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Ischemic stroke/transient ischemic attack events and carotid artery disease in the absence of or with minimal coronary artery calcification: Results from the Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background and aims: The association between minimally elevated coronary artery calcification (CAC) and cerebrovascular disease is not well known. We assessed whether individuals with minimal CAC (Agatston scores of 1–10) have higher ischemic stroke or transient ischemic attack (TIA) frequencies compared with those with no CAC. We also investigated the relative prevalence of carotid atherosclerosis in these two groups.

Methods: A total of 3924 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) without previous cardiovascular events, including stroke, and with baseline CAC scores of 0–10 were followed for the occurrence of incident ischemic stroke/TIA. We used carotid ultrasound to detect carotid artery plaques and to measure the intima-media thickness (IMT).

Results: During a median follow-up of 13.2 years, 130 participants developed incident ischemic stroke/TIA. There was no significant difference in the ischemic stroke/TIA incidence between those with minimal CAC and no CAC (3.7 *versus* 2.7 per 1000 person-years). In participants with minimal CAC, we observed a significant association of the condition with an internal carotid artery (ICA) that had a greater-than-average IMT (ICA-IMT; $\beta = 0.071$, $p = 0.001$) and a higher odds ratio (OR) for carotid artery plaques (OR 1.46; with a 95% confidence interval [CI] of 1.18–1.80; $p < 0.001$).

Conclusions: A CAC score of 0–10 is associated with a low rate of ischemic stroke/TIA, and thus a minimal CAC score is not a valuable predictive marker for ischemic stroke/TIA. A minimal CAC score may, however, provide an early and asymptomatic sign of carotid artery disease.

1. Introduction

Coronary artery calcification (CAC) is an established marker of subclinical atherosclerosis and an independent predictor of future coronary heart disease (CHD) [1–3], cardiovascular disease (CVD) [4] and all-cause mortality [5]. Individuals with even minimal CAC scores may have a higher risk of CHD and atherosclerotic cardiovascular disease including stroke compared with those without CAC, which suggests that patients with minimal CAC represent a distinct risk group [6–9]. In contrast, the negative predictive value of the absence of CAC is also well established for major adverse cardiovascular events [10], and individuals with an absence of CAC have a low mortality rate regardless of risk factors [3,11]. Similar associations with ischemic stroke/transient ischemic attack (TIA) have been reported for coronary atherosclerosis as assessed by CAC [12–17].

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A recent publication from the Multi-Ethnic Study of Atherosclerosis (MESA) showed an increase in ischemic stroke/TIA risk in individuals with a low CAC score of 1–99 compared with those without CAC [15,18]. In contrast, the prognostic value of a minimal CAC score of 1–10, compared with no CAC, relative to the incidence of ischemic stroke/TIA has not been fully investigated. We hypothesize that individuals with minimal CAC could have a higher risk of ischemic stroke/TIA compared with those without CAC. Moreover, carotid artery atherosclerosis, which potentially causes ischemic stroke/TIA, could be greater in individuals with minimal CAC relative to those without CAC because of a positive association of CAC and carotid artery atherosclerosis [19,20].

In this study, we assessed whether individuals with minimal CAC (corresponding to an Agatston score of 1–10) have similar or higher ischemic stroke/TIA event rates when compared with those without CAC. We also investigated the prevalence of carotid artery atherosclerosis in individuals with minimal or no CAC.

2. Materials and methods

2.1. Study population

The MESA design has been described in detail [21]. The MESA is a prospective observational cohort of 6814 men and women who, at baseline, were free of clinical cardiovascular disease and were 45–84 years old. Patient history of clinical cardiovascular disease was assessed by self-reported information of a physician-diagnosed heart attack or angina or the prescribed use of nitroglycerin; physician-diagnosed stroke or TIA; physician-diagnosed heart failure; current atrial fibrillation or having undergone procedures related to cardiovascular disease (coronary artery bypass graft surgery, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries). The participants were recruited from six field centers in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York and St. Paul, Minnesota. The specific racial/ethnic groups recruited were Caucasian, African-American, Hispanic and Chinese. Participants were enrolled from July 2000 through September 2002. The study was approved by the Institutional Review Boards at each site, and all participants gave written informed consent. In this study, we included 3924 MESA participants with baseline CAC scores of 0–10.

2.2. Risk factors

As part of the baseline examination, staff at each of the six centers collected information about cardiovascular risk factors. Medical history, anthropometric measurements and laboratory data were collected during the first examination of individuals from the MESA cohort (July 2000 to August 2002). Information about age, gender, ethnicity and medical history was obtained through questionnaires. “Current smoking” was defined as cigarette smoking in the last 30 days, whereas “former smoker” was defined as an individual who had not smoked in the last 30 days but had smoked ≥100 cigarettes in his/her lifetime. Diabetes was defined as fasting glucose of ≥7.0 mmol/l (126 mg/dl) or use of hypoglycemic drugs. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg or use of antihypertensive medication. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels from blood samples obtained after a 12-h fast were measured at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation [22].

2.3. CAC measurements

The MESA methods for computed tomography (CT) scanning and interpretation have been published [23]. CAC was assessed at all six MESA sites during the first examination of individuals from the MESA cohort by using either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles and New York field centers) or a multi-detector CT system (Baltimore, Forsyth County and St. Paul field centers). We used the average Agatston score from the two scans in all analyses, and the results were calibrated against a phantom containing known densities of calcium hydroxyapatite. All CT scans were read by a trained radiologist or cardiologist at a central reading center (Los Angeles Biomedical Research Institute at Harbor UCLA), who were blinded to all clinical and demographic patient information.

2.4. Carotid artery assessments

At the first examination, B-mode ultrasonography was used to image the near and far walls of the right and left distal CCA, carotid bulb and proximal ICA using a Logiq 700 ultrasound system (General Electric Medical Systems, 13 MHz transducer). The carotid bifurcations and ICAs were examined thoroughly at 9 MHz from both longitudinal and transverse approaches to identify the thickest regions. Images were stored on super-VHS videotape and digitized on a workstation at the Tufts Medical Center Ultrasound Reading Center. Methods for measuring and interpreting carotid intima-media thickness (IMT) have been reported [24]. Carotid artery assessments were made by blinded researchers. The mean maximal IMTs of the CCA (CCA-IMT) and carotid bulb + internal carotid artery (ICA) (ICA-IMT) were obtained by averaging the bilateral maximal measurements from the near and far walls at each projection. Carotid lesions were screened in either the CCA or ICA/carotid bulb. Carotid lesions was classified into six categories, numbered 0–5, with a 0 indicating no lesion, and 1–5 indicating various levels of stenosis (1, 1–24%; 2, 25–49%; 3, 50–74%; 4, 75–99%; 5, 100%) and, moreover, we further subdivided these categories into those with and without stenotic lesion, which were defined as the presence or absence of carotid artery plaques, respectively [25].

The inter-scan reproducibility was obtained by having the same reader blindly read a baseline scan and a separate repeat ultrasound examination. The correlation coefficients were 0.92 (95% CI: 0.89 to 0.94) for the CCA-IMT ($n = 143$) and 0.90 (95% CI: 0.86–0.95) for the ICA-IMT ($n = 140$). Moreover, for carotid plaque presence/absence, intra-reader reproducibility was $\kappa = 0.89$ (95% Cl, 0.85–0.92).

2.5. Stroke/TIA

Participants were followed from baseline examination (2000–2002) through 2016. They were contacted by telephone every 9–12 months to inquire about interim hospital admissions, cardiovascular outpatient diagnoses and deaths. To verify self-reported diagnoses, information was collected from death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses [26]. Stroke was defined as the rapid onset of documented focal neurological deficit lasting 24 h or until death, or, if the deficit lasted <24 h, a diagnosis of stroke was confirmed if there was a clinically relevant lesion on brain imaging (typically CT or magnetic resonance imaging) and no nonvascular cause. TIA was defined as a focal neurological deficit lasting <24 h without detection of stroke by brain imaging. Patients with focal neurological deficits secondary to brain trauma, tumor, infections or other non-vascular cause were excluded. Stroke/TIA events were