SUPPLEMENTAL MATERIAL

Association of Coronary Artery Atherosclerosis with Brain White Matter Hyperintensity

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Supplemental Methods:

Coronary CTA Methods:

A noncontrast scan was first performed to determine the coronary artery calcium (CAC) volume. Subsequently C-CTA was performed to examine the presence and severity of any coronary plaque. Approximately 80 mL of isosmolar contrast agent (320 mg iodine/mL) was injected at 6 mL/s. Prospective ECG-gating was used in patients with low, steady heart rates (<65 bpm) and little heart rate variability. For patients with variable heart rates or heart rates >65 bpm, retrospective gating with dose modulation was used.[19] Tube potential was selected on a per patient basis by the performing technologist assessment of patient size; 100 kV was used for patients that were not overweight or obese, otherwise 120 kV was used. We reconstructed 0.75-mm thick axial slices at 0.4-mm intervals with a B26 kernel; 10 reconstructions were done at 10% increments in the R-R interval. All scans were evaluated with the CT radiologist blinded to the participants' risk factor profiles. The coronary arterial tree was segmented according to the standard American Heart Association classification[42], and the segments were investigated for plaque and luminal narrowing. Any focal stenoses >50% in severity were identified with the use of quantitative software (COR Analyzer System, Rcadia Medical Imaging, Haifa, Israel)[43,44] and verified by the expert reader.

The volume of calcified coronary plaque was measured on a workstation (Leonardo Multimodality Workstation, Syngo, Siemens Medical Solutions, Malvern, PA) using noncontrast images. Regions of interest were placed over each of the coronary arteries and a threshold of >130 HU was used for determining per vessel volumes of calcified coronary plaque (mm^3) using standard validated methods.[45,46] Vessel calcified coronary plaque volumes were summed for a total calcified coronary plaque volume. For each affected coronary segment, noncalcified plaque volumes (mm3) were quantified using AUTOPLAQ (Cedars-Sinai Medical Center, Los Angeles, CA), as previously described.[47] This automated method of noncalcified plaque measurement has high interobserver correlation (r=0.97), and has been previously validated against intravascular ultrasound (IVUS).[47] For the present study, we also found excellent reproducibility for measured noncalcified plaque volumes (intraobserver r=0.99, mean percent error 3.6%) based on two blinded reads performed 6-12 months apart on a random sample (N=30). To quantify each affected segment, CTA images were examined in multiplanar format and proximal and distal limits of the plaque were manually marked. Control points defining the lumen center-line were placed. Subsequent noncalcified plaque quantification was then fully automated using adaptive algorithms that are scan specific per individual.[47] Segmental noncalcified plaque volumes were summed for a total noncalcified plaque volume per vessel, including the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). The vessel specific volumes were summed for a total volume. Total coronary plaque was calculated as the sum of calcified + noncalcified plaque.[48] The percent of total plaque consisting of calcified plaque and noncalcified plaque was calculated by dividing by total coronary plaque for each.

Supplemental References:

42. Austen WG, Edwards JE, Frye RL, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the ad hoc

committee for grading of coronary artery disease, council on cardiovascular surgery, American heart association. Circulation 1975;51:5-40.

43. Kelm BM, Mittal S, Zheng Y, Tsymbal A, Bernhardt D, Vega-Higuera F, Zhou SK, Meer P, Comaniciu D. Detection, grading and classification of coronary stenoses in computed tomography angiography. Med Image Comput Comput Assist Interv 2011;14:25-32.

44. Halpern EJ, Halpern DJ. Diagnosis of coronary stenosis with CT angiography comparison of automated computer diagnosis with expert readings. Acad Radiol 2011;18:324-33.

45. Ohnesorge B, Flohr T, Fischbach R, Kopp AF, Knez A, Schroder S, Schopf UJ, Crispin A, Klotz E, Reiser MF, et al. Reproducibility of coronary calcium quantification in repeat examinations with retrospectively ECG-gated multisection spiral CT. Eur Radiol 2002;12:1532-40.

46. McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD, Kalender WA. Coronary artery calcium: A multi-institutional, multimanufacturer international standard for quantification at cardiac CT. Radiology 2007;243:527-38.

47. Dey D, Schepis T, Marwan M, Slomka PJ, Berman DS, Achenbach S. Automated three-dimensional quantification of noncalcified coronary plaque from coronary CT angiography: Comparison with intravascular US. Radiology 2010;257:516-22.

48. Kral BG, Nyquist P, Vaidya D, Yousem D, Yanek LR, Fishman EK, Becker LC, Becker DM. Relation of subclinical coronary artery atherosclerosis to cerebral white matter disease in healthy subjects from families with early-onset coronary artery disease. Am J Cardiol 2013;112:747-52.