Carotid intima-media thickness is associated with incidence of hospitalized atrial fibrillation

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ABSTRACT

Objective: Carotid intima-media thickness (IMT) is a measure of arterial thickening and a risk predictor for myocardial infarction and stroke. It is unclear whether IMT also predicts atrial fibrillation (AF). We explored the association between IMT and incidence of first AF hospitalization in a population-based cohort.
Methods: IMT was measured in 4846 subjects from the general population (aged 46–68 years, 60% women) without a history of AF, heart failure or myocardial infarction. The Swedish in-patient register was used for retrieval of AF cases. IMT was studied in relation to incidence of AF.
Results: During a mean follow-up of 15.3 years, 353 subjects (181 men, 172 women, 4.8 per 1000 person-years) were hospitalized with a diagnosis of AF. After adjustment for cardiovascular risk factors, the hazard ratio (HR) for incidence of AF was 1.61 (95% confidence interval (CI): 1.14–2.27) for 4th vs. 1st quartile of IMT in the common carotid artery. This relationship was also independent of occurrence of carotid plaque. The results were similar for IMT in the bifurcation.
Conclusion: Carotid IMT was independently associated with incidence of hospitalized AF in this study of middle-aged subjects from the general population. The results suggest that arterial thickening can predict future AF.

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1. Introduction

Atrial fibrillation (AF) is a highly prevalent condition in the elderly. AF is associated with substantial morbidity and mortality, with a five-fold increased risk of stroke and a three-fold increased incidence of congestive heart failure (HF) [1]. AF is a heterogeneous disorder and different disease processes, such as ischemia, fibrosis or myocardial strain, could ultimately result in the substrates necessary to cause and sustain AF. Many risk factors for atherosclerosis are associated with increased incidence of AF, but there are also interesting exceptions. For example, higher levels of low-density lipoprotein (LDL) cholesterol and physical inactivity have shown to be protective of AF in some studies [2].

Atherosclerosis develops slowly and a long subclinical period precedes the clinical manifestations. It has been reported that the coexistence of AF and clinical manifestations of atherosclerosis increases the risk of future cardiovascular events dramatically [3]. AF has been associated with peripheral artery disease and atherosclerotic plaque in the carotid arteries [4,5]. It was also reported that flow-mediated dilatation, a measure of endothelial dysfunction, was impaired in patients with AF [6].

Carotid intima-media thickness (IMT) is widely accepted as a measure of arterial thickening. Increased carotid IMT is a risk predictor for acute myocardial infarction (MI) and stroke and has also been associated with incidence of HF [7–10]. Few studies have explored whether carotid IMT is a risk predictor of AF, and the results are inconsistent [11–13]. The Cardiovascular Health Study (CHS) found no association between carotid IMT or carotid stenosis and incidence of AF [11,12]. In contrast the Rotterdam Study showed a significant association between carotid IMT and incidence of AF, especially among women, and a recent case–control study found carotid IMT to be associated with lone AF [13,14]. Hence, it is still unclear whether IMT predicts future AF. This population-based

cohort study sought to investigate whether carotid IMT is associated with incidence of first AF hospitalization.

2. Materials and methods

2.1. Study population

All men born between 1923 and 1945 and women born between 1923 and 1950 living in Malmö, Sweden, were invited to participate in the Malmö Diet and Cancer (MDC) study. Details of the study have been described previously [15]. Between March 1991 and September 1996, the respondents participated in clinical examinations at the screening centre and a self-administered questionnaire including a dietary assessment. A total of 30 447 individuals from the eligible population of 74 000 individuals attended the baseline examinations. After excluding 1998 individuals who failed to complete either the questionnaire, the clinical examinations or the dietary assessment, the cohort consisted of 28 449 subjects (11 246 men and 17 03 women). A random 50% of participants who entered the MDC study between October 1991 and February 1994 were also invited to take part in a study of the epidemiology of carotid artery diseases [16]. During this period, a total of 6103 subjects (2572 men and 3531 women) were examined by B-mode ultrasound of the right carotid artery, and 5540 participants returned to donate fasting blood samples for measurements of blood lipids and glucose.

Subjects with a history of hospitalization due to AF, HF or MI (in total 159 subjects) were excluded from analysis. Furthermore, 536 subjects with missing information on carotid IMT, high-sensitive C-reactive protein (hs-CRP), waist circumference, lipoproteins and education level were also excluded (Fig. 2).

Mean age was 57.4 ± 5.9 in excluded subjects ($n = 1257$) and 57.5 ± 6.0 in those who were included in the study ($n = 4846$). The proportion of men was 50% and 40% respectively. Incidence of first AF hospitalization was higher in excluded subjects (7.7 per 1000 person years vs. 4.8 per 1000 person years).

The study was approved by the ethics committee at Lund University, Lund, Sweden (LU 51/90). All participants provided written informed consent.

2.2. Baseline examinations

A self-administered questionnaire was used to obtain information on smoking habits, alcohol use, education, physical activity, marital status, medical history and current medications. Smoking was classified into 3 categories: smokers, former smokers and never-smokers. Marital status was classified into 2 groups: unmarried (single, divorced, or widowed) or married (cohabiting). Educational level was classified into low (8 years), moderate (9–12 years), and high (college/university) levels. Information on physical activity was explored through 18 questions covering a range of activities in the 4 seasons. An overall leisure time physical activity score was created by multiplying the number of minutes per week for each activity by an intensity coefficient. The scores were divided into quartiles of physical activity when used in the analysis. Information on daily alcohol intake was assessed through a validated diet history method where food and beverages was registered in a "menu book" on 7 consecutive days [17]. Daily alcohol consumption in men/women was classified as low (<20/15 g), medium (20–40/15–30 g), and high (>40/30 g). Blood pressure was measured once in the supine position after 10 min rest using a mercury-column sphygmomanometer. Hypertension was defined as systolic blood pressure ≥140/90 mm Hg or current use of blood pressure lowering medication. Body weight, height and waist circumference was measured. Presence of diabetes mellitus was defined as a self-reported physician's diagnosis of diabetes, use of anti-diabetic medications or a fasting whole blood glucose level ≥6.1 mmol/L. Blood glucose, total and high-density lipoprotein (HDL)-cholesterol, were measured from fasting blood samples, according to standard procedures at the Department of Clinical Chemistry, Malmö University Hospital. The LDL-cholesterol concentration was calculated according to Friedewald's formula [18]. Hs-CRP was analyzed in frozen plasma, gathered at the baseline examination, using Tina-quant CRP latex high-sensitivity assay (Roche Diagnostics) on an ADVIA 1650 Chemistry System (Bayer Healthcare). Total leukocyte count was analyzed using an SYSMEX K1000 fully automated assay (Sysmex Europe, Norderstedt, Germany). The analyses were performed consecutively at the time of the screening examination, at the central laboratory of the Malmö University Hospital, using fresh heparinized blood.

2.3. Carotid artery measurement

Participants underwent B-mode ultrasonography of the right carotid artery by trained certified sonographers, using an Acuson 128 (Acuson, Mountain View, California). Presence of carotid plaque, defined as a focal thickening of the IMT >1.2 mm, was assessed. In short, the bifurcation area of the right common carotid artery was scanned within a predefined "window" comprising 3 cm of the right common carotid artery (CCA), the bifurcation, and 1 cm of both the internal and external carotid artery for the presence of plaque. IMT was measured off-line in the far wall of the right distal CCA as the mean thickness over a 10-mm segment proximal to the bifurcation according to the leading edge principle, using a specially designed computer-assisted analyzing system [19]. The maximum IMT in the bifurcation was also measured. [20–23]

Intra-observer and inter-observer variability with regard to IMT was checked regularly. The mean intra-observer difference was $8.7 \pm 6.2\%$ ($r = 0.85$) and the mean inter-observer difference $9.0 \pm 7.2\%$ ($r = 0.77$). [16]

2.4. Follow-up and definitions of end-points

AF was defined as a primary or contributory diagnosis of AF or atrial flutter as in previous studies [24,25]. All subjects were followed from baseline until the first hospitalization with a diagnosis of AF, death, emigration from Sweden or end of follow-up (June 30, 2009). In secondary analyses, subjects who experienced a nonfatal MI or HF during the follow-up period were followed until the day of hospitalization and censored thereafter. Subjects who were diagnosed with AF concomitantly with the MI or HF diagnosis during follow-up were also censored from this secondary analysis, given the close relationship between these diagnoses. Cases were retrieved by linkage of Swedish personal identification numbers to the Swedish Hospital Discharge Register and the Swedish Cause of Death Register using diagnosis codes 427.92 for the International Classification of Diseases 8th edition (ICD-8), 427D (ICD-9), and I48 (ICD-10). A validation study of 100 cases with AF diagnosis in the present cohort showed that AF was definite in 95%, probable in 2% and incorrect in 3% [24].

2.5. Statistics

IMT and hs-CRP were log-transformed due to skewed distributions. The sample was categorized into sex-specific quartiles of IMT in the CCA and in the bifurcation, respectively, i.e. four groups with equal proportions of men and women in each quartile. One-way ANOVA and logistic regression was used to compare risk factor distributions across the quartiles of IMT. Cox proportional hazards regression was used to estimate hazard ratios (HR) adjusted for