Relation between Cardiovascular Disease Risk Markers and Brain Infarcts Detected by Magnetic Resonance Imaging in an Elderly Population

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Background: Established cardiovascular risk markers, such as hypertension, are associated with increased risk of brain infarcts. The newer markers N-terminal pro-brain natriuretic peptide, troponin I, C-reactive protein, and cystatin C may affect the risk of cardiovascular events and potentially, thereby, also stroke. We investigated the association between established and new risk markers for cardiovascular disease and brain infarcts detected by magnetic resonance imaging (MRI) at age 75. *Methods:* Four hundred six randomly selected subjects from the Prospective Investigation of the Vasculature in Uppsala Seniors study were examined with MRI of the brain at age 75. Blood samples, measurements, and dedicated questionnaires at age 70 were used for analysis of risk markers. A history of diseases had been obtained at age 70 and 75. MRI was evaluated regarding lacunar and cortical infarcts. Univariate associations between outcomes and risk markers were assessed with logistic regression models. *Results:* One or more infarcts were seen in 23% of the subjects (20% had only lacunar infarcts, 1% had only cortical infarcts, and 2% had both). Hypertension (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.4, 4.7) and obesity (OR 1.3; CI 1.0, 1.8) were significantly associated with increased risk of brain infarction. The newer risk markers were not significantly associated with the brain infarcts. *Conclusions:* The new markers were not associated with the predominantly lacunar infarcts in our 75-year-old population, why troponin I and NT-proBNP may be associated mainly with cardioembolic infarcts as shown recently. **Key Words:** Magnetic resonance—stroke—lacunar infarctions—risk factors—hypertension.

Introduction

Established cardiovascular risk markers, such as hypertension, diabetes, obesity, and smoking, are associated with an increased risk of stroke.[1,2] Early detection and treatment of these risk markers, and preventive efforts to reduce smoking, could reduce the risk of stroke.[1,2] Many studies have investigated the association of established cardiovascular risk factors with brain infarcts in populations.[2-5] Among these risk factors, hypertension is most widely associated with stroke[1,5] and with silent brain infarcts.[2,4] Cortical and lacunar infarcts may have different risk factor profiles because

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cortical infarcts often are caused by large-vessel disease and lacunar infarcts by small-vessel disease.[6] Cardioembolic infarcts are usually large and include the cortex but may sometimes be lacunar.[7,8] Silent brain infarcts are detected in approximately 20% of healthy elderly people, and most of the silent infarcts are lacunar.[2] The location of a brain infarct in the acute stage determines if it is symptomatic (ie, recognized) or silent, and because cortical infarcts are larger than lacunar they are more often symptomatic. Thus, a difference in risk factor profile is more dependent on the type of infarct than if it is symptomatic or silent.

B-type natriuretic peptide (NT-proBNP), a neurohormone secreted from the cardiac ventricles, is a recognized marker of myocardial wall tension and established biochemical marker of increased mortality and morbidity in cardiovascular events.[9,10] Cardiac troponin (troponin I) is an intracellular protein involved in heart muscle contraction and is a biochemical marker of myocardial damage.[11] C-reactive protein (CRP) is a marker of inflammation, involved in endothelial inflammatory response, predicting stroke and cardiovascular events.[10,12,13] Cystatin C is mainly used as a marker of renal function and has been reported as a strong predictor of cardiovascular death in elderly people.[10] The addition of NT-proBNP, troponin I, CRP, and cystatin C to the established risk factors for cardiovascular disease was reported to improve risk stratification for death from cardiovascular causes in elderly men.[10] Troponin I and NT-proBNP were recently found to be independently related to increased risk of stroke, systemic embolism, and vascular event mortality in a population with atrial fibrillation.[11,14] In a review and meta-analysis, NT-proBNP was found to have a reasonable accuracy in the diagnosis of cardioembolic stroke.[7] The "new" markers have, however, not been investigated regarding the risk of different types of brain infarcts seen on magnetic resonance imaging (MRI).

The aim of the present study was to investigate the associations between established cardiovascular risk factors and 4 new risk markers and brain infarcts detected on MRI in a 75-year-old population.

Materials and Methods

Ethics Statement

The Regional Ethical Review Board in Uppsala, Sweden, approved the study, and all subjects provided written informed consent.

Study Population

We studied 406 subjects at the age of 75 years from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study.[15] The subjects had been chosen in a randomized manner from the register of the municipality. Out of 964 subjects, 827 agreed and gave written informed consent to participate in the study. From this cohort, 406 randomly selected subjects (210 men) underwent MRI of the brain at the age of 75 years.

Risk Markers

Cardiovascular risk factor/marker data were obtained from blood samples and measurements performed at age 70, from the patient clinical records, and from dedicated questionnaires in the PIVUS study at age 70 and 75. This information was used for the statistical analysis of association with the cerebral infarcts.

The following variables obtained at age 70 were assessed: systolic blood pressure (SBP), diastolic blood pressure [DBP], hypertension prevalence (SBP $\geq$ 140 mm Hg, DBP $\geq$ 90 mm Hg, or the use of antihypertensive medication), diabetes mellitus (defined as fasting blood sugar $>$ 6.1 mmol/L or history of diabetes mellitus), body mass index (weight divided by the square of the height), waist circumference, current smoking (daily), former smoking (nonsmoker with history of smoking), total smoking (current and former smoking), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum triglyceride, lipid-lowering treatment, NT-proBNP, troponin I, CRP, and cystatin C.

All subjects were investigated in the morning after an overnight fast. No medication or smoking was allowed after midnight. After recordings of height, weight, waist, and hip circumference, blood pressure measurements and blood sampling were performed with the subjects lying supine in a quiet room.[16] Blood pressure was measured by a calibrated mercury sphygmomanometer in the noncannulated arm to nearest mm Hg after at least 30 minutes of rest, and the average of 3 recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques.

NT-proBNP was measured using the Elecsys proBNP sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics, Roche Diagnostics Scandinavia AB, Bromma, Sweden). Troponin I was analyzed using the high-sensitive ARCHITECT *STAT* hsTnI assay on an Architect $i2000_{SR}$ platform. CRP, cystatin C, etc., were analyzed on the Architect 8000 Instrument (Abbott Diagnostics, Lake Forest, IL).

Stroke Verification

The subjects answered a questionnaire at age 70 and 75 regarding the history of diseases. If hospital-treated stroke was indicated, the diagnosis was validated by the hospital records.

Image Acquisition

Imaging was performed at age 75 on a 1.5 T MRI system (Gyroscan Intera; Philips Medical Systems, Best, The