinic, Rochester, MN (Charles Bruce (site PI), Sue Milbrandt, Anne Odland), New York Physicians, New York, NY (John Postley, MD (site PI), Maria Chan), University of Chicago Pritzker School of Medicine, Chicago, IL (Jeanne M. DeCara, MD (site PI), Kathy Furlong), University of Minnesota School of Public Health and Minneapolis Heart Institute Foundation, Minneapolis, MN (Alan T. Hirsch, MD (site PI), Andrey Zenovich, Troy Decker), University of Pennsylvania Medical School, Philadelphia, PA (Emile R. Mohler, MD (site PI), Wendy S. Tzou, MD). The steering committee included Dr. Stein (study PI), Dr. Hirsch (study Co-PI), Dr. DeCara, Patrick E. McBride, MD, MPH (University of Wisconsin School of Medicine and Public Health, Madison, WI), Christopher M. Rembold, MD (University of Virginia Medical School, Charlottesville, VA), Neil Stone, MD (Northwestern University Feinberg School of Medicine, Chicago, IL), and Dr. Tzou.

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