Risk Stratification for Cardiovascular Disease in Women in the Primary Care Setting

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Background: Traditional risk assessment tools classify the majority of middle-aged women at low risk despite cardiovascular (CV) disease's affecting >50% of women and remaining the leading cause of death. Ultrasound-determined carotid intima-media thickness (CIMT) and/or computed tomographic coronary artery calcium score (CACS) quantify subclinical atherosclerosis and add incremental prognostic value. The aim of this study was to assess the utility of CIMT and CACS to detect subclinical atherosclerosis in younger women.

Methods: Asymptomatic women aged 50 to 65 years with at least one CV risk factor and low Framingham risk scores were identified prospectively at primary care and cardiology clinics. Mean intimal thickness, plaque on CIMT, and Agatston calcium score for CACS were obtained.

Results: Of 86 women (mean age, 58 ± 4.6 years; mean Framingham risk score, 1.9 ± 1.2; mean low-density lipoprotein cholesterol level, 138.9 ± 37.0 mg/dL), 53 (62%) had high-risk CIMT (51% plaque, 11% CIMT > 75th percentile). In contrast, three women (3.5%) had CACS > 100, all of whom had plaque by CIMT. Of the 58 women with CACS of 0, 32 (55%) had high-risk CIMT (48% plaque, 7% CIMT > 75th percentile).

Conclusions: In patients referred by their physicians for assessment of CV risk, CIMT in asymptomatic middle-aged women with at least one CV risk factor and low risk by the Framingham risk score identified a large number with advanced subclinical atherosclerosis despite low CACS. Our results suggest that CIMT may be a more sensitive method for CV risk assessment than CACS or traditional risk tools in this population. Further studies are needed to determine if earlier detection would be of clinical benefit. (J Am Soc Echocardiogr 2015;28:1232-9.)

Keywords: Carotid ultrasound, Calcium score, Women, Risk

Fifty-six percent of adult women in the United States will develop clinical cardiovascular disease (CVD) in their lifetimes,[1] and CVD remains the number one cause of mortality in women, resulting in one death per minute in the United States.[2-4] Importantly, in up to 45% of women, their first presentation of CVD may be sudden death, which occurs without antecedent symptoms, further emphasizing the importance of primary prevention of CVD.[4-7]

Although effective means for preventing CVD are available, current methods for identifying those at risk before events occur are limited.[8,9] Population-based risk algorithms such as the Framingham risk score (FRS), Reynolds risk score (RRS), and pooled cohort equation are used to assess cardiovascular risk, yet 75% of myocardial infarction and CVD deaths occur in the low- and intermediate-risk populations.[7-13]

Both computed tomographic coronary artery calcium score (CACS) and carotid intima-media thickness (CIMT) and plaque detection on ultrasound measure subclinical atherosclerosis and have been shown to independently add incremental predictive value to traditional risk factors, although the correlation between the two is weak.[10-12]

In this study, we evaluated the prevalence of advanced subclinical atherosclerosis as assessed by CACS and carotid ultrasound in middle-aged women with at least one cardiovascular risk factor but low FRS.

METHODS

This protocol was approved by the Mayo Clinic Institutional Review Board. Asymptomatic women between 50 and 65 years of age with at least one cardiovascular risk factor (hyperlipidemia, hypertension, family history of premature coronary disease, current tobacco use, or elevated high-sensitivity C-reactive protein) and classified at low risk by the FRS were included in the study. Women were identified by their

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Abbreviations

ASCVD = Atherosclerotic cardiovascular disease

CACS = Coronary artery calcium score

CAD = Coronary artery disease

CI = Confidence interval

CIMT = Carotid intima-media thickness

CVD = Cardiovascular disease

FRS = Framingham risk score

HR = Hazard ratio

RRS = Reynolds risk score

primary care physicians or cardiologists at the Mayo Clinic Arizona from December 1, 2010, to January 31, 2013. The initial history, physical examination, and laboratory testing was performed by the referring physician and was accessible via the electronic medical record. Informed consent was obtained by the Protocol Development Office. FRS were calculated for all participants, and only those at low risk (<10% risk for a cardiovascular event over 10 years) were included. The RRS was also calculated when data were available, and the race- and sex-specific pooled cohort equation to calculate the 10-year atherosclerotic CVD (ASCVD) risk estimate[13] was calculated for all patients. Hyperlipidemia was defined as a low-density lipoprotein cholesterol level ≥ 100 mg/dL; hypertension as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive therapy; and family history of premature coronary disease as a first-degree male relative <55 years of age or a female first-degree relative <65 years of age with a cardiac event. Subjects were excluded if they were on lipid-lowering therapy, had histories of coronary artery disease (CAD) or CAD equivalent such as peripheral vascular disease, cerebrovascular disease, or diabetes mellitus.

Patients were assessed for waist circumference, body mass index, current tobacco use, family history, and hypertension. Laboratory studies including a fasting lipid profile, plasma glucose, and high-sensitivity C-reactive protein were performed and CIMT assessment was performed in all subjects. Low-risk CIMT was classified as <50th percentile, intermediate-risk CIMT as 50th to 75th percentile, and high-risk CIMT as >75th percentile or the presence of plaque. Computed tomography for CACS was also performed, and an Agatston score was assigned on the basis of age- and sex-matched control subjects.[14]

CIMT was defined as the distance between the lumen-intima interface and the media-adventitia interface. All patients were scanned by one of two experienced cardiac sonographers (C.K. and C.B.) using a multifrequency linear-array transducer in fundamental frequency > 7 MHz on a high-resolution B-mode ultrasound system (Siemens Acuson Sequoia C512; Acuson Inc, Mountain View, CA). All studies followed the CIMT protocol approved by the Mayo Clinic Arizona echocardiography laboratory and included screening for carotid artery plaque and common CIMT analysis. For the carotid artery plaque screen, the transverse and longitudinal axes of the right and left common carotid arteries, the carotid bulb, and the proximal internal and external carotid arteries were imaged. Measurements for CIMT were obtained at the distal 1-cm far wall of the common carotid artery at end-diastole (within one or two frames of the onset of the electrocardiographic Q wave) averaged over three cardiac cycles from two separate angles of insonation (Figure 1A). All CIMT images were transferred and stored digitally on a server for analysis using Arterial Health Package (Siemens Syngo Ultrasound Workplace; Siemens Medical Inc, Malvern, PA).

Plaque was defined as a focal intima-media thickening of the arterial wall that was ≥1.5 mm thick and/or >50% thicker than the surrounding arterial wall (Figure 1B). If plaque was identified, the location was noted, and a three-beat clip that best demonstrated the plaque was obtained. Measurements were performed using semiautomated border detection software and obtained from two optimal angles of incidence (middle, anterior, and posterior). Three measurements at each angle were evaluated at end-diastole (within one or two frames of the Q wave on the electrocardiogram) for a total of 12 measurements, resulting in a composite mean CIMT measurement. There were two independent cardiologists experienced in reading CIMT studies, to minimize interobserver variability.

Electron-beam computed tomography with 3-mm slice thickness was used to assess for coronary artery calcification (Figure 2). If coronary artery calcium was detected, using the Agatston method, an automated score was generated.[15] CACS were based on age- and sex-matched control patients.[14] A CACS of 0 was suggestive of no disease, 1 to 99 of mild disease, 100 to 399 of moderate disease, and >400 of severe disease.

Carotid ultrasound was compared with CACS in the detection of subclinical atherosclerosis. Patients were classified with low-risk CIMT (<50th percentile), intermediate-risk CIMT (50th to 75th percentile), or high-risk CIMT (>75th percentile or the presence of plaque) for CVD on the basis of age-, sex-, and race-matched percentile.[16] A CACS Agatston score was assigned to age- and sex-matched patients. SAS version 9.2 (SAS Institute Inc, Cary, NC) was used for data analysis. Continuous variables are presented as mean ± SD. Categorical variables are presented as counts and percentages. Sample size calculation was performed by our Department of Biostatistics. A sample of 70 patients was found to have 80% power if the percentage of patients at high risk by CIMT and by CACS differed by 25 points (i.e., 63% vs 38%). With additional patients, the power would be greater to detect a difference.

RESULTS

Baseline Data

A total of 90 patients were assessed and four excluded. Exclusions included a screen failure due to lipid-lowering therapy ($n = 1$), one subject at intermediate risk by FRS, and two subjects who later refused computed tomography. Thus, 86 women were included in the study (mean age, 58 ± 4.6 years) with an average FRS of 1.9 ± 1.2, an average RRS of 2.2 ± 2.1, and an average 10-year ASCVD risk estimate of 3.1 ± 2.0. Eighty-two of 86 women (95%) had 10-year ASCVD risk < 7.5%. Ninety-five percent of women were Caucasian, three were Asian-Pacific Islanders, and one was African American. The average body mass index was 26.1 ± 4.9 kg/m^2, waist circumference 93.1 ± 12.9 cm, systolic blood pressure 117.6 ± 15.2 mm Hg, fasting glucose 92.7 ± 13.3 mg/dL, and low-density lipoprotein cholesterol level 138.9 ± 37.0 mg/dL (Table 1). Thirty-two patients (37.2%) had family histories of CAD, 11 (12.8%) were smokers, and 23 (26.7%) were on antihypertensive medications. The mean high-sensitivity C-reactive protein level was 2.9 mg/L.

CIMT Findings

Of the participating women, 44 (51.2%) had evidence of plaque on CIMT, with an additional nine subjects (10.5%) demonstrating high risk CIMT > 75th percentile for age-, gender-, and race-matched control subjects. Figure 3 illustrates the CIMT percentile breakdown among those with plaque. Of the four women who had 10-year ASCVD risk estimates ≥ 7.5%, three had plaque on CIMT, and the fourth had high-risk CIMT falling into the >75th percentile. Thus, 53 of participants (61.6%) were found to have either plaque on