What Do Carotid Intima-Media Thickness and Plaque Add to the Prediction of Stroke and Cardiovascular Disease Risk in Older Adults? The Cardiovascular Health Study

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Background: The aim of this study was to evaluate whether the addition of ultrasound carotid intima-media thickness (CIMT) measurements and risk categories of plaque help predict incident stroke and cardiovascular disease (CVD) in older adults.

Methods: Carotid ultrasound studies were recorded in the multicenter Cardiovascular Health Study. CVD was defined as coronary heart disease plus heart failure plus stroke. Ten-year risk prediction Cox proportional-hazards models for stroke and CVD were calculated using Cardiovascular Health Study–specific coefficients for Framingham risk score factors. Categories of CIMT and CIMT plus plaque were added to Framingham risk score prediction models, and categorical net reclassification improvement (NRI) and Harrell's c-statistic were calculated.

Results: In 4,384 Cardiovascular Health Study participants (61% women, 14% black; mean baseline age, 72 ± 5 years) without CVD at baseline, higher CIMT category and the presence of plaque were both associated with higher incidence rates for stroke and CVD. The addition of CIMT improved the ability of Framingham risk score–type risk models to discriminate cases from noncases of incident stroke and CVD (NRI = 0.062, $P = .015$, and NRI = 0.027, $P < .001$, respectively), with no further improvement by adding plaque. For both outcomes, NRI was driven by down-classifying those without incident disease. Although the addition of plaque to CIMT did not result in a significant NRI for either outcome, it was significant among those without incident disease.

Conclusions: In older adults, the addition of CIMT modestly improves 10-year risk prediction for stroke and CVD beyond a traditional risk factor model, mainly by down-classifying risk in those without stroke or CVD; the addition of plaque to CIMT adds no statistical benefit in the overall cohort, although there is evidence of down-classification in those without events. (J Am Soc Echocardiogr 2014;27:998-1005.)

Keywords: Aging, Cardiovascular disease, Carotid arteries, Stroke, Risk factors

The Framingham risk score (FRS) and other traditional cardiovascular disease (CVD) risk factors and algorithms have important predictive value for stroke and other CVD end points.[1] Nonetheless, the majority of incident stroke and other CVD events occur in the low- and intermediate-risk groups characterized by these risk factor predictors. Previous reports have documented an association between carotid intima-media thickness (CIMT) and/or plaque with stroke, transient ischemic attacks, and other clinical manifestations of CVD.[2-16]

Despite what is known regarding the importance of traditional CVD risk factors and measures of subclinical disease such as CIMT and plaque in predicting future stroke and other CVD events, there is a paucity of information regarding the relative prognostic value of adding carotid ultrasound measurement information to traditional risk factors in elderly individuals. Consequently, we evaluated, in a multicenter cohort of older adults without CVD at baseline, whether CIMT measurements and plaque could add incremental value to traditional risk factors in predicting the 10-year risk for incident stroke and CVD.

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Abbreviations

ARIC = Atherosclerosis Risk in Communities

CCA = Common carotid artery

CHD = Coronary heart disease

CHS = Cardiovascular Health Study

CIMT = Carotid intima-media thickness

cNRI = Clinical et reclassification improvement

CVD = Cardiovascular disease

FRS = Framingham risk score

HF = Heart failure

ICA = Internal carotid artery

IMT = Intima-media thickness

NRI = Net reclassification improvement

PAD = Peripheral arterial disease

METHODS

Study Population

The Cardiovascular Health Study (CHS) is a population-based prospective study of men and women aged ≥65 years at baseline. The mean age of the study population at baseline was 72.8 ± 5.6 years. The overall study design for CHS has been previously published.[17] Briefly, between 1989 and 1990, CHS enrolled 5,201 participants using Medicare eligibility lists in four communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. A second cohort of 687 black participants was recruited between 1992 and 1993. Participants included in this analysis had no evidence of coronary heart disease (CHD), heart failure (HF), or stroke at baseline. All participants underwent a baseline clinical examination that included history, physical examination, blood drawing, carotid ultrasound, and other tests.

Carotid Ultrasonography

Carotid arteries were evaluated at baseline using high-resolution B-mode ultrasonography (model SSA-270A ultrasound machine; Toshiba, Tustin, CA). The scanning protocol has been previously described in detail.[3] The protocols for recording carotid ultrasound studies and measuring CIMT were the same for the scans performed in 1989–1990 and 1992–1993. Both examinations used on-site videotapes as well as direct image capture to a Macintosh II computer, with the digital images and videotapes sent to the Ultrasound Reading Center for subsequent review and processing. The CHS protocol was such that after imaging of the common carotid artery (CCA) below the carotid artery bulb, images were acquired—with the ultrasound beam centered on the internal carotid artery (ICA) flow divider—from the anterolateral, lateral, and posterolateral projections. Plaque measurements were made in either the proximal ICA or the bulb, whichever site had the largest wall protrusion. If a protrusion was not seen, imaging was centered on the carotid bulb.

Quantitative measurements of CIMT were performed on one longitudinal image of the CCA and three longitudinal images of the ICA recorded from both the right and left carotid arteries. Measurements were performed on an image that was selected from a sequence of images replayed from a digital playback buffer. Frames that were free of motion (i.e., in which the preceding and following images showed no motion) were selected. Although there was no attempt to select on the basis of the cardiac cycle, subsequent review of the images has shown that this tended to be at end-diastole. A mouse-activated drawing tool was used to trace the boundaries of the lumen-intima and media-adventitia interfaces of the arterial wall. The distance between these two lines corresponded to the combined thickness of the intima and media.[2,3] Maximal intima-media thickness (IMT) of the CCA and ICA was calculated as the mean of the maximal IMT of the near and far walls from both left and right carotid arteries.[4] The CIMT measure used in these analyses was the average of maximal CCA and ICA IMT as defined above after standardization (i.e., after subtraction of the mean and division by the standard deviation of the measurement). Focal plaque, when present, was included in the maximum IMT measurement. Gender-specific percentile categories were created using cut points at the 25th and 75th percentile of standardized CIMT for each gender.

Plaque was defined on the basis of the presence of the greatest perceived protrusion of the carotid wall (specifically the IMT) in either the carotid bulb or the proximal ICA. Three plaque categories were defined, no plaque, intermediate risk, and high risk, on the basis of lesion surface, echogenicity, and texture characteristics.[2] High-risk plaques were defined as having at least one of the following characteristics: irregular or ulcerated surface, echolucency, or heterogeneous texture. Individuals with no plaque had lesion surfaces specified as smooth, with lesion density and morphology both specified as "no lesion." Any other combinations of lesion characteristics were defined as intermediate risk.

Data on intersonographer and interreader variability for CCA and ICA far wall thickness and residual lumen have been previously published.[3] The mean ± SD maximal absolute intersonographer difference for the far wall CCA IMT measurement was 0.20 ± 0.26 mm ($R = 0.52$) and for the far wall ICA IMT was 0.65 ± 0.69 mm ($R = 0.52$). The mean ± SD maximal absolute interreader differences in IMT measurements were lower for the interreader comparisons: 0.09 ± 0.05 mm for the CCA IMT ($R = 0.91$) and 0.41 ± 0.57 mm for the ICA IMT ($R = 0.81$).

Cardiovascular Event Ascertainment

Methods used to assess CVD events including stroke and CHD in CHS have been reported previously.[18] Briefly, in CHS, potential clinical events were identified through (1) clinic visits and surveillance calls by the field centers, (2) participant-initiated reports, and (3) secondary sources of events, including review of medical records and Medicare hospitalization data. The CHS Events Committee adjudicated CVD events by reviewing all pertinent data, including history, physical examination, chest radiography report, and medication use. CHD was defined as angina as well as nonfatal and fatal myocardial infarction, coronary artery bypass grafting, or angioplasty. CVD was defined as a composite of nonfatal or fatal CHD, HF, or stroke during the follow-up period. Cause of death was adjudicated by the Events Committee. All deaths due to atherosclerotic CHD were captured in the CHS definition, and all deaths due to atherosclerotic CHD or cerebrovascular disease were captured in the CVD definition. Individuals were censored at the earliest of the following: date of death, date of loss to follow-up, or 10 years.

Statistical Analyses

Stata version 12 software (StataCorp LP, College Station, TX) was used for analyses. Baseline characteristics were summarized according to gender-specific categories of CIMT (<25th percentile, 25th to 75th percentile, and >75th percentile). Incidence rates of stroke and CVD were calculated per 1,000 person-years as a function of CIMT percentile categories and plaque (absent, intermediate risk, and high risk). Cox proportional-hazards models were used to determine—after